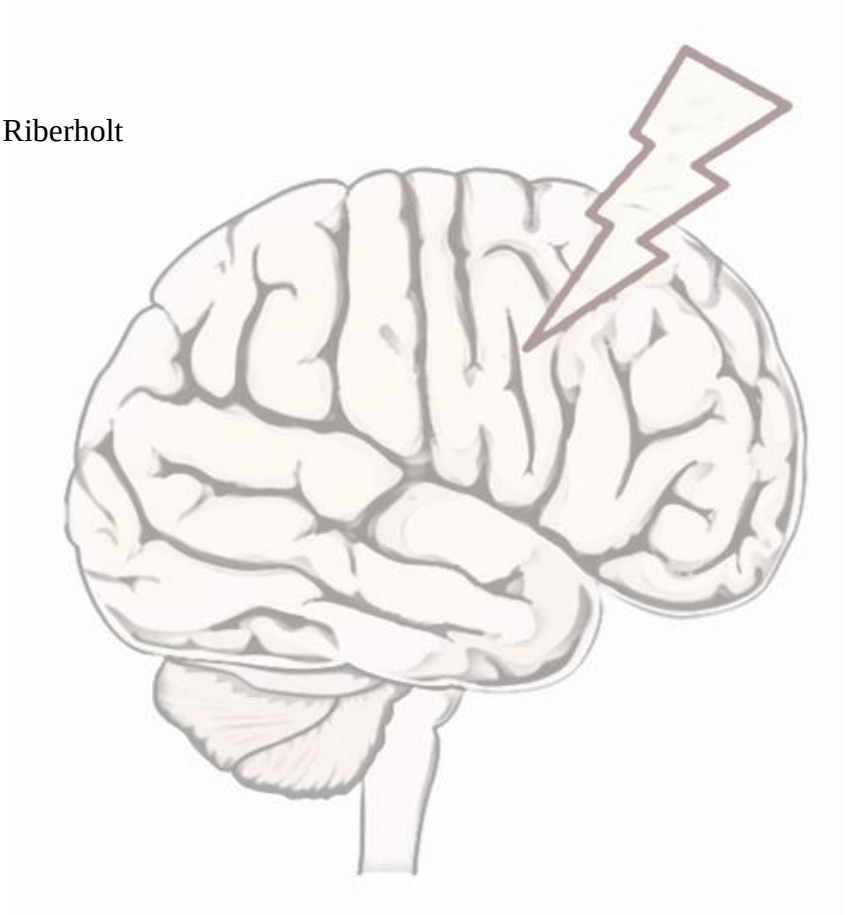
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Early orthostatic exercise in patients with severe traumatic or acquired brain injury

PhD Thesis

Christian Gunge Riberholt



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Early orthostatic exercise in patients with severe traumatic or acquired brain injury.

Department of Neurorehabilitation, Traumatic Brain Injury

Copenhagen University Hospital, Rigshospitalet.

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   Christian Gunge Riberholt, Jane Lindschou, Christian Gluud, Jesper Mehlsen and Kirsten Møller.
   Trials 2018 Nov. 8; 19(1):612
2. **Statistical analysis plan for: Early mobilization by head-up tilt with stepping versus standard care after severe traumatic brain injury.**
   Christian Gunge Riberholt, Christian Gluud, Christian Ovesen, Janus Jakobsen, Jesper Mehlsen and Kirsten Møller.
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   Christian Gunge Riberholt, Markus Harboe Olsen, Christian Baastrup Søndergaard, Christian Gluud, Christian Ovesen, Janus Christian Jakobsen, Jesper Mehlsen and Kirsten Møller.
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4. **Early head up mobilisation versus standard care for patients with severe acquired brain injury: a systematic review with meta-analysis and Trial Sequential Analysis.**
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5. **Reliability of the transcranial Doppler ultrasound-derived mean flow index for assessing dynamic cerebral autoregulation in healthy volunteers.**
   Christian Gunge Riberholt, Markus Harboe Olsen, Lene Theil Skovgaard, Ronan MG Berg, Kirsten Møller, Jesper Mehlsen.
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6. **Dynamic cerebral autoregulation during early orthostatic exercise in patients with severe traumatic brain injury: results from a randomised clinical feasibility trial.**
   Christian Gunge Riberholt, Markus Harboe Olsen, Ronan Berg, Jesper Mehlsen, Kirsten Møller.
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Preface

I submitted this PhD thesis as part of the mandatory requirements for obtaining a PhD-degree at the University of Copenhagen, Faculty of Health and Medical Sciences. Three departments participated in conducting the clinical trial: the Department of Neuroanesthesiology, Rigshospitalet, the Department of Intensive Care (Y13), Rigshospitalet, and the Department of Neurorehabilitation, Traumatic Brain Injury, Rigshospitalet. The systematic review, the trial protocol, the central randomisation (generation of allocation sequence and allocation concealment), the statistical analysis plan, and the statistical analyses were prepared together with the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet.

I prepared the three projects (systematic review, reliability study and clinical trial) while working as a physical therapist in 2016 and the clinical trial started patient recruitment in January 2017 alongside recruitment of healthy persons for the feasibility study. Kirsten Møller (Department of Neuroanesthesiology, Rigshospitalet) and Jesper Mehlsen (Surgical Pathophysiology Unit, Rigshospitalet) supervised the projects.

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Acknowledgements

This thesis marks the end of my PhD project, candidature, and a personal journey. It would not have been possible to complete this journey without a long list of people.

First and foremost, I wish to thank all the patients and their relatives who consented for participation in the clinical trial. It is a difficult situation to accept involvement on behalf of loved ones in a critical condition. Nevertheless, without these consents, it is not possible to improve the treatment of patients with traumatic brain injury.

A sincere and respectful thanks go to my supervisors whose support has been invaluable. Kirsten Møller, thank you for supporting the project from the beginning, and always taking time out of your busy schedule and Jesper Mehlsen, for support throughout the years and pushing me to do this thesis. I am genuinely proud that you have taken me under your wings and have enjoyed every second.

Clinical research takes more than funding and hard work. Sometimes you meet people who through their positive attitude, inspires and believes in you. Therefore, I would like to thank Christian Gluud, first for insights into clinical trial research, always being positive and constructive in your feedback and secondly, for the enormous amount of knowledge I feel you have given me.

A special thanks to Ronan M.G. Berg for all the inspiring insights in physiology and helping me whenever needed.

I want to share a unique and heartfelt thanks to the fellow PhD candidates in the "cave". Without your companionship and support, this would have been a tiresome and lonely journey. And a warm gratitude to Markus Harboe Olsen whose support, curiosity, commitment and problem-solving skills have led me to strive harder.
Since 2016, people from different institutes and departments have shared their thoughts, intellect, and at times hard work to help me finish the projects. Therefore, I would like to thank Jane Lindschou, Janus Christian Jakobsen, Christian Ovesen (Copenhagen Trial Unit, Rigshospitalet) and Christian Baastrup Søndergaard (Department of Neurosurgery, Rigshospitalet),

The Department of Neuroanesthesiology, the Department of Intensive Care (Y13), the Department of Neurorehabilitation and the Department of Physical Therapy, Rigshospitalet:
It is always challenging to change daily routines in a busy day, but having the capacity to change, be curious and asking questions, makes the people at the departments unique and is probably one of the reasons for the high level of care you deliver to the patients. Therefore, a special thanks go to the staff at these departments for helping to make this project succeed.
A few have made an exceptional contribution. Marie Glover and Sofie Gruelund who supported the project, worked hard to recruit patients and shared their knowledge on treatment and exercise of patients at the neurointensive care unit.

I want to thank Vibeke Wagner for help in assisting with the systematic review and for always working hard and vigorously when needed.

Moreover, head of research, associate at the department of Neurorehabilitation, Traumatic Brain Injury, professor Ingrid Poulsen for all her support and practical guidance during the last three years as well as Hanne Munk and Marianne Telling for believing in the project from the beginning.

Finally, I also wish to acknowledge my family for their support. To my wife Nina for her endless support and companionship, for not discarding my crazy ideas right away, for going that extra mile to make things work out. I love you, dearly. To my three boys Bertram, Malte, and Walter, who (most of the time) give me the energy to perform. Thank you for asking those intriguing questions that only kids can ask. To Anette and Finn, for looking after our kids when we need extra time and for always being there, and to my sisters-in-law and brothers-in-law – Vibeke, Pernille, Andreas, and Bjarke – thank you for all your support and great times.

October 2020

Christian Cronge Ribenhoff

Summary

Patients with acquired brain injury undergo extensive rehabilitation, which, depending on the severity and general clinical state, may start early. Studies have found a positive effect of starting rehabilitation as soon as possible in patients with severe traumatic brain injury. In contrast, patients with stroke are generally recommended to be cautious with mobilisation in the early phase due to results from the AVERT III trial. Previous trials have mostly included stroke patients or patients with mild injuries, whereas patients with severe acquired brain injuries are few.

As a starting point, we investigated the benefits and harms of early mobilisation in patients with severe acquired brain injury through a systematic review. In total, four trials were identified, assessed for risk of bias and analysed with meta-analysis and Trial Sequential Analysis. We found no evidence of a difference between early mobilisation compared with standard care measured at the end of intervention or the longest follow-up on outcomes such as death or poor functionality, serious adverse events, non-serious adverse events, or consciousness. We found evidence of no effect on the quality of life at the longest follow-up, albeit these trials only included patients with stroke.

As previous trials had primarily focused on stroke, we designed a feasibility trial for severe traumatic brain injury and included 38 patients. We wanted to assess the feasibility of conducting early mobilisation in an ERIGO® tilt-table. The trial showed that early mobilisation is feasible in trials in terms of including patients and completing the exercises. We observed no effects of early mobilisation versus standard care on a number of outcomes, but the trial lacked sufficient power.

One of the arguments for avoiding head-up mobilisation is the potentially harmful effects of reducing cerebral blood flow if autoregulation fails. To examine dynamic cerebral autoregulation in patients before and during head-up tilt in the trial, we first did a study investigating the relative and absolute reliability of the non-invasive mean flow index (nMxa) in a healthy population. We analysed the recordings using three different variations of block sizes for calculating the nMxa. Here we found that the 3-second block sizes yielded fair reliability with smaller confidence intervals, standard error of the measurements, and limits of agreements than

the 5- and 10-seconds block sizes. All indicated difficulties in determining changes in an individual patient.

Thirty-four of the 38 patients with traumatic brain injury from the feasibility trial, were measured with non-invasive mean arterial pressure and middle cerebral artery flow velocity at baseline, after two weeks, and after four weeks before and during head-up tilt. Although we lost many patients to follow-up and given the limits in the reproducibility of the autoregulation index, our analysis did not indicate that early orthostatic exercise affects the systemic or cerebral haemodynamic response to head-up tilt adversely. Head-up tilt does not protect against orthostatic reactions.

Resumé (dansk)

Patienter med erhvervet hjerneskade gennemgår omfattende rehabilitering, der afhængigt af sværhedsgraden og den generelle kliniske tilstand, kan starte tidligt. Studier har fundet en positiv effekt af at starte rehabilitering så tidligt som muligt hos patienter med svær traumatisk hjerneskade, mens det hos patienter med stroke generelt er blevet anbefalet at være forsigtige i den tidlige fase på grund af resultaterne fra AVERT III-studiet. Ikke desto mindre er patienter med svær erhvervet hjerneskade ofte i undertal i studierne i forhold til de hyppigere lettere erhvervede hjerneskader.

Som udgangspunkt undersøgte vi gavnlige og skadelige virkninger ved tidlig mobilisering hos patienter med svær erhvervet hjerneskade gennem en systematisk litteratur gennemgang. I alt blev fire forsøg identificeret, vurderet for risiko for bias og analyseret gennem metaanalyse og sekventiel analyse af forsøg (*Trial Sequential Analysis*). Vi fandt ingen videnskabelig dokumentation for en forskel mellem tidlig mobilisering, sammenlignet med standard behandling, på effekt mål såsom død eller lavt funktionsniveau, alvorlige bivirkninger, ikke alvorlige bivirkninger eller bevidsthedsniveau målt efter intervention eller ved den længste opfølgning. Vi fandt bevis for, at der *ikke* var nogen effekt på livskvaliteten ved den længste opfølgning, omend disse forsøg kun havde inkluderet patienter med stroke.

Da forudgående forsøg primært havde fokus på stroke, inkluderede vi 38 patienter med alvorlig traumatisk hjerneskade i et randomiseret forsøg af graden af gennemførlighed af at sammenligne tidlig mobilisering i et ERIGO® vippeleje med standard behandling. Forsøget viste, at et tidligt mobiliseringsstudie er muligt at gennemføre med hensyn til at inkludere patienter og gennemføre, træningsseancerne. Der var ingen forskel mellem de to interventioner på en række effektmål, men forsøget er uden en tilstrækkelig statistisk styrke.

Et af argumenterne for at undgå tidlig mobilisering er den potentielt skadelige effekt der kan opstå, hvis den cerebrale blodgennemstrømning reduceres når autoregulationen ikke fungerer. For at undersøge dynamisk cerebral autoregulering hos patienter før og under vippeleje træning i forsøget, udførte vi først et reliabilitetsforsøg, der undersøgte den relative og absolutte pålidelighed af *mean flow index* (nMxa) i en rask population. Vi analyserede målingerne ved hjælp af tre forskellige variationer af blokstørrelser til beregning af nMxa. Her fandt vi, at 3-sekunders blokstørrelser gav rimelig pålidelighed med mindre konfidensintervaller og grænser

for overensstemmelse end 5- og 10-sekunders blokstørrelse. Alle indikerede vanskeligheder med at bestemme ændringer hos en individuel patient.

Fireogtredive af de 38 patienter med traumatisk hjerneskade fra gennemførlighedsforsøget blev målt med ikke-invasivt blodtryk og blodgennemstrømningen af den midterste cerebrale arterie ved baseline, efter to uger og efter fire uger. Selvom mange patienter ikke medvirkede til opfølgning og vi medregner begrænsningerne fra resultaterne af reproducerbarheds-undersøgelsen, indikerede vores analyse, at tidlig mobilisering ikke påvirker systemisk eller cerebral haemodynamik. Dog beskytter træningen heller ikke mod forekomsten af ortostatiske reaktioner.

Abbreviations

95% CI:	95% confidence interval
CRS-R:	Coma Recovery Scale-Revised
CVR:	Cerebrovascular resistance
DARIS:	Diversity-adjusted required information size
DATSACI:	Diversity-adjusted trial sequential analysis confidence interval
dCA	Dynamic cerebral autoregulation
EFA:	Early Functional Abilities
FIM:	Functional Independence Measure
GCS:	Glasgow Coma Scale
GOSE:	Glasgow Outcome Scale Extended
GPI:	Gosling's Pulsatility Index
HR:	Heart rate
HUT:	Head-up tilt
ICC:	Intraclass correlation coefficient
ICF	The international classification of functioning, disability, and health
ICU:	Intensive care unit
IQR:	Interquartile range
MAP:	Mean arterial pressure
MCAv	Middle cerebral artery blood flow velocity
NICU:	Neurointensive care unit
nMxa:	Non-invasive mean flow index
SD:	Standard deviation
SEM:	Standard error of the measurement
TSA:	Trial Sequential Analysis

Table of contents

Chapter 1

1.0 Introduction

Forces applied directly and indirectly to the head can result in traumatic brain injury [1]. The initial injury (the primary traumatic brain injury) causes focal injuries, contrecoup lesions, haematomas, shearing of white matter tracts, diffuse axonal injury and swelling [2,3]. The secondary injury evolves over hours or days. It consists of brain swelling, increased intracranial pressure, decreased cerebral perfusion pressure and systemic insults which can cause ischaemia or hypoxia due to different mechanisms [2].

Patients with traumatic brain injury surviving the initial phase in the neurointensive care unit (NICU) have a pallet of different deficiencies in the physical, mental, and social areas [1]. In an attempt to make the patients return to a more normal or acceptable lifestyle, they receive extensive rehabilitation efforts [4]. One of the prognostic factors for a poor outcome is the prolongation of disorders of consciousness and post-traumatic amnesia [5]. Treatments that can reduce the length of a vegetative state or minimally conscious state could be beneficial to the patients and the entire rehabilitation effort.

Several observational studies have shown that patients with acquired brain injury and prolonged disorders of consciousness have signs of increased arousal when positioned in a more upright posture, such as sitting or standing [6–8]. Reports of patients experiencing orthostatic reactions during the initial treatment at the rehabilitation departments have also been published [8,9], with almost 40% of the patients experiencing orthostatic reactions during mobilisation on a tilt-table [8,9]. The origin of these orthostatic reactions is multifactorial. However, it may in part come from the initial brain damage (especially if parts of the lower brain stem are involved) or it may be a consequence of inactivity and prolonged bed rest [9,10].

1.1 Rationale behind the studies in this thesis

Patients with traumatic brain injury and disorders of consciousness may experience orthostatic reactions while undergoing rehabilitation. The feasibility and effects of early (i.e. starting in the intensive care unit (ICU)) orthostatic exercise are uncertain. A feasibility trial may help establish

if this treatment modality is fair to use and provide information relevant for a larger randomised trial (paper I, II, III).

Patients with severe acquired brain injury account for many of the resources spent in the healthcare and social sector. The physiological response to and recovery from early mobilisation could be the same for patients with severe damage compared to patients with mild or moderate brain damage. Even so, patients with severe acquired brain injury are at higher risk of having immobility related deficits and could, therefore, benefit more from early mobilisation than patients with mild brain injury. Through a systematic review, we attempted to investigate the benefits and harms of early mobilisation in patients with severe acquired brain injury (paper IV).

Studies have shown that patients with severe traumatic brain injury have impaired cerebral autoregulation in the early stage. Thus, an essential confounder for effect in this patient group could be orthostatic hypotension resulting in decreased cerebral blood flow and further ischemic brain damage. We, therefore, assessed cerebral autoregulation before and after the intervention period in our randomised clinical feasibility trial (paper VI).

Though the method used for assessing cerebral autoregulation has been published in multiple studies, the reliability of the method has not been thoroughly investigated, in particular during head-up tilt (HUT). We investigated three different ways of analysing the mean flow index on a healthy population using the same tilt-table procedure as in our feasibility trial (paper V).

1.2 Objectives

The overall primary purposes of this PhD thesis were:

1. to establish the feasibility of a four-week early orthostatic exercise intervention initiated in the NICU
2. to examine harms and benefits of early mobilisation in patients with severe acquired brain injury as measured by mortality or poor functional outcome, quality of life and serious adverse events
3. to investigate the difference in dynamic cerebral autoregulation (dCA) in a population that has received early orthostatic intervention for four weeks versus standard care
4. to examine the intra-tester reliability of a dynamic autoregulation index (nMxa) in a healthy population using three different methods for the analysis.

1.3 Hypotheses

1. Early orthostatic exercise is feasible in patients with traumatic brain injury
2. Early mobilisation versus standard care for patients with a severe acquired brain injury has beneficial effects and reduce the number of harms
3. Patients with impaired dCA receiving early orthostatic intervention have fewer orthostatic reactions during HUT than patients treated with standard care
4. The reliability of nMxa depends on the analysis approach

1.4 The thesis at a glance

Chapter 1 is an introduction to the thesis and the objectives.

Chapter 2 is a brief introduction to acquired brain injury with further elaboration on traumatic brain injury. A short expansion on disorders of consciousness will be presented.

C**hapters 3 and 4** present the field of rehabilitation and the early orthostatic intervention used in the randomised clinical trial of this thesis.

Chapter 5 concerns cerebral autoregulation after brain injury and considers a method for measuring cerebral autoregulation.

Chapter 6 is a summary of the main methods used in the review, trial, and reliability study.

C**hapter 7** presents the results of the papers.

Chapter 8 covers the discussion of the thesis as well as the strengths and limitations of the papers.

C**hapter 9** gives overall conclusions and remarks on perspectives for future directions and related research.

Chapter 2

In the previous chapter, a short introduction to this thesis was given along with the clinical queries that preceded the questions in this thesis. This chapter will elaborate on the conditions of the patients and their symptoms.

2.0 Acquired brain injury

Acquired brain injury is a broad term used to describe brain injuries that occur after birth not due to congenital or degenerative conditions [11]. It consists of a combination of diseases such as ischaemic and haemorrhagic stroke, traumatic brain injury, subarachnoid haemorrhage, intracerebral haematoma, and diffuse brain injury (anoxic or toxic). Although cerebral stroke is by far the largest group among patients with acquired brain injury, traumatic brain injury affects the much younger population with a high incidence of traffic injuries and falls [12].

Many of the clinical symptoms in patients with acquired brain injury are similar (paresis, speech deficits, cognitive impairments), but the lesions differ according to pathogenesis. Ischaemic stroke is located to the area of the vasculature in focus and is therefore often primarily associated with lesions in one side of the brain [13]. Traumatic brain injury often results in a one-sided primary trauma which can be very localised to specific spaces (subarachnoid, subdural, epidural). However, the trauma also often results in a contrecoup lesion due to the whip-lash or rotational movement of the brain, causing macro and micro damage to the tissue, nerves, and small blood vessels [1]. Furthermore, these injuries are often associated with microscopic injuries in the white matter and the tearing of axons and nerves in the brain – so-called ‘diffuse axonal injuries’ [14]. As a secondary injury, mitochondrial dysfunction can occur after traumatic brain injury alongside other mechanisms such as excitotoxicity, activation of injurious intracellular enzymes and free radical production, among others [15].

2.1 Traumatic brain injury

Traumatic brain injury can be a devastating and life-changing event that is considered a public health problem worldwide [2]. It is estimated that 69 million people worldwide will suffer a traumatic brain injury each year with the highest percentages in the low and middle-income countries [12]. The vast majority of traumatic brain injuries are mild (81%) or moderate in severity (11%), and only a few are characterised as severe (8%) [12]. But still, each year a population size equal to Denmark's population suffers a severe brain injury. In Europe, estimates of the all-cause incidence rate of traumatic brain injury are about 1,012 patients per 100,000 people [12]. It is a leading cause of mortality and morbidity in the young and healthy population and therefore the post-rehabilitation results can not only be devastating for the patients and relatives but also a cause of severe burden and cost for society [12]. While traumatic brain injury has an enormous human consequence with mortality in Europe of approximately 12% [16], knowledge of the economic consequence is much more scarce as estimates of the cost of mild traumatic brain injury and the rehabilitation efforts and support services by caregivers and family members of patients with severe traumatic brain injuries are often not evaluated [17]. Nevertheless, a study from The Netherlands estimated the average cost of traumatic brain injury at € 16,040 per patient and an annual cost of € 314.6 million per year with a population of 17 million people [18].

Traumatic brain injury occurs in a wide variety of age-groups, and causes are often related to different lifestyles within these age-groups. Studies have found a higher incidence in the age group between 16 and 35 years of age, primarily related to traffic accidents, and after 65 years of age primarily attributed to falls. In the emergency room, men are more frequently represented than women [19]. Over the last couple of years, reports have shown an increase in the number of elderly people with a traumatic brain injury [20].

2.1.1 Severity in traumatic brain injuries

The severity of traumatic brain injury is usually categorised in mild, moderate, or severe. In the emergency room, the Glasgow coma scale (GCS) score is the most frequently used to measure severity [19]. A score between 3 to 8 is considered as severe, between 9 to 12 as moderate, and 13 to 15 as mild traumatic brain injury. Significant variance has been reported when allocating scores, and this is highly dependent on the timing and treatments at the time of the scoring [2,15].

Another widely used method for establishing severity and long term outcome is by using the length of post-traumatic amnesia [5]. A post-traumatic amnesia period from 0 to 14 days is categorised as moderate, from 15 to 28 days as moderately severe, from 29 to 70 days as severe, and more than 70 days as extremely severe [21,22]. Alongside disorders of consciousness, post-traumatic amnesia is the best predictor of outcome for patients with severe traumatic brain injury, although assessment is only possible retrospectively, which limits its clinical use and use in research [5]. In general, the prediction of outcome is complicated, with some of the best-established models, such as MRC CRASH or IMPACT, showing some predictive capabilities for death or poor outcome at six months. These models, when calculated in their basic form, incorporate age, GCS (motor capabilities), pupil reactivity, and the presence of extracranial injury. The extended model incorporates results from CT-scan but only increases the prediction value slightly [23,24]. To some extent, cerebral autoregulation has also been used to predict mortality and morbidity. A recent systematic review found that especially the PRx (correlation between mean arterial pressure (MAP) and intracranial pressure (ICP)), the Mx (correlation between cerebral perfusion pressure and mean cerebral flow velocity), and the autoregulation index (ARI; a correlation between MAP and cerebral blood flow velocity) were able to predict poor or favourable outcome [25].

2.1.2 Consciousness in traumatic brain injury

The most severely injured patients with traumatic brain injury experience a prolonged state of reduced consciousness, following which a process of gradual wakening occurs (**Figure 1**) [26]. Approximately 14% of patients are discharged from NICU in a vegetative state [27]. From a cohort of 434 patients, still in a vegetative state one month after injury, it was found that 52% were still in a vegetative state after three months and 15% were still in a vegetative state after one year. Eventually, 33% of the patients died after one year and out of the 52% of the patients who recovered consciousness, 45% had moderate to severe disabilities [28]. When awareness returns, it often does so in several stages. A return of arousal without signs of awareness defines the vegetative state [28] and is followed by the minimally conscious state. The minimally conscious state is characterised by inconsistent but clearly discernible behavioural evidence of consciousness [29]. Finally, a state of confusion can be present before returning to a more normalised state [30].

The unresponsive conscious syndrome has been proposed as a new term for the vegetative state [31].

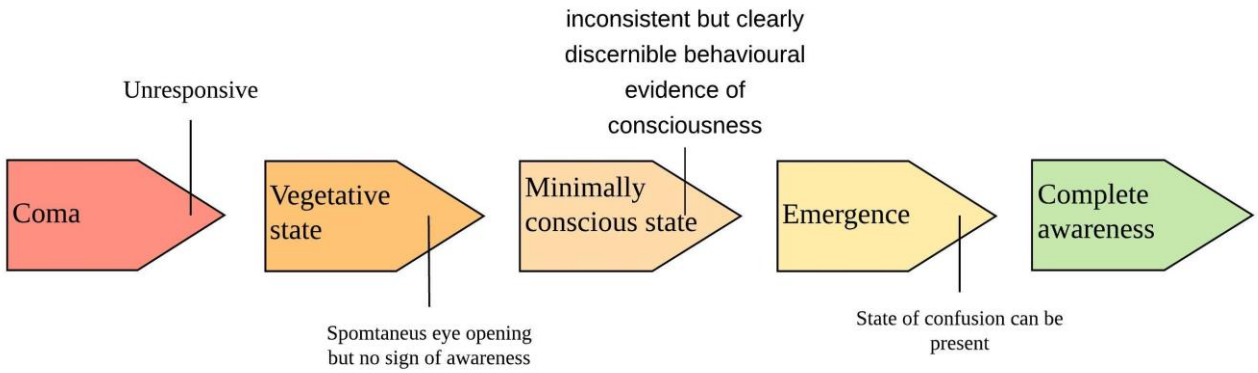

Figure 1. Stages of consciousness

One of the fundamental processes in acquiring new skills or adapt existing skills is the ability to participate actively [32]. As a large part of the rehabilitation process is to relearn skills or adapt existing skills to specific handicaps, the ability to actively participate in the process is of utmost importance. Therefore, any treatment that can increase the energy level and awareness of the patient will help the rehabilitation process.

Increasing arousal through drug therapy as a supplement to rehabilitation has been attempted. Among the most investigated are drugs that act on the gamma amino-butyric acid system and the monoamine systems, but strict randomised clinical trials have not been carried out [33–35]. Amantadine, an N-methyl-D-aspartate antagonist and indirect dopamine agonist, is one of the drugs examined in randomised clinical trials with beneficial effects on the rate of recovery of disorders of consciousness after traumatic brain injury [36]. Newer treatments involving electrical stimulation of the vagal nerve have been found feasible in a small study [37].

Chapter 3

In chapter 2, epidemiological information on patients with a brain injury was presented as well as one of the tragic consequences of traumatic brain injury – disorders of consciousness. Chapter 3 will describe the concept of rehabilitation in the context of brain injury as well as the outcomes used in our clinical trial.

3.0 Rehabilitation and research

As described by Wade and de Jong in 2000: "Rehabilitation is a reiterative, active, educational, problem-solving process focused on a patient's behaviour (disability)" [38]. Furthermore, rehabilitation aims at maximising the patient's participation and minimising pain and distress on the patient and those nearest to them, and it involves multidisciplinary teams [38]. It has been highlighted that research within the field of rehabilitation can be challenging due to its multifactorial construct [39]. Nevertheless, establishing an evidence-based foundation for rehabilitation is vital for patients and caregivers. Specialised wards for acute stroke rehabilitation provide more effective care for patients and studies have illustrated the need for a continuous, multidisciplinary rehabilitation for patients with traumatic brain injury starting as early as possible [40–42]. Trials done on drugs with different mechanisms of action have also been published [36,43]. But the treatment delivered by nurses and therapists have been less examined, although these treatments account for the most time spent with the patient [44].

For clinicians to efficiently deliver the most suitable treatment to the right patient at the right time, more targeted research of rehabilitative efforts is needed [45–47]. To do this, it is important to derive precise identification of the prognosis and stratify in relevant subdivisions [48]. Better and more precise definitions of the rehabilitation modalities are just as essential to provide efficacy and valid data on the treatments beyond the trial [47]. Fortunately, more precise and specified evidence of rehabilitative efforts is continuously emerging as exemplified in the AVERT-DOSE trial (ACTRN12619000557134).

3.1 Rehabilitation after acute brain injury

Rehabilitation after brain injury has been standard care in most western countries over recent decades [49]. However, little emphasis has been made on studies determining when to start physical rehabilitation and how to conduct it. A recently published systematic review on the effects of neurorehabilitation in patients with traumatic brain injury found benefits of a number of different rehabilitation strategies when starting early after the injury [50]. Rehabilitation efforts are often pooled in studies and analysed as one, due to the definition of rehabilitation, but trials studying specified interventions within the rehabilitation have been done. Mobilising patients out of bed at the earliest possible time point has been credited for positive effects in the prevention of contractures, increasing pulmonary ventilation, and general awareness [7,8,51,52]. However, concerns have been raised that mobilisation too early could reduce cerebral blood flow and thus, the blood supply to areas close to or directly affected by the injury. This could cause biochemical changes in otherwise healthy areas resulting in further damage to the brain [53–56].

A trial by Anderson et al. investigated the effect of 30 degrees head-up bed rest compared with the horizontal position within the first 24 hours of stroke and found no difference in outcome after 90 days [57]. Other trials conducted in ICUs on critically ill patients (some of whom had brain injury) found coupling between early mobilisation and early discharge, functional status, and decreased mortality when compared with standard care [58].

Stroke rehabilitation units reduce deaths and improve functional outcome, and these effects have been credited mainly to early mobilisation and intensive training [40]. Contrarily, the AVERT trial in patients with acute stroke showed a decrease in the odds of getting a favourable outcome three months after stroke when starting out of bed mobilisation within 24 hours of stroke onset and continuing with higher intensity mobilisation compared with usual care [59].

3.1.1 Measuring functional improvement

Many classification systems have been developed as an outcome measure in patients with traumatic brain injury. The challenge for quantifying long-term outcome is to have a scale that encompasses from the severely traumatised patient in the acute phase with disorders of consciousness and to patients returning to work a year after the injury. The international

classification of functioning, disability, and health (i.e. ICF) is often used to illustrate the need to measure several aspects regarding patients' capabilities [60]. Interventions often target one aspect of the disease for instance on body function and structures, which in the end may or may not transfer into effects on disability or participation, that most patients would wish to improve [38,45]. In our clinical trial, the following assessment scales have been used: Coma Recovery Scale-Revised (CRS-R) [61], Early Functional Abilities (EFA) scale [62], Functional Independence Measure (FIM) [63] and the Glasgow Outcome Scale Extended (GOSE) [64]. The CRS-R, FIM and GOSE are all recommended core or supplemental outcomes in brain injury research (**Figure 2**) [65].

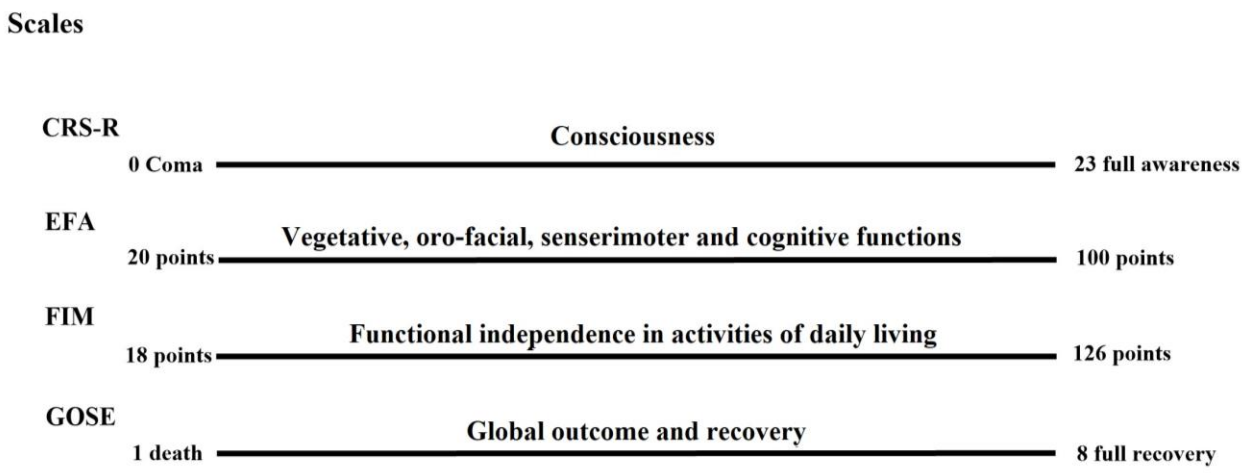

Figure 2. Scales for measuring outcomes in patients with traumatic brain injury.
CRS-R: Coma Recovery Scale-Revised; EFA: Early Functional Abilities; FIM: Functional Independence Measure; GOSE: Glasgow Outcome Scale Extended

3.1.2 Coma Recovery Scale-Revised

The CRS-R is used to measure neurobehavioral function in patients with disorders of consciousness and thus evaluates the level of consciousness. The scale comprises six subscales and ranges from a score of 0 (coma) to 23 (full awareness) [61]. It consists of elements for diagnostic criteria for determining the unresponsive wakefulness syndrome, minimally conscious state and emergence from the minimally conscious state [65]. The validity has been examined and shows both diagnostic and prognostic abilities, and it has been found to have good inter-rater reliability [66]. It mainly operates on body function and structure of the ICF.

3.1.3 Early Functional Abilities

The EFA scale was initially developed to capture the gap between the GCS Score and the FIM [62]. The scale assesses important aspects of brain function after traumatic brain injury, such as vegetative, oral, motor and cognitive functions [67]. The score ranges from 20 (lowest) to 100 (highest) and consists of 20 items in four categories of vegetative functions, oro-facial-functions, sensorimotor abilities and cognitive abilities [62]. The concurrent validity is good, and reliability is good to moderate [62,68].

A recent study did criticise the scale for not being unidimensional and recommended the removal of one item and not using subscale calculation [67]. It is mainly designed to illustrate improvements on body function and structure of the ICF but parts of the scale deal with items of activity as well.

3.1.4 Functional Independence Measure

The FIM is a general measure of patients' ability to independently perform physical activities and activities of daily living and is recognised as a core measure in cognitive and physical limitations in traumatic brain injury [65]. It is a generic scale and has been validated across a range of different diagnoses such as brain injury, burns, and back injury [69]. The scale ranges from a low score of 18 points to 126 points for fully independent functioning and has good validity and adequate reliability [69]. One study recommends using the EFA as a supplement to FIM when the FIM score is below 36 points [70]. The FIM operates mainly on the activity level of the ICF but has a few items involving participation and body function and structure.

3.1.5 Glasgow Outcome Scale Extended

The GOSE was developed as an attempt to measure patients from coma-like conditions to good recovery of functions and returning to a normal life [71]. The lowest score is death (1) and the highest score is recovery with no problems relating to the injury (8). The scale is valid and has good reliability but is considered crude and can be difficult to score as not all the patient's problems are easy to assess during in-hospital rehabilitation (e.g. able to return to work) [64]. The scale can,

therefore, be highly dependent on the environment. The GOSE operates mainly on activities and participation of the ICF.

3.1.6 Measuring adverse events and reactions

Reporting of adverse events is a key factor in determining the harms of interventions [72]. Given that most interventions examined in randomised clinical trials reveal a rather small clinical effect compared with alternative treatments, the evaluation of harms could create valuable knowledge for preferring one treatment over another [72,73]. Furthermore, observational cohorts tend to underestimate harms, which further highlights the importance of investigating harms in randomised clinical trials [74].

The ICH Harmonized guidelines [75] defines an event as:

- Adverse event: any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.
- Adverse reaction: any undesirable and unintended medical response related to the intervention occurring to a participant during a clinical trial.
- Serious adverse event: any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
- Serious adverse reaction: any adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
- Suspected unexpected serious adverse reaction: any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with the information available to date).

Several reviews of randomised clinical trials have highlighted the lack of reporting harms or selective reporting harms [73,76,77].

Chapter 4

In the previous chapter, a methodological approach was taken to the rehabilitation and research process. The present chapter will focus solely on the rehabilitation modality, which is the centre of this thesis. The reader should keep in mind that though early orthostatic exercise is the focus of this thesis, other treatments were administered simultaneously.

4.0 Early orthostatic exercise

In 1999, a review was published investigating the effect of bed rest on a variety of different diagnoses. Few included trials found a positive effect of bed rest on conditions such as acute low back pain, pulmonary tuberculosis, and spontaneous labour [78]. Almost simultaneously, a wave of early mobilisation of patients undergoing different kinds of surgery was implemented [79]. Most guidelines on acute stroke rehabilitation had recommended early mobilisation as a part of effective treatment [80,81]. Guidelines defined early mobilisation as starting within 24-48 hours of stroke onset, but most guidelines have now adopted recommendations from the AVERT trial in exercising caution when mobilising patients within the first 24 hours [59]. Nevertheless, studies have also emphasised the harmful effects of long-term bed rest [82,83].

The interest in early mobilisation has moved from stroke and postoperative care and into the more severely injured or diseased patients in the ICU. A recent systematic review identified 23 trials investigating early mobilisation of critically ill patients in the ICU. They concluded that early mobilisation decreased the incidence of acquired weakness, improved functional outcome, and increased the number of ventilator-free days and discharged-to-home rate [84].

Patients with severe acquired brain injury and prolonged disorders of consciousness often experience orthostatic reactions. An orthostatic reaction is a fall in systolic and/or diastolic pressure of 20 mmHg and 10 mmHg, respectively, or an increase in heart rate (HR) of 30 beats per minute within the first three minutes of free-standing [85]. Studies have shown that orthostatic reactions reduce the time of mobilisation to minutes in the rehabilitation phase [8,9,86]. The reason for these reactions has not been thoroughly investigated, but a combination of cerebral damage and bed rest altering the cardiovascular and endocrine systems involved in the maintenance of

body fluid levels could be an explanation [87,88]. Furthermore, studies have found a decrease in baroreceptor sensitivity in patients with severe acquired brain injury [89,90]. One study found a beneficial reduction in the number of orthostatic reactions (i.e. drop in blood pressure or increase in HR) by using the ERIGO® tilt-table with a stepping device instead of a regular tilt-table [9]. This effect is most likely symptomatic, and it is still unknown whether it can translate into an improvement in cardiovascular regulation.

In patients with traumatic brain injury, only a few studies examining early rehabilitation have been conducted. A quasi-randomised study showed that an early and continuous chain of rehabilitation leads to less disability after one year. The study did not clearly describe the rehabilitation programme itself, which they started 12 (IQR 8) days after injury, but the early rehabilitation could potentially contain mobilisation [42]. A randomised pilot study that included 40 patients (35% of which had a traumatic brain injury) showed improvements in consciousness and less disability at discharge from ICU and the rehabilitation unit after early mobilisation in an ERIGO® tilt-table. They managed to start mobilisation after 12 (IQR 7) days [91].

Patients with severe traumatic brain injury differ in the early phase from patients with other types of acquired brain injury because the condition is often further complicated by cerebral oedema, ischaemic or hypoxic damage, raised intracranial pressure, hydrocephalus and infections leading to secondary brain damage [1]. Most patients will experience a worsening, with more sedation or neurosurgical treatments, offered such as craniectomy and removal of haemorrhages making the early period heterogeneous and complex.

The primary aim of early mobilisation is to improve functional outcome and avoid secondary complications. As the method has yet to be examined, its effects remain hypothetical. Studies have shown positive signs with fewer contractures in the lower extremity in patients with acquired brain injury and improved lung function in critically ill patients in the ICU [51,52]. Furthermore, studies have shown an increase in arousal in patients with severe acquired brain injury and disorders of consciousness [6–8]. Change in these conditions can have a significant impact on rehabilitation after NICU stay. The intervention was named “early orthostatic”, as one of the motivations for investigating the intervention was to see if it caused patients to become more stable haemodynamically.

4.1 Pros and cons of early mobilisation

The tilt-table mobilisation has the advantage of safely mobilising patients to the standing position without sudden strains on patients or therapists. The elevation is thought to release vasoconstricting hormones and hormones for retention of sodium and water [92] as well as to stimulate afferent nerve fibres and thus stimulate awareness [8,93]. The ERIGO® tilt-table (**Figure 3**) has a built-in stepping device that activates passive muscle pump increasing the venous return of blood to the heart and thereby preventing orthostatic reactions. This results in more exercise and hopefully, an increased effect. The table tilts from zero degrees to 90 degrees, and the stepping device can be set at a desired frequency between 8 and 80 repetitions per minute [94].

Figure 3. The ERIGO® tilt-table. Picture: Hocoma, Switzerland

Inactivity has shown to increase the risk of type 2 diabetes, colon cancer, Alzheimer's disease, and depression in otherwise healthy people [83]. The first bed-rest study by Saltin et al. showed that only 20 days of bed rest in healthy young men caused a decrease in maximal oxygen uptake, heart and stroke volume, as well as maximal cardiac output [95]. Preventing or reducing these cardiovascular deteriorations may lead to the ability to decrease orthostatic reactions during the rehabilitation phase and improve the physical health of the patients. However, there is a lack of evidence, and further observational studies and randomised clinical trials are needed to generate and test hypotheses and validate efficacy.

On the downside, patients in a critical state, such as traumatic brain injury, could be vulnerable to orthostatic changes. The possibility of adverse effects of gravity on cerebral blood flow in patients that may or may not have impaired cerebral autoregulation has been raised [55,96]. The ERIGO® tilt-table was designed to counteract orthostatic reactions during mobilisation [9] and could be an excellent solution for this problem. Nevertheless, one trial found lower awareness in a group of patients one to six months after acquired brain injury, when mobilised in the ERIGO® compared with a regular tilt-table for three weeks. Based on these results, they hypothesised that the increased stimulation from the ERIGO® stepping device acted as a depressor on consciousness [86]. Albeit, this trial had a small sample size.

Should early mobilisation be considered for patients with traumatic brain injury, the window of opportunity could be when stable periods of intracranial pressure are reached, as was attempted in our exercise protocol [97] (see paper I to III).

Chapter 5

Chapter 4 described the rationale behind early orthostatic intervention used in our randomised clinical trial in this thesis. The intervention has only been used in a few studies and trials on patients with severe acquired brain injury. The present chapter will deal with physiological reactions during HUT and cerebral autoregulation, as this is an essential issue in the treatment of patients with traumatic brain injury.

5.0 Systemic and cerebral haemodynamics during head-up tilt

Models of orthostatic stress and cerebral circulation can be applied by passive HUT and induce a physiological adaptation through gravitational pull [98]. This gravitational pull depends on the angle of the tilt-table. The percentage of gravitational pull is equal to the sine of this angle [99]. As tilt degree is increased, a certain point (hydrostatic indifference) will remain at the same level of pressure. The pressure above the point of hydrostatic indifference will decrease, and pressure below will increase [100]. This pooling of blood volume towards the legs will force the cardio-vascular system to react in order to maintain cardial and cerebral perfusion pressure by increasing HR and MAP as well as the peripheral vascular resistance, thus maintaining cardiac output at a lower but sufficient level [101,102]. In the standing position, the gravitational pull also decreases intracranial pressure allowing easier blood flow to the brain [100]. Hence, studies have shown that the cerebrovascular resistance (CVR) in healthy people will slightly decrease when standing compared to the supine position [103]. Whether this is directly translated to a vasodilation of the middle cerebral artery is unknown [103,104]. One study concluded that there was no change in the diameter of the middle cerebral artery during hypocapnia or hypercapnia breathing in healthy participants [105]. On the other hand, an increase in sympathetic activity during HUT has been reported and would result in vasoconstriction if any, although this has only been observed under extreme conditions in animals [106].

When tilting to 70 degrees standing position in healthy humans, the MAP and cerebral perfusion pressure will have a small intermittent drop and then increase. The MAP thus stabilises at a higher level, but the cerebral perfusion pressure remains at a lower level than in supine. This has also been shown in the mean middle cerebral artery flow velocity which decreases and stabilise at a

lower rate [89,102,107,108]. All these changes occur within 15 to 20 seconds after HUT [108]. A recent study has shown that tilting to 70 degrees for 25 to 30 minutes results in a total decrease of cerebral blood flow of approximately 6% [109], much less than what leads to a loss in consciousness [100].

5.1 Cerebral autoregulation

Cerebral autoregulation is a protective mechanism ensuring a stable supply of blood to the brain under circumstances where the cerebral perfusion pressure is decreasing or increasing to a certain point [110]. Cerebral blood flow responds to changes in O_2 demand, the arterial partial pressure of carbon dioxide ($PaCO_2$) and blood pressure, and is therefore not solely a phenomenon isolated to the brain, but an integrated process involving the entire cardiovascular system [111].

Cerebral autoregulation is typically divided into two entities; static cerebral autoregulation and dCA. In 1959, the Danish professor Niels Lassen constructed a relationship curve between MAP and cerebral blood flow from seven different studies investigating 11 different diagnoses [112]. This came to be known as the ‘static autoregulation curve’ (**Figure 4**).

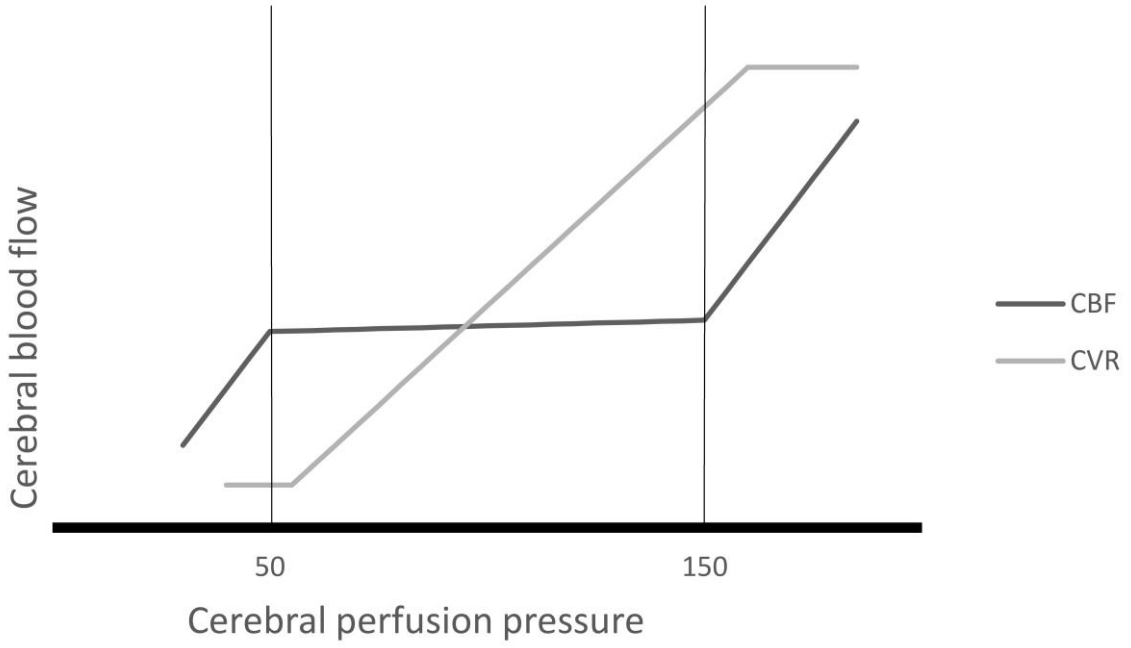

Figure 4. The autoregulation curve. The curve illustrates the association between cerebral blood flow (CBF) and cerebral perfusion pressure. Cerebral blood flow is the supply of blood to the brain at any given time. Cerebrovascular resistance (CVR) is the resistance created by the brain vessels to control CBF. CBF is equal to cerebral perfusion pressure divided by CVR.

As a schematic understanding of cerebral autoregulation, Lassen's curve provides valid information, but cerebral autoregulation should not be seen as rigid as this. Reanalysis of older studies on healthy people shows much more active autoregulation against an increase in MAP than decrease and that the autoregulation plateau may not be as broad as first suggested (50 to 150 mmHg) [111,113]. Furthermore, the plateau is not as horizontal as shown, and elevation of cerebral perfusion pressure will result in a steeper increase of cerebral blood flow. Studies have found that the plateau has a slope of 3-8% per 10 mmHg change in MAP [114,115]. The static cerebral autoregulation operates at a slow pace (15 to 30 seconds) [116,117].

The dCA describes changes in cerebrovascular circulation due to sudden alteration in MAP. It was first presented by Aaslid and colleagues in 1989 when they discovered that the autoregulation works faster after a thigh cuff deflation test than previously thought [118]. The measure of interest is, therefore, the rate of regulation (i.e. how the CVR operates in respect to the change or recovery in the first seconds after a decrease in MAP) [118]. Aaslid and colleagues found that the dCA works within the first two seconds after a sudden drop in MAP and has a complete regulation in ten to fifteen seconds [118].

The brain has, under normal conditions, a blood flow of 50 mL per 100 g of brain tissue per minute [112]. During the autoregulation plateau (**Figure 4**), the CVR increases when the cerebral perfusion pressure is elevated and decreases when the cerebral perfusion pressure is lowered, thereby maintaining the relative constant blood flow [112,114,115]. The cerebral vascular tone is affected by $PaCO_2$ [112] as the blood-brain barrier is impenetrable to hydrogen ions and bicarbonate, only CO_2 can reach the smooth muscles of the cerebral arterioles and thereby cause vasoconstriction or dilation by changing pH in this area [119]. To illustrate this, experiments with direct manipulation of arterial pH does not regulate cerebral blood flow if $PaCO_2$ is maintained [120]. Therefore, the cerebral autoregulation is controlled by the CVR in the large vessels (responsible for about 60%) and the smaller vessels [114,121,122]. Thus, an increase in $PaCO_2$ would dilate the vessels allowing the cerebral blood flow to increase and vice versa (**Figure 5**) [111,123–126].

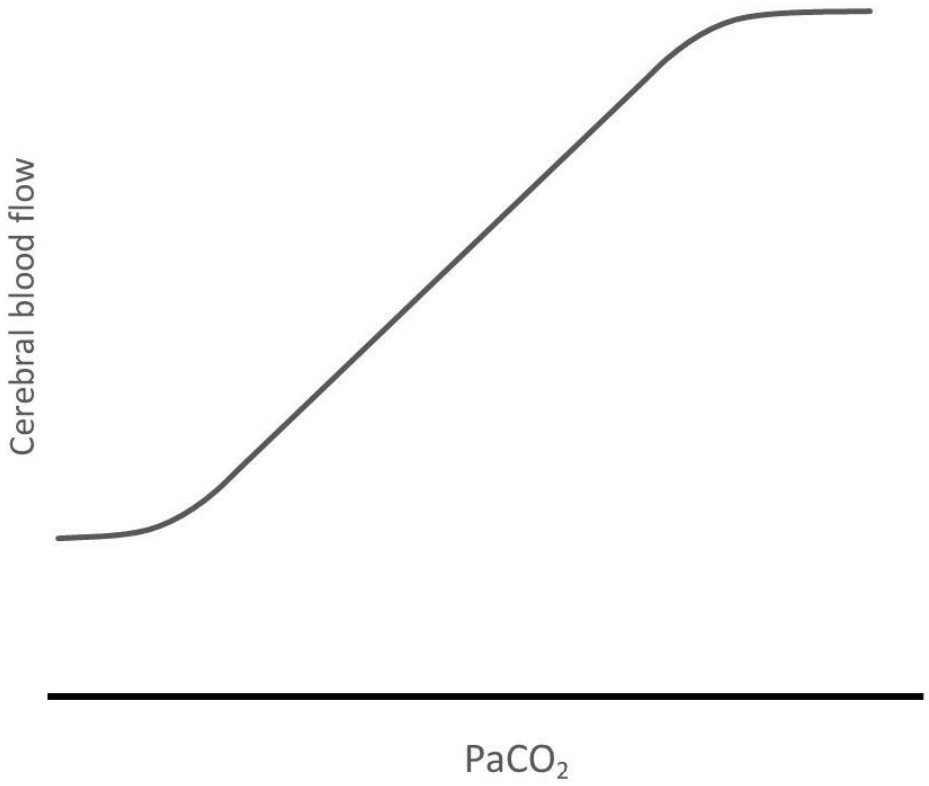

Figure 5. Relationship between arterial partial pressure of carbon dioxide ($PaCO_2$) and cerebral blood flow. Blood flow changes with every change in $PaCO_2$ within the physiological range. In the low and high range of $PaCO_2$, no effect of blood flow is observed [111].

The lower limit of the autoregulation curve is reached when the arteries are maximally dilated [127]. The brain can compensate if a further decrease in blood pressure occurs by increasing the oxygen extraction so that the metabolic needs are maintained [128]. When cerebral blood flow decreases even further, it will reach an ischemic threshold below which the reduction in flow can result in diffuse neuronal loss [129,130]. At the upper end of the curve, a further increment in pressure will result in maximal vasoconstriction [131,132]. If continued, the arterioles will forcefully dilate [133,134], and eventually, this will disrupt the blood-brain barrier, and vasogenic oedema may occur [122].

There have been found regional variations in both intensity of this regulation and the effect of $PaCO_2$ [123–126]. Differences between the cerebrum, cerebellum and brain stem under various conditions have been reported [122,135]. The small vessels of the brain such as the pial arterioles also play a part in the autoregulation, but more importantly, the arteriole downstream from the penetrating arteriole plays an active role in cerebral autoregulation [122,136–138].

Patients with severe brain injury often present with impaired cerebral autoregulation within the first days to weeks after brain injury, and this has been associated with increased morbidity and mortality [139,140]. The clinical factors associated with impaired cerebral autoregulation are primarily too low or too high cerebral perfusion pressure [140].

5.1.1 Transcranial Doppler for measuring cerebral blood flow

Cerebral blood flow can be measured regionally or globally using a variety of methods, but essential for determining dCA is high-resolution data. Of the most common regional non-invasive measures are near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) [141]. In our clinical trial patients were examined using transcranial Doppler for high-resolution data, which will be further elaborated in the following section.

Transcranial Doppler uses a frequency of 1 to 2 MHz, as the bone attenuates higher frequencies at the choice of insonation [142]. The temporal window serves for a good site for insonation of the middle cerebral artery just downstream from the Circle of Willis (**Figure 6**) [142].

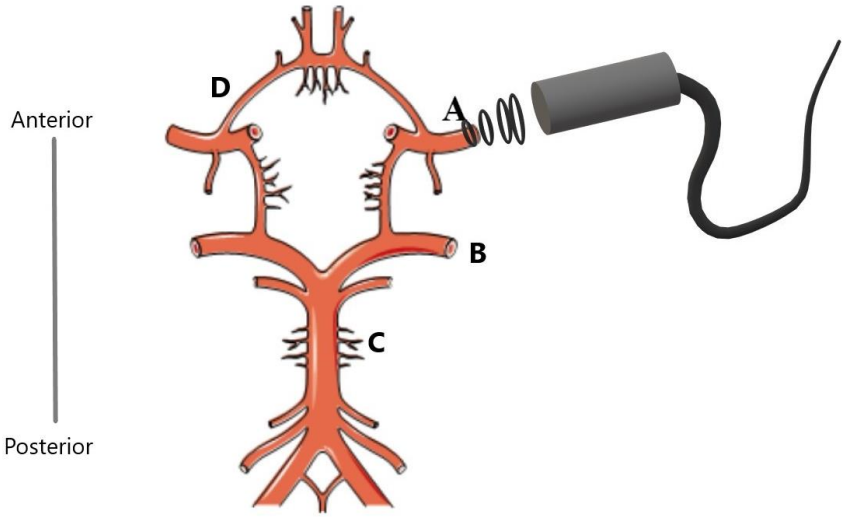

Figure 6. The circle of Willis. The middle cerebral artery (A) is insonated through the temporal window. B: Posterior cerebral artery; C: Basilar artery; D: Anterior cerebral artery.

This typically gives an insonation depth of 40 to 65 mm with the bloodstream coming towards the ultrasound probe [143]. When the Doppler signal reaches the blood vessels, a frequency signal is

returned and the difference the Doppler shift is received by the probe. [142]. The velocity can then be expressed as:

$$blood\ flow\ velocity = \frac{\Delta FC}{2F_0 \cos\theta}$$

Where ΔF is the Doppler shift and C is the wave velocity in the bloodstream, which is then divided by the transducer frequency (F_0) and cosine to the angle (θ) of the probe on the artery [144]. There are many assumptions or limitations to this method, some of which are generally accepted. The blood flow is assumed to be equal and constant in the artery (plug flow) but can also be laminar (lowest flow along the artery wall) or turbulent due to obstacles or reverse flow. The angle of insonation is incorporated in the equation, but too large an angle will result in higher velocity, and the artery diameter is assumed to be constant [145]. Lastly, some patients present with no window for insonation due to thick bone, anatomical variations or disease making the assessment quality poor [146,147].

5.1.2 Measuring cerebral autoregulation

Several methods exist for quantifying cerebral autoregulation, and every method has its limitations [111]. For this thesis, a version of the mean flow index (known as the "Mx index") first presented by Czosnyka in 1996 is used [148]. The original index was based on continuous measurements of cerebral perfusion pressure (measured as intracranial pressure subtracted from mean arterial blood pressure) and transcranial Doppler flow velocity in the middle cerebral artery. This was an invasive measure because the intracranial pressure was needed for the calculation [148]. The advantage of the Mx index is that it evaluates spontaneous fluctuations in blood pressure and cerebral blood flow so that no manipulation of blood pressure is needed to determine if cerebral autoregulation is impaired or intact [148]. As a non-invasive alternative, the Mxa index was developed. This index uses mean arterial blood pressure instead of cerebral perfusion pressure [149]. Mean arterial blood pressure can be measured using an arterial catheter or noninvasively using photoplethysmography, although one study has shown that the non-invasive measure (nMxa) tends to yield a higher index value than the invasive (Mxa) [150]. As for all measurements using transcranial Doppler, the assumption that the artery remains at a somewhat static diameter must be assumed. Therefore, it is important to control for $PaCO_2$, as explained above.

For calculation of the nMxa, a certain amount of data must be present. Studies have shown that at least five to six minutes of arterial flow and pressure sampling is necessary for a stable calculation [151,152]. After removal of artefacts in the mean flow velocity and MAP curves, data are divided into short blocks of 3 to 10 seconds and averaged within each block [149,153]. Depending on the recording length, 20 to 30 blocks of averaged mean arterial blood pressure are then correlated with mean flow velocity, yielding several epochs. Finally, to end up with one nMxa value, all epochs from the period are averaged (**Figure 7**).

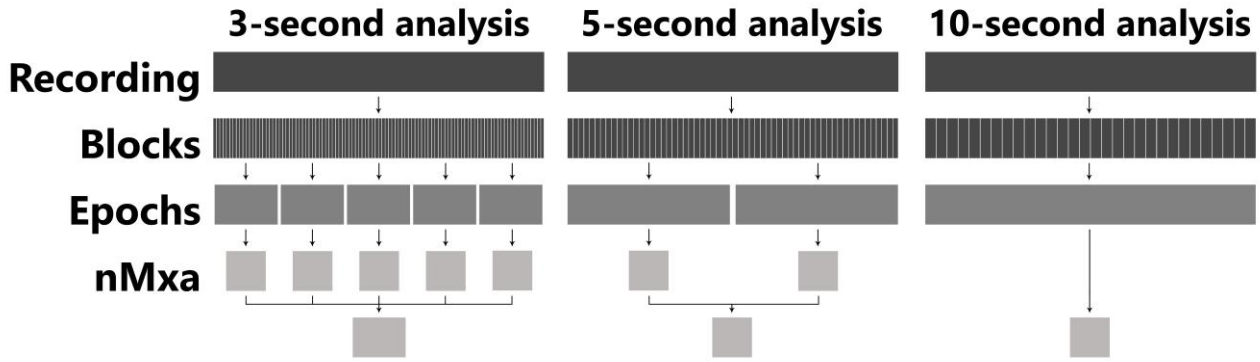

Figure 7. Graphical representation of data analysis for the non-invasive mean flow index (nMxa) using 3, 5 and 10-second blocks. (*Figure reproduced from paper V*)

There have been some discrepancies in the literature regarding when the nMxa expresses impaired cerebral autoregulation. The general understanding is that a high nMxa up towards 1 is a total lack of autoregulation as the cerebral flow velocity is directly depended on mean arterial blood pressure, and an nMxa at or below 0 equals intact autoregulation [148]. However, several studies in healthy persons have shown an nMxa around 0.4 [89,154,155]. The initial indication of impaired cerebral autoregulation has been proposed as nMxa at values above 0.3. It has later been suggested that this cut-off should be set at 0.0 or 0.45 when using non-invasive blood pressure measures [150,156]. In this thesis, we chose the original threshold of 0.3 [157,158] when preparing, gathering, analysing and interpreting the data.

The validity of the nMxa was examined by comparing measurements to the invasive counterpart (Mx) when analysing cerebral autoregulation in 37 patients with severe traumatic brain injury [149]. A significant correlation between Glasgow outcome scale and nMxa (r -0.42) or Mx (r -0.56) was found. In one of the earlier studies on the Mx index, a positive correlation between Mx and rate of regulation using the Aaslid's leg cuff test was found on 14 healthy subjects [159].

A few studies have examined the relative reliability of the nMxa. The nMxa has shown fair reliability in healthy persons, with an ICC of 0.41 and 0.45 in the right and left hemisphere, respectively [154]. Another study found a markedly increased ICC when healthy persons stand. They measured 18 subjects of different age groups for five minutes in the seated position and one minute while standing and found that the ICC of the nMxa increased from just below zero to above 0.7 [155]. Details of the method used to calculate the nMxa are not well described in the two studies. The reliability has not been tested in patients with severe traumatic brain injury.

Chapter 6

Chapters 1 to 5 were an introduction to the field on which this thesis is based. In the following chapter, the main methods used in the studies in this thesis are described.

6.0 Summary of main methods

The studies presented in this thesis consists of a randomised clinical feasibility trial (paper I to III), a systematic review (paper IV), a reliability study (paper V), and tha last paper (paper VI) concerns the reporting from the clinical trial on haemodynamic changes and cerebral autoregulation during HUT in patients with severe traumatic brain injury.

6.1 Paper I-III. Randomised clinical feasibility trial

This trial was registered at clinicaltrials.org in October 2016 (NCT02924649). A trial protocol was published on the 8th of November 2018 in Trials, and the statistical analysis plan was submitted under open review (DOI: 10.21203/rs.2.468/v3) in March 2019 before beginning the analysis.

This trial was designed as a randomised clinical feasibility trial as the purpose of the trial was to assess the possibility of investigating an early tilt-table mobilisation. Patients with traumatic brain injury were screened for inclusion from January 2017 to December 2018 from the department of Neuroanesthesiology at Rigshospitalet, Denmark. The trial was carried out following the principles of the Helsinki Declaration [160] and the ICMJE Recommendations for Protection of Research Participants (www.icmje.org).

6.1.1 Participants

When admitted to the NICU, the patients were screened by the primary investigator (CGR) or a physical therapist at the department. Eligible patients with a traumatic brain injury were 18 years or older, had a GCS < 11, a suspected tentative diagnosis of a disorder of consciousness after sedation was removed and the nearest relative willing to consent to participation. Patients with

spinal cord injury, fractures of the lower extremities (mobilisation contraindicated), and relatives who could not or would not consent, were excluded.

Before the patients could be included an informed consent was obtained from the nearest relative and a trial guardian (physician not involved in the project). Patients were enrolled in the trial after 24 hours of stable intracranial pressure (defined as ICP < 20 mmHg). If patients regained consciousness and could consent, they were asked to do so.

6.1.2 Randomisation, blinding and intervention

Randomisation is essential in controlled trials to increase the chance that risk factors are equally balanced in groups, and to avoid selection bias. Stratification is a tool that will further balance a specific risk factor. Participants were randomly assigned to either early orthostatic exercise or standard care (SC) at a 1:1 ratio using web-based computer-generated block randomisation. Block sizes were randomly assigned as either 4, 6, or 8 participants per block unknown to the investigators. The randomisation was further stratified according to GCS as either low (GCS 3 to 6) or high (GCS 7 to 10).

We were not able to blind the intervention to the treating staff or the patients. The outcome assessors scoring the CRS-R and the number of adverse events were blinded to group allocation. The staff assessed the EFA and FIM at the department, and they were not masked to the intervention.

The early orthostatic exercise consisted of daily exercise on a tilt-table with an integrated stepping device (ERIGO®) for up to four weeks and was carried out by two physiotherapists and supervised by one nurse. The stepping device aimed at counteracting orthostatic reactions during exercise and was set at an intensity of 50 to 60 steps per minute. The patient was tilted to 70 degrees, in a stepwise fashion, pausing at 30 degrees and 50 degrees. The exercise lasted for 20 minutes unless interrupted by orthostatic reactions as defined in our protocol [97]. If orthostatic reactions occurred, the patient was lowered to zero degrees, and the intervention was continued when the blood pressure resumed previous levels. The intervention was finished when the patient had been in the standing position for 20 minutes. During the exercises, patients were monitored for changes

in MAP, cerebral perfusion pressure, intracranial pressure, HR, and O_2 saturation when in the NICU, but we were not able to measure cerebral perfusion pressure or intracranial pressure at the rehabilitation department.
Standard care was administered by a staff consisting of physicians, nurses, and therapists, who jointly decided what the proper treatment was for each patient. The primary focus was on stable haemodynamic values and respiratory function but could consist of mobilisation.

During the four-week intervention period patients were included from the NICU, then moved directly to the rehabilitation department or intermediately to another NICU involved in the project. If patients were temporarily moved to a department not involved in the project, the intervention was paused until they returned to the rehabilitation department.

6.1.3 Outcomes and follow-up

The outcomes of this trial were divided into three separate groups: feasibility outcomes (primary), clinical exploratory outcomes, and physiological outcomes.

Feasibility outcomes
To establish if the intervention was feasible, we monitored three primary outcomes: 1) the ratio of included patients over eligible patients; 2) the ratio of completed exercises over the number of planned exercises; 3) the number of serious adverse events and reactions and the number of adverse events and reactions not considered serious. The target for the first outcome was a lower 95% CI of our trial to be above 60%, and for the second outcome, the lower 95% CI of our trial should be above 52%, which corresponds to a one-sided significance of 2.5%. The adverse events and the adverse reactions (serious and not considered serious) were counted by two physicians blinded to treatment allocation (independently) at the end of the intervention period. For the trial to be feasible, the target for the two first outcomes should be achieved, and there should not be an over-representation of adverse events or reactions in the intervention group. Feasibility outcomes were registered from the start of intervention until the end of the intervention (up to four weeks).

Clinical exploratory outcomes

For exploratory outcomes, we assessed the CRS-R at four weeks, the EFA and FIM at three months after randomisation and the GOSE at one-year follow-up. These outcomes are intended to be hypothesis-generating with the possibility of informing future and more extensive trials.

Physiological exploratory outcomes

A HUT test was done at baseline, two-weeks, and four-weeks after randomisation. For details on the procedure, please refer to chapter 6.4.1 in paper VI.

Figure 8 shows a timeline of the trial.

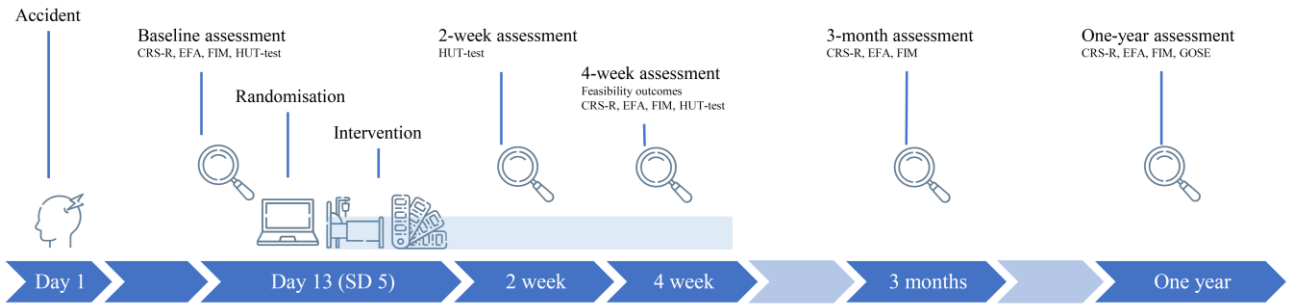

Figure 8. Trial overview. CRS-R: Coma Recovery Scale-Revised; EFA: Early Functional Abilities; FIM: Functional Independence Measure; HUT: Head-up tilt; GOSE: Glasgow Outcome Scale Extended

6.1.4 Sample size

We estimated a sample size of 60 patients pragmatically to be sufficient for gathering enough data on the feasibility outcomes for a realistic judgement of the feasibility. As no prior feasibility trials on patients with severe traumatic brain injury and early orthostatic exercise had been published, we found no grounds for a formal sample size calculation. As recommendations vary on the sample size of external feasibility trials, there are no grounds for saying that this trial should be used to calculate the sample size of a future definitive trial (as this would require a much larger sample) but only to gain experience for conducting a larger definitive trial [161,162]. Our trial could, therefore, inspire the estimation of a future trial which then should be further qualified with more data from future pilot trials.

6.1.5 Statistical analysis

The lower limit of the confidence intervals for the feasibility outcomes, the ratio of included patients and successful interventions, were compared to our pre-estimated lower limit confidence intervals. As this is equivalent to a one-sided test, we did not do a formal statistical analysis of the data. Patients with at least one adverse event, serious adverse event, adverse reaction and serious adverse reaction were compared between groups using Fischer's exact test. All three feasibility outcomes should be achieved to conclude that the intervention is feasible.

The clinical exploratory outcomes, CRS-R, EFA, FIM and GOSE, were not normally distributed, so we used a van Elteren's test for non-parametric data adjusting for the stratification variable (GCS high or low – please refer to section 6.1.2). The CRS-R was compared at the four-week time-point, the EFA and FIM at the three-month time point, and the GOSE at the one-year time point.

Trial Sequential Analysis (TSA) was performed on the dichotomised outcome's (patients with at least one serious adverse event or adverse event not considered serious) and the continues outcomes (CRS-R, EFA, and FIM). For the dichotomised outcomes the proportion of events in the control group was inserted in the analysis with a relative risk reduction of 20%, an alpha of 2.5%, and a beta of 10% to calculate the diversity-adjusted TSA confidence interval and the required information size for dichotomised outcomes. For continuous outcomes, the variance from the trial control group was embedded in the analysis alongside an alpha of 2.5% and a beta of 10%. All analysis was carried out according to the predefined time-points of interest.

6.2 Paper IV. Systematic review

6.2.1 Criteria for considering studies

In this systematic review, we aimed to include randomised clinical trials of patients with a severe acquired brain injury. The protocol was made public on PROSPERO (CRD42018088790 - April 2018) before performing the final literature search. The purpose of the review was to investigate the benefits and harms of early mobilisation in patients with severe acquired brain injury. Hence, we defined the population in three main categories as major stroke, severe traumatic brain injury and severe diffuse brain injury. Although the aetiology may differ in these patients (as described in chapter 2), the adverse effects of prolonged bed rest are the same. The inclusion criteria were any intervention comparing any early intervention of head and torso mobilisation to at least 50 degrees (as this expresses more than ¾ of gravitational pull), compared with a control intervention with mobilisation of under 50 degrees. We aimed at including only randomised clinical trials, but relevant observational studies reporting harms were also included if we encountered them. This was done as randomised clinical trials may miss rare and late adverse events. We assessed all outcomes at the end of the intervention (as defined by the authors) as our primary outcome and the longest follow-up as our secondary outcome.

Primary outcomes

- Mortality or poor functional outcome on any scale
- Quality of life on any scale
- The proportion of participants with at least one serious adverse event

Secondary outcomes

- The proportion of participants with one or more adverse events not considered serious
- The level of consciousness as measured by the Coma Recovery Scale-Revised [61] or other relevant scales as defined in the individual trial

Exploratory outcomes

- Individual serious adverse events
- Individual adverse events not considered serious

6.2.2 Search methods

A pre-search was done in February 2017, and corrections were made to get a balance between sensitivity and specificity in the search results. In short, the search was constructed from the PICO-model (patient, intervention, comparison, outcome) using only patient and intervention as search groups. Thus, different search terms for acquired brain injury (i.e. stroke, cerebral haematoma) and mobilisation, standing, positioning, among others, for the intervention. Where possible medical subject headings were used. For details on search terms, please refer to supplement 1 of paper IV. The primary literature search was conducted in cooperation with a specialist at the Copenhagen Trial Unit. We searched Medline (Ovid); Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library); EMBASE (Ovid); CINAHL (EBSCO); PsycINFO; Science Citation Index Expanded on Web of Science; and PEDro. The primary search was done in May 2018 and an updated version in April 2020. A Cochrane sensitivity-maximising clinical trial filter was modified and used in the Medline search and the other databases except for CENTRAL.

All references were transferred to the Covidence database, and duplicates were removed. A total of 13,480 references were found through this search when excluding duplicates.

Two authors independently screened all titles and abstracts and full-text articles. A third author resolved any disagreement. A total of 13,393 records were excluded after screening title and abstracts. The remaining 87 articles went through a full-text screen (**Figure 9**).

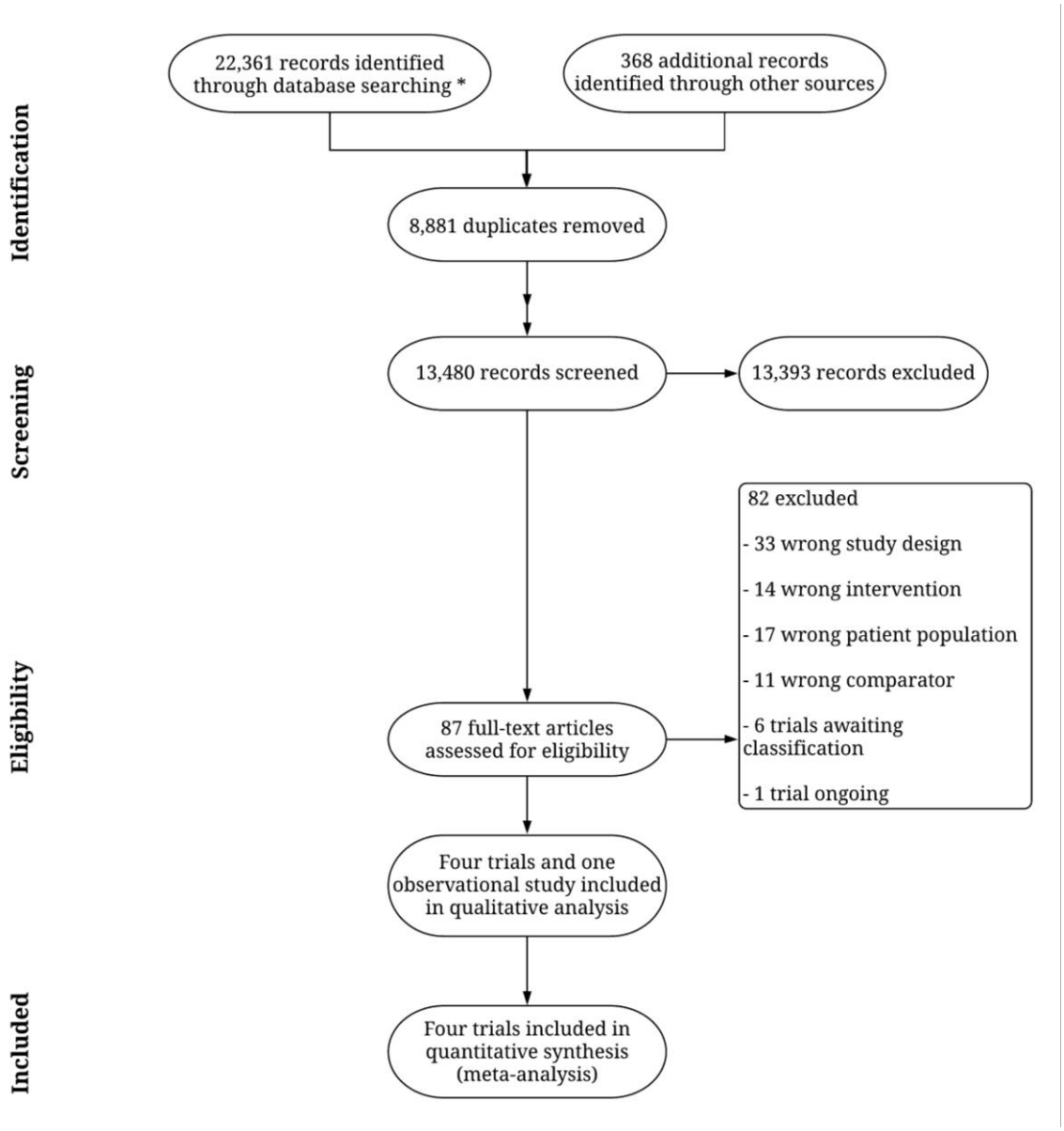

Figure 9. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. (*Figure reproduced from paper 1V*)

6.2.3 Risk of bias assessment

Randomised controlled trials are considered to provide the most reliable evidence on the effect of interventions [163,164]. If the sample size is large enough, flaws on the design, the analyses or reporting of the results can lead to underestimation or overestimation of the actual effect. A thorough evaluation of the risk of bias is, therefore, essential when conducting systematic reviews so that these fallacious effects are not carried over in the meta-analytic results.

After selecting trials, the risk of bias assessment was made by two assessors independently and compared for agreement. The following bias characteristics were evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and treatment providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other bias. Furthermore, the domains ’blinding of outcome assessor’ and ’incomplete outcome data’ were assessed for each outcome result. Data extraction was done by the same two assessors independently and compared for agreement. One study had the main author of this thesis as primary investigator, and another researcher was included for risk of bias assessment and data extraction of this trial.

To assess the overall risk of bias in the included trials, we used the Cochrane Collaboration's tool for assessing the risk of bias in randomised controlled trials and judged all trials as high or low risk of bias [164].

6.2.4 Data analysis

For the meta-analysis, we used both fixed-effect and random-effects models (inverse-variance methods) and chose the one with the most conservative estimate (wides confidence interval). The inverse-variance method is so-called because the inverse of the variance of the effect estimate is used to give weight to each trial. In this way, larger trials are typically given a higher weight due to smaller standard errors. Fixed-effect models assume a similar variance across all included trials, while the random-effects model does not. The fixed-effect meta-analysis is operating under the assumption that the difference in estimates observed in the trials are random and, therefore, no heterogeneity exists. The random-effects model assumes that the intervention effect is normally distributed across trials and that any differences between trials are partly random and partly a real difference. Hence, if there is no heterogeneity, there is no difference between fixed- and random-effects models [165].

For dichotomised outcomes, we analysed the relative risk and for continues outcomes the mean difference, both with 95% confidence interval (95% CI). If estimates were equal between the two models, we used the one with the widest 95% CI. Due to multiple outcomes, the risk of type I error

increases due to multiplicity issues. As recommended by the Cochrane Collaboration, we assessed three primary outcomes. This creates a multiplicity testing issue and has been recommended to divide the adjusted P-value between the conventional (0.05) and the Bonferoni-adjusted confidence interval. We, therefore, used a *P*-value of 2.5% for our three primary outcomes and a *P*-value of 3.33% for our two secondary outcomes [166]. If trials used different outcome measures for measuring the patients' functional outcome, we dichotomised these outcomes in "good" or "poor" outcome. A score on the modified Rankin scale was considered a poor outcome if the score was 5 (severe disability) or 6 (death) [167]. The disability rating scale was considered as poor outcome between 12 and 30 [168]. If information of these cut-off limits were not available, we defined a poor outcome as an improvement of less than 0.5 standard deviations (SD) derived from the study data [169].

The exploratory analyses of individual adverse events were reported as relative risk with 95% CI. If no event was present in one of the groups, a relative difference was calculated with 95% CI.

Heterogeneity will always occur in systematic reviews to some extend [170]. When different studies are pooled, methodological and clinical considerations inevitably differ, and therefore statistical heterogeneity will also be present [170]. The clinical and methodological heterogeneity was examined during the GRADE assessment (please see section 6.2.7). Statistical heterogeneity was examined between trials using I^2 statistics. The I^2 was interpreted as in the Cochrane Handbook for Systematic Reviews of interventions as “might not be important” (0%-40%); “may represent moderate heterogeneity” (30% to 60%); may represent substantial heterogeneity (50% to 90%); considerable heterogeneity (75% to 100%) [165]. As these intervals are overlapping, the size and direction of the estimated effects were considered as well as the significance level of the I^2.

6.2.5 Controlling for random error in a meta-analysis using Trial Sequential Analysis

TSA was used in all primary and secondary outcomes (not sub-groups) to calculate the diversity-adjusted required information size (DARIS) and the diversity-adjusted TSA CI (DATSACI) using the Lan-DeMets trial sequential monitoring boundaries [166,171]. TSA can be used to control for random errors and to assess the risk of imprecision [166,172], as systematic reviews with few

studies included can show misleading results when the required information size is not reached [173]. Furthermore, when studies are added to a systematic review, this may be interpreted as equivalent to an interim-analysis, thus increasing the risk of type I error due to multiplicity [174]. To account for this, the alpha-level needs to be controlled so that the type I error rate is kept at the desired level. This can be done using the Lan-DeMets sequential monitoring boundaries [172,174]. When calculating the DARIS in a meta-analytic study, the heterogeneity or diversity of the included trials must be taken into account as this eventually will affect the required information size [174]. Finally, futility boundaries can be constructed in the TSA with a function like that of the Lan-DeMets sequential monitoring boundaries. The area of futility is a beta-spending boundary and interpreted as the assumed clinically relevant effect could not be achieved [172,174].

In our systematic review of the dichotomous outcomes, we used the proportion of events in the control group, the assumption of a relative risk reduction and the diversity of the meta-analysis to calculate the required information size [171,175]. TSA was done using an alpha of 2.5% for primary outcomes and 3.33% for secondary outcomes, a relative risk reduction of 20% and a beta of 10% (power 90%). For continuous outcomes such as quality of life and consciousness, we were unable to identify valid previous data on effect sizes, so we used the observed SD from control interventions derived from the included trials divided by two as the anticipated minimal relevant intervention effect [169]. The TSA was then assessed using an alpha level of 2.5% for primary outcomes and 3.33% for secondary outcomes, a beta of 10%, and the variance suggested by the trials.

6.2.6 Subgroup analysis

In the protocol, we had pre-planned several sub-group analyses for this systematic review. Due to the low number of included trials, many of these were redundant. Therefore, we only conducted the methodological sub-group analysis between trials of a low risk of bias compared to trials of a high risk of bias and a comparison between patients with stroke (ischaemic or haemorrhagic) and patients with other types of acquired brain injury. The methodological sub-group analysis was like the other pre-planned subgroup analysis such as the type of mobilisation used as intervention; duration of the intervention period; the intensity of the intervention; and the timing of the intervention.

6.2.7 GRADE

For assessment of the certainty of the body of evidence, we used the Grades of Recommendation (GRADE) assessment. This evaluates the pooled evidence by down (or upgrading) after assessment of the risk of bias, inconsistency in the individual trial estimates, indirectness in the populations, interventions and outcomes, imprecision due to wide confidence intervals and risk of publication bias. The final evaluation is in terms of confidence in estimates expressed as high, moderate, low or very low. We used the GRADE approach utilising the DATSACI for investigating imprecision [176,177]. A summary of findings table was produced with downgrading if evidence of publication bias, heterogeneity, imprecision, or indirectness was found [178,179]. It is recommended to assess up to seven different outcomes in systematic reviews (**Table 1 and 2**) [180].

6.3 Paper V. Reliability study of the nMxa index

This study was designed as an intra-observer reliability study as only one tester was used for test and re-test. Healthy persons were recruited from the Copenhagen area through a free newspaper circulated to the university and hospitals in the area. All procedures were done in compliance with the Helsinki Declaration [160] and approved by the Research Ethics Committees of the Capital Region of Denmark (H-16042103).

6.3.1 Participants

This study included healthy participants recruited from the capital region of Copenhagen.

We included 14 healthy participants (5 males, age: 28 ± 9 (mean ± SD) years, height: 175 ± 7 cm, weight: 72 ± 12 kg, BMI: 23 ± 4 $kg \cdot m^{-2}$) with no prior history of neurologic disease, diabetes, or psychiatric illness.

6.3.2 Procedure and measurements

All measurements were made at the same time of day for each participant with an approximately four-week interval (23 ± 3 days, mean ± SD) in a room with a constant temperature of 22° C. When arriving at the session, the participant rested for approximately 30 minutes, while they were strapped to the tilt-table and equipment for measuring middle cerebral artery blood flow velocity (MCAv) (transcranial Doppler), non-invasive blood pressure (Finometer) and HR (electrocardiography) was attached. A five-minute baseline recording was made at 0° supine, and the participant was afterwards tilted to 30 degrees for one minute, to 50 degrees for one minute and remained at 70 degrees for five minutes. During the measurements, participants were instructed not to speak unless experiencing discomfort such as pre-syncope symptoms (dizziness, light-headedness, sweating or other complaints).

A constant diameter of the middle cerebral artery was assumed in all healthy volunteers, and no blood samples were taken.

6.3.3 Data-analysis

Data analysis was performed using MATLAB 2017b (Mathworks, Natick, USA). All data were visually inspected according to current guidelines, and artefacts from the transcranial Doppler signal or the blood pressure signal were removed or interpolated accordingly [181].

The baseline period (5-minutes) and the maximum tilt period (5 minutes) were divided into 3-second, 5-second and 10-second blocks. The two periods were then separately divided into epochs as follows: Twenty 3-second blocks were assembled into one epoch to yield five epochs of 60 seconds per period; thirty 5-second blocks were assembled into one epoch to yield two epochs of 150 seconds per period; and thirty 10-second blocks were assembled into one 300-second epoch per period (**Figure 7**) [153,182,183]. Within each epoch, MAP values were correlated against the corresponding MCAv from each block using a Pearson correlation, producing the Mxa. When there was more than one epoch and consequently, more than one Mxa value per period (i.e., for the 3-second and 5-second blocks), the average of these values was calculated, yielding one Mxa value at baseline and one at HUT.

6.3.4 Statistics

The sample size was based on data from the study by Liu et al. (2015), who studied patients with traumatic brain injury and reported a Mxa based upon invasive arterial blood pressure and MCAv of 0.18 with an SD of ± 0.24 [153]. Assuming a similar SD in healthy volunteers, we found that 14 subjects would be necessary to detect a test-retest difference in Mxa of 0.3 at an alpha level of 0.05 and a power of 80%, using the sample size equation suggested by Hopkins [184].

Differences between HR, MAP and MCAv were examined using paired t-tests.

Relative reliability was assessed by a one-way mixed-effects model (intraclass correlation coefficient [$ICC_{1.1}$]) with corresponding 95% CI for investigating consistency taking into account the difference between tests when using a single rater (CGR) [185]. $ICC_{1.1}$ was interpreted as suggested by Cicchetti [186], with $ICC_{1.1}$ below 0.40 indicating poor, between 0.40 and 0.59 fair, between 0.60 and 0.75 good, and above 0.75 excellent reliability.

Systematic variations between test sessions were tested using paired t-tests and visualised through Bland-Altman plots. The latter was used for evaluation of heteroscedasticity and detection of outliers.

Absolute reliability was calculated as the standard error of measurement (SEM) using a one-way random effects model as well as the SEM95 (SEM x 1.96) to express the variation with 95% certainty for individual participants [187]. Limits of agreement were calculated from the Bland-Altman plot under the assumption that the mean value was zero.

To compare the agreement between repetitive measurements for the different averages (3, 5, and 10 seconds), we used a generalised linear model for the squared day-to-day differences, using a gamma distribution with log-link. The estimation was performed using generalised estimating equations to take account of the correlation between the three differences for each individual, and the quoted p-values are for score tests.

6.4 Paper VI. Dynamic cerebral autoregulation in patients with severe traumatic brain injury during a tilt-table test

This paper is an extension of the randomised feasibility trial described in papers I to III above. Patients included in the trial were before randomisation tested on a tilt table. We performed the tilt test at baseline, after two weeks, and after four weeks.

6.4.1 Procedure and measurements

With the patient secured on the tilt-table, the tilt-table was elevated from 0 degrees supine position to 30 degrees tilt. The patient stayed in this position for 60 seconds before elevating further to 50 degrees and remained there for one minute. Lastly, the patient was elevated to 70 degrees and remained in this position for 5 minutes. We did not activate the stepping device on the ERIGO® during HUT test. During the tilt-table test, the patient's arterial blood pressure, cerebral perfusion pressure, HR and intracranial pressure were monitored as part of the routine treatment at the NICU. If values crossed the predetermined limits as described in our trial protocol, the patient was lowered to 0 degrees supine. During the HUT test, transcranial Doppler of the middle cerebral artery (flow velocity), non-invasive arterial blood pressure of the middle finger (photoplethysmography) and HR (three-lead electrocardiography) were recorded.

During baseline measurements, an arterial blood sample was obtained from the radial artery contralaterally to the plethysmography and another at the end of the tilting period after approximately 5 minutes of standing, and both samples were immediately analysed on a nearby blood gas analyser (ABL800, Radiometer, Copenhagen, Denmark).

6.4.2 Data-analysis

Data in the supine position and during HUT was visually inspected using Labchart reader (ADInstruments, Oxford, UK). Two data files, containing periods of artefacts in the continuous blood pressure and Doppler signals were generated alongside the visual inspection and were analysed using an R-script (R version 3.6.1, R Core Team, Vienna, Austria**)**. Quality control of the data was done through the R-script and presented as supplementary material. After inspection, the

following indices were calculated: the nMxa, the CVR index and the Gosling's Pulsatility index (GPI).
The CVR and GPI were calculated as follows [188]:

$$CVR = MAP/MCAv$$

$$GPI = (\frac{MCAv^{systolic} - MCAv^{diastolic}}{MCAv^{mean}})$$

6.4.3 Statistics

The statistical analysis plan for the present sub-study was prepared before the data analysis for this study and made publicly available on a web page [189]. However, due to an unexpected amount of missing data, we were unable to comply entirely with the original plan.

Briefly, the nMxa was used as a continuous variable for analysing patients dCA. Firstly, we compared the nMxa after four weeks for between-group differences using a mixed-effects model. Secondly, the mixed-effects model was used to investigate differences over time and between groups for the nMxa and each of the other haemodynamic variables. Thirdly, the association between the level of the nMxa and orthostatic reactions were applied to the model. Finally, we tested the association between impaired dynamic autoregulation (nMxa > 0.3) and the occurrence of orthostatic reactions.

All statistical analyses and graphical presentations were done using SAS/STAT software and SAS/GRAPH version 3.71 (SAS Institute Inc., Cary, NC, USA).

Chapter 7

The previous chapter described the methods used for examining the main objectives in this thesis. In the following chapter, the results from the studies are reported.

7.0 Summary of results

This chapter summarises the results of the systematic review, the randomised feasibility trial, the reliability study on the nMxa index, and the exploratory study on dCA in patients with severe traumatic brain injury.

7.1 Paper I to III. Randomised clinical feasibility trial

During the inclusion period, we identified 50 eligible patients with traumatic brain injury and managed to include 38 patients (**Figure 10**). Thus, we achieved a percentage of included participants of 76% (95% CI 63% to 86%). Of the 19 patients allocated to the early orthostatic intervention group 14 patients completed at least 60% of the intended interventions, yielding a proportion of patients with completed exercises of 74% (95% CI 52% to 89%).

Of the 38 patients, four were transferred to other hospitals not participating in the trial and therefore lost to follow-up. Furthermore, two participants died, and another two participants had their active care stopped due to an expected poor prognosis that was considered out of therapeutic reach (see flow chart).

The 19 patients in the early orthostatic intervention group completed a total of 203 interventions. Eight of the 19 participants experienced no orthostatic reactions during the intervention period, and we observed a median of 2 (IQR 0 to 3) reactions.

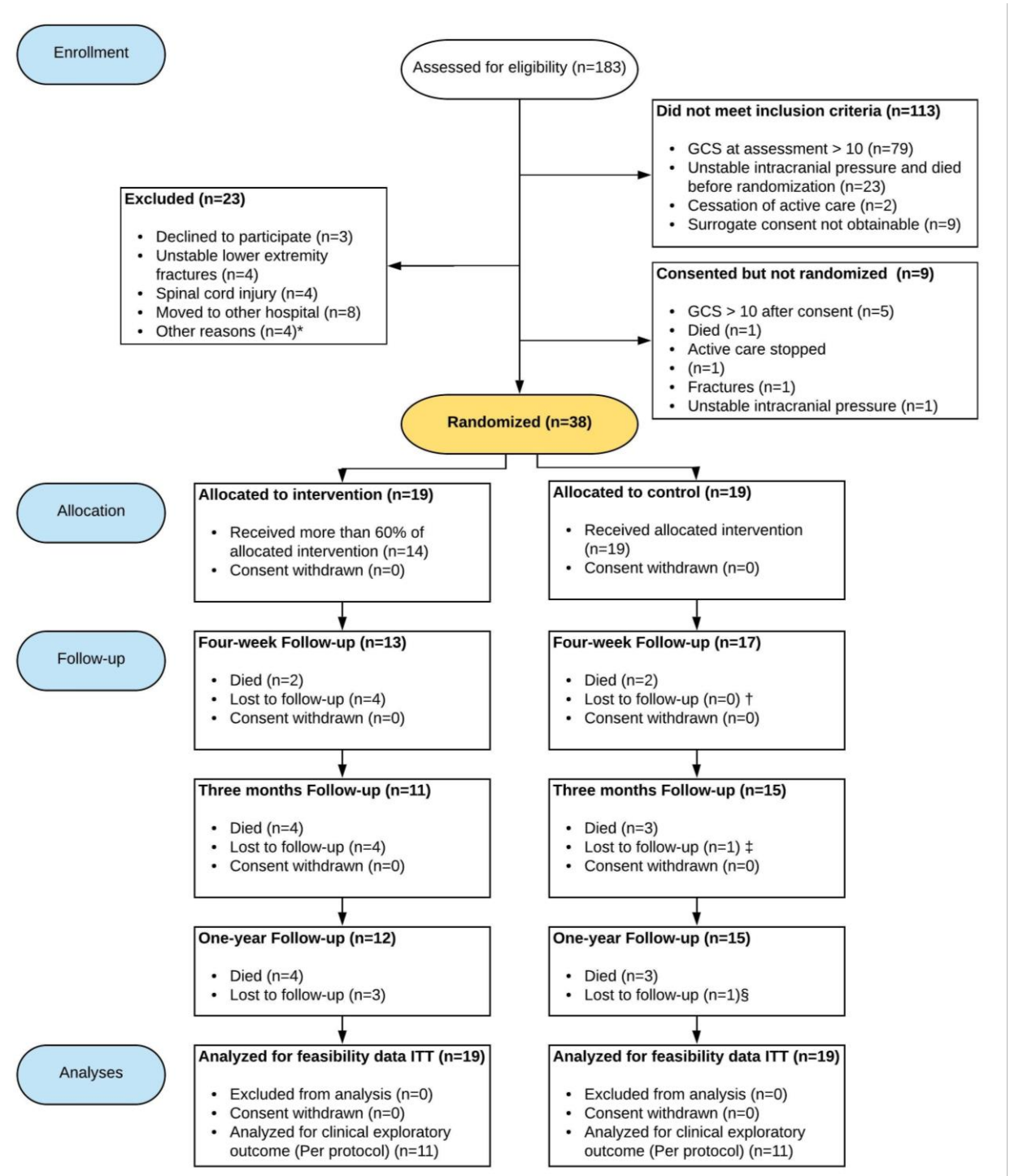

Figure 10. The flow of participants through the trial. GCS: Glasgow coma scale; ITT: intention to treat; *Other reasons include: High frequency of dialysis, waiting for a pacemaker, obesity; †CRS-R (n=16) one patient discharged before the test; ‡ Early discharge from the rehabilitation department before assessments (n=1); § In the intervention group one patient was not assessed with CRS-R and EFA and in the standard care group one patient was not assessed with CRS-R. Due to the nature of GOSE (one equals death), all participants were scored in the standard care group. In the early orthostatic intervention group, three were lost to follow-up. (*Figure reproduced from paper 1II*).

During the intervention period, 202 adverse events and reactions were observed, with 46 determined to be serious adverse events, and seven were adverse reactions during the tilt-table intervention or test. We found no significant difference in the number of patients experiencing at least one adverse event, serious adverse event or adverse reaction between the two groups and no serious adverse reactions were registered during the trial.

The TSAs of patients experiencing at least one serious adverse event and at least one adverse event not considered serious showed that we reached only 6% and 16%, respectively, of the required information size. There was no difference in the relative risk between intervention groups with the DATSACI ranging from 0.2 to 5.7 for serious adverse events and from 0.5 to 2.0 for adverse events.

7.1.1 Clinical exploratory outcomes

The CRS-R, EFA and FIM showed improvements for both intervention groups at each measurement. The SC group tended to have a higher increase in the CRS-R and EFA than the early orthostatic exercise group at four weeks. At three months, both groups had almost reached the highest score on the CRS-R, and the SC group were still higher on the EFA and FIM. At one year, all outcomes were at the higher end of their scale, but the early orthostatic exercise had a considerable variation indicated by the wide interquartile range. We found no significant difference when adjusting for the stratification variable (GCS low or high). The GOSE was similar between groups at one year.

Per protocol analysis (of patients that completed more than 60% of the exercises) did not show any difference in any outcomes.

We did not find any suspected unexpected serious adverse reactions during the intervention.

7.2 Paper IV. Systematic review

We included four trials with a total of 385 participants; three of these had been published [59,91,190] whereas one study is unpublished [paper III of this thesis]. The included patients had a severe traumatic brain injury (n=50), severe anoxic brain injury (n=3), severe other brain injuries (n=1), or severe stroke (n=331). The trials used two types of mobilisation, mobilisation to the edge of the bed and standing/walking [59,190] or tilt-table mobilisation [90, III]. Two trials performed a high daily frequency of early intensive mobilisation within 24 hours versus standard care [59,190]. The other two trials mobilised patients in the intervention group on a tilt table daily starting as early as possible (mean 14 ± 6 days from injury when studies are combined) and performed standard mobilisation in the control group [90, III].

7.2.1 Primary outcomes

Mortality and poor functional outcome were reported in three trials at the end of intervention [90, 189, III] and all four trials reported on mortality and poor functional outcome at maximal follow-up [58, 90, 189, III]. The fixed-effect meta-analysis showed no difference between groups at the end of the intervention (relative risk 1.19, 95% CI 0.93 to 1.53; I^2 0%) and the diversity-adjusted TSA CI was between 0.43 to 3.29 [GRADE certainty LOW] (**Table 1**) or at the longest follow-up (relative risk 1.03, 95% CI 0.89 to 1.21; I^2 0%) with diversity-adjusted TSA CI between 0.78 and 1.38 [GRADE certainty LOW].

Quality of life was reported in two trials at maximal follow-up [59,190]. We found no evidence of a difference between the early mobilisation group versus standard care with a mean difference of 0.0 points (95% CI -0.05 to 0.05; I^2 0%) and the diversity-adjusted TSA CI was -0.2 to 0.2 [GRADE certainty LOW].

We found no evidence of a difference between early mobilisation and standard care on serious adverse events at the end of the intervention (relative risk 1.10, 95% CI 0.86 to 1.39) with a diversity-adjusted TSA CI from 0.41 to 3.12 [GRADE certainty LOW] and at maximal follow-up, the relative risk was 1.08 (95% CI 0.87 to 1.35), and the diversity-adjusted TSA CI was 0.53 to 2.42 [GRADE certainty LOW].

Table 1. Point estimates for primary outcomes, Trial Sequential Analysis, and quality of the evidence for early mobilisation versus standard care

Primary outcomes	Measured at	No. of patients evaluated	Relative effect (95% CI)	P-value	I^2	DARIS (% of DARIS obtained)	DATSACI	TSA boundaries crossed?		Certainty of the evidence (GRADE)
								Superiority boundaries	Futility boundaries	
Mortality or PFO	Intervention	91	RR 1.19 (0.93 to 1.53)	0.16	0%	14%	0.43 to 3.29	No	No	⊕⊕◯◯ LOW [a, b]
	Follow-up	381	RR 1.03 (0.89 to 1.21)	0.66	0%	45%	0.78 to 1.38	No	No	⊕⊕◯◯ LOW [a, b]
Mortality	Intervention	385	RR 1.32 (0.88 to 1.98)	0.17	0%	7%	0.25 to 6.89	No	No	NA
	Follow-up	385	RR 1.26 (0.93 to 1.72)	0.14	0%	12%	0.36 to 4.47	No	No	NA
PFO (survivors)	Intervention	72	RR 1.22 (0.89 to 1.68)	0.23	0%	9%	0.32 to 4.41	No	No	NA
	Follow-up	265	RR 1.12 (0.84 to 1.49)	0.44	0%	14%	0.35 to 3.53	No	No	NA
QOL	Follow-up	208	MD 0.00 (-0.05 to 0.05)	0.93	0%	105%	-0.2 to 0.2	No	Yes	⊕⊕◯◯ LOW [a, b]
Serious AE	Intervention	385	RR 1.1 (0.86 to 1.39)	0.45	0%	18%	0.41 to 3.12	No	No	⊕⊕◯◯ LOW [a, b]
	Follow-up	308	RR 1.08 (0.87 to 1.35)	0.49	0%	24%	0.53 to 2.42	No	No	⊕⊕◯◯ LOW [a, b]

PFO: poor functional outcome; QOL: quality of life; AE: Adverse events; 95% CI: 95% confidence interval; I2: Percentage of heterogeneity; DARIS: diversity adjusted required information size; DATSACI: diversity adjusted Trial Sequential Analysis 95% confidence interval; TSA: Trial Sequential Analysis; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RR: risk ratio;

a: downgraded for indirectness b: downgraded for imprecision. (*Table reproduced and altered from paper 1V*)

7.2.2 Secondary outcomes

Adverse events not considered serious were reported in all four trials at the end of the intervention [58, 90, 189, III]. The fixed-effect meta-analysis revealed no difference between early mobilisation and standard care at the end of the intervention (relative risk 1.02, 95% CI 0.88 to 1.19; I^2 0%) and the diversity-adjusted TSA CI ranged from 0.68 to 1.50 (**Table 2**). At the maximal follow-up, only two trials reported data [59,190] with no difference between groups (relative risk 1.07, 95% CI 0.84 to 1.37; I^2 30%). The diversity-adjusted TSA CI for adverse events not considered serious was between 0.39 and 3.20 at maximal follow-up.

Two trials measured the level of consciousness using the Coma Recovery Scale-Revised at the end of the intervention and maximal follow-up [90, III]. We found no evidence of a difference between groups at the end of the intervention (mean difference -0.00 points, 95% CI -8.23 to 8.23; I^2 80%) and a diversity-adjusted TSA CI from -33.60 to 33.60 [GRADE certainty VERY LOW]. At maximal follow-up, we found a mean difference of 0.62 (95% CI -4.82 to 6.06; I^2 65%) and a diversity-adjusted TSA CI from -21.57 to 22.81 [GRADE certainty VERY LOW].

Table 2. Point estimates for secondary outcomes, Trial Sequential Analysis, and quality of the evidence for early mobilisation versus standard care

Secondary outcomes	Measured at	No. of patients evaluated	Relative effect (95% CI)	P-value	I^2	DARIS (% of DARIS obtained)	DATSACI	TSA boundaries crossed?		Certainty of the evidence (GRADE)
								Superiority boundaries	Futility boundaries	
Not serious AE	Intervention	386	RR 1.02 (0.88 to 1.19)	0.8	0%	23%	0.61 to 1.67	No	No	NA
	Follow-up	308	RR 1.07 (0.84 to 1.37)	0.59	30 %	9%	0.39 to 3.20	No	No	NA
CRS-R	Intervention	60	MD 1.0 (-8.23 to 8.23)	1.0	80 %	7%	-33.60 to 33.60	No	No	⊕◯◯◯ VERY LOW [b, c,]
	Follow-up	56	MD 0.62 (-4.82 to 6.06)	0.82	65 %	10%	-21.57 to 22.81	No	No	⊕◯◯◯ VERY LOW [b, c,]

AE: Adverse events; CRS-R: Coma Recovery Scale-Revised; 95% CI: 95% confidence interval; I^2: Percentage of heterogeneity; DARIS: diversity adjusted required information size; DATSACI: diversity adjusted Trial Sequential Analysis 95% confidence interval; TSA: Trial Sequential Analysis; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RR: risk ratio; MD: mean difference;

b: downgraded for imprecision; c: downgraded for high risk of bias; d: downgraded for inconsistency. (*Table reproduced and altered from paper 1V*)

7.2.3 Exploratory outcomes

All individual serious adverse events were analysed. We found two categories of serious adverse events that should be considered in future trials.

Myocardial infarction occurred in three patients in the early mobilisation group. The risk difference between early mobilisation group compared with the standard care group was 0.50 (95% CI 0.44 to 0.55), three trials, 346 patients [58, 189, III].

Confusion occurred in three patients in the early mobilisation group. The risk difference between early mobilisation group compared with the standard care group was 0.54 (95% CI 0.38 to 0.71), one trial, 38 patients [III].

For a complete list of individual adverse events, see paper III.

7.3 Paper V. Reliability study of the nMxa index

None of the volunteers showed clinical signs of syncope during the experiments. We did all of the assessments using the right temporal window for insonation of the ipsilateral middle cerebral artery in all volunteers.

There was no difference in changes of MAP, HR, or MCAv between the two study days. At all assessments, we observed an increase in MAP and HR and a decrease in MCAv. We did not see any difference between Mxa in supine and HUT.

The scatter plot showed a higher variation when increasing the block size from 3-seconds towards 10-seconds (**Figure 11**). There were no signs of heteroscedasticity in the Bland-Altman plots, and only the 10-second block averages showed some outliers (**Figure 12**).

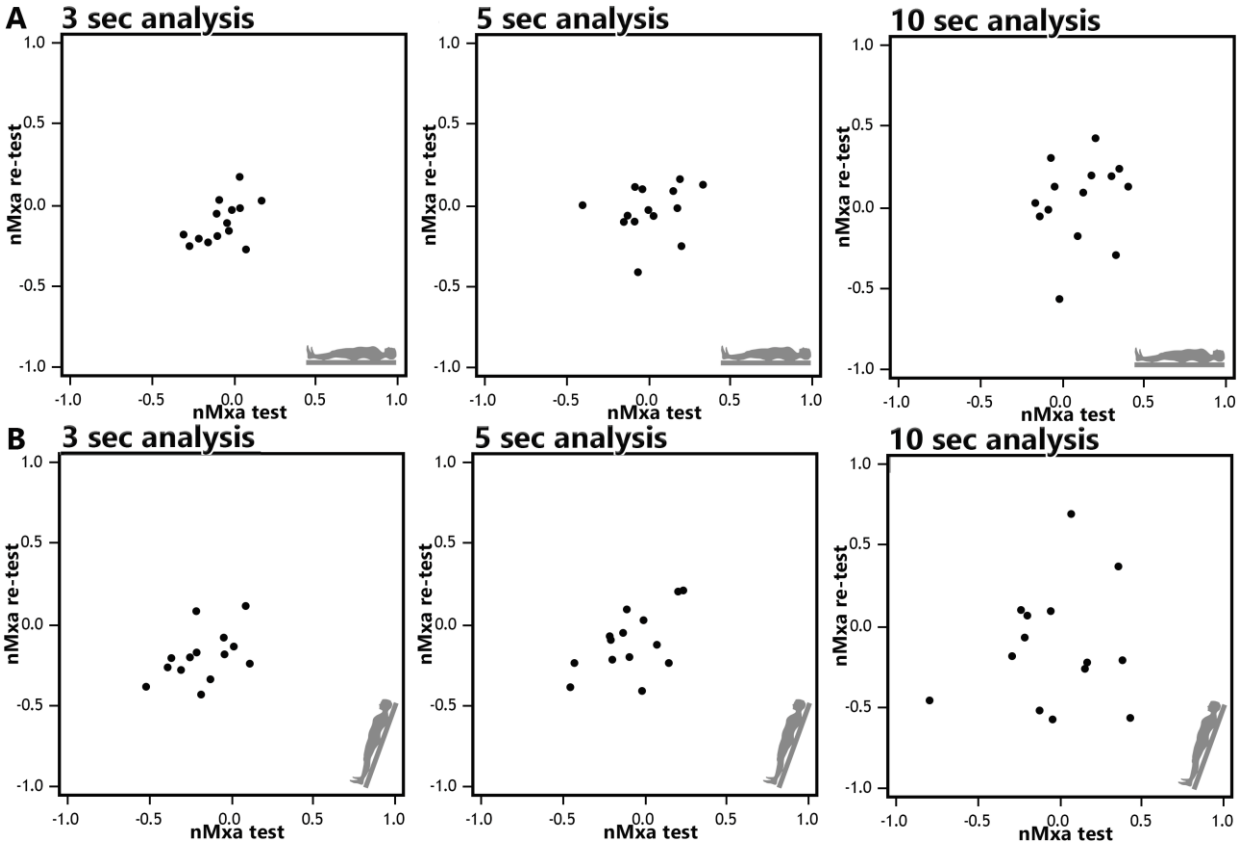

Figure 11. Scatter plot for the test and re-test of the non-invasive mean flow index (nMxa) in supine and during head-up tilt. (*Figure reproduced from paper V*)

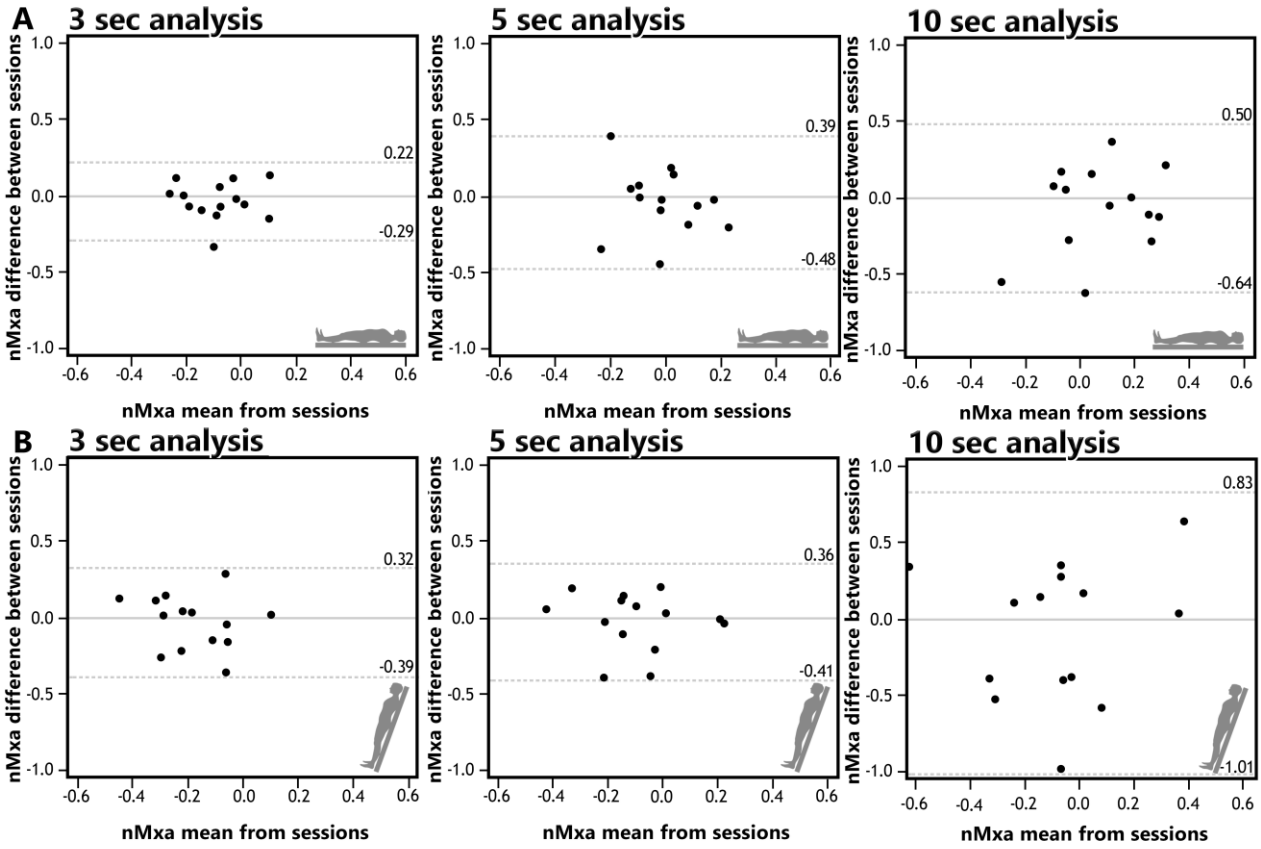

Figure 12. Bland-Altman plots illustrating the mean non-invasive mean flow index (nMxa) from both sessions and the difference between nMxa of the first and second test session in supine and during HUT. (*Figure reproduced from paper V*)

The relative reliability ($ICC_{1.1}$) tended to be higher with shorter average blocks both in supine and during HUT (**Table 3**). The 3-second averages yielded fair reliability that was similar in both supine and HUT. The 5-second averages provided poor reliability in the supine position and fair during HUT. We found poor reliability for the 10-second averages in both positions. SEM and limits of agreement were lowest for the 3-second blocks and tended to increase, regardless of position, with an increase in time used for averaging blocks. No significant difference was found in the squared day-to-day differences between analysis methods (3-, 5-, and 10-seconds) in supine or during HUT (P=0.096 and P=0.086, respectively).

	$ICC_{1.1}$ (LL_{95}; UL_{95})	SEM	SEM_{95}	LOA
nMxa supine				
3-second blocks	0.53 (0.04; 0.82)	0.09	0.18	0.25
5-second blocks	0.22 (-0.32; 0.66)	0.15	0.30	0.43
10-second blocks	0.21 (-0.33; 0.65)	0.20	0.39	0.57
nMxa HUT				
3-second blocks	0.46 (-0.05; 0.79)	0.12	0.24	0.35
5-second blocks	0.57 (0.10; 0.84)	0.13	0.26	0.37
10-second blocks	0.15 (-0.38; 0.61)	0.32	0.63	0.90

Table 3. Relative and intra-observer reliability of the non-invasive mean flow index (nMxa) in healthy volunteers. HUT: head-up tilt to 70 degrees; ICC: Intra-class correlation coefficient; LL_{95} and UL_{95}: Lower and upper limit of the 95% confidence interval, respectively; SEM: Standard error of measurement; SEM_{95}: SEM with 95% confidence interval; LOA: Limits of agreement under the assumption that the mean is zero (corresponding to the 95% limits in a Bland-Altman plot). (*Table reproduced from paper V*)

7.4 Paper VI. Dynamic cerebral autoregulation in patients with severe traumatic brain injury during a tilt-table test

We were able to investigate 34 out of the initially included sample of 38 patients with severe traumatic brain injury. At the follow-up at four weeks, we were only able to include 16 patients (9 in the early orthostatic exercise group and 7 in the standard care group).

During tilt-table test MAP increased with a consequent increase in HR from supine to standing at all time points. MCAv decreased similarly in both groups during HUT at all time points with an increase in CVR.

The nMxa increased from the supine position to HUT ($P < 0.05$) at all time-points without any between-group difference, except for the two-week time-point where the increase in the early orthostatic exercise group was larger than that of the standard care group ($P < 0.05$). We found no association between the nMxa and the development of orthostatic reactions during HUT test. The model was adjusted for $PaCO_2$ and estimated a decrease in nMxa when orthostatic reactions where present (0.048 (P=0.64)). We found no association between the dichotomised nMxa (>0.3) and orthostatic reactions (Fisher's exact test P=1.00).

Chapter 8

In this chapter, the results from the previous chapter will be discussed in relation to other studies within the field of early mobilisation after a summary of our results. Strengths and limitations of the methodology presented in chapter 6 will be discussed in the final part of the chapter.

8.0 Discussion

The studies and trials of this thesis have indicated that more evidence is needed to firmly conclude that patients with a severe acquired brain injury can benefit from or be harmed by an early mobilisation intervention. Evidence is currently insufficient for patients with severe traumatic brain injury. Thus, the systematic review did not show any evidence of a difference between early mobilisation compared with standard care in patients with severe acquired brain injury. We did find evidence that early mobilisation will likely not improve the quality of life in patients with severe stroke. Our TSAs showed that dependent on the outcome, hundreds or thousands of patients are needed in trials for establishing evidence. Future trials should carefully consider if acute myocardial infarction and confusion are more frequently occurring in early mobilisation groups, as we found a risk difference in the systematic review.

Our feasibility trial indicated that the treatment is feasible to conduct in patients with severe traumatic brain injury in the NICU with no apparent increased risk of harm. Future trials should take initiatives to secure a higher follow-up of the patients and a higher successful intervention percentage. Our analysis of dCA indicated that patients with severe traumatic brain injury mobilised on average 13 days after the injury did not experience a high rate of orthostatic reactions, and those who did was not associated with impaired cerebral autoregulation. However, the use of the ERIGO® may explain the generally low number of orthostatic reactions observed in the intervention group during all experimental exercises in the feasibility trial but if it translates into physiological improvement regarding processes involved in vascular tone or fluid retention remains to be investigated. In this regard, the stepping device on the ERIGO® may effectively counteract pooling of blood in the lower extremities and secure enough cardiac output without further adaptation to gravitational pull. Nevertheless, these results should be carefully interpreted due to the low number of patients at follow-up and our reliability study that found a rather large SEM and limits of agreement in the nMxa index.

8.1 Comparison with other systematic reviews, trials, and studies

A published Cochrane review has confirmed the results from the AVERT III trial in patients with stroke, that early mobilisation does not improve survival or favourable outcome [191]. While they still highlighted the uncertainties of the effect estimates included in the review, they concluded that more detailed research is essential. These results do not differ from our review (paper IV), although our estimates are even more uncertain due to the low number of patients included. However, more detailed research also means details about the intervention that is investigated concerning dose, intensity, and frequency and details concerning the patients the interventions are applied to.

A randomised clinical trial on surgical ICU patients, investigating early goal-directed mobilisation compared with standard care, found benefits of the former on length of stay and improved functional mobility at hospital discharge [192]. This trial included a few patients with brain injury, further confirming that early mobilisation is feasible in the ICU. However, the efficacy has limited external validity due to the considerable variation in the patients' diagnoses – yet again indicating that more detailed knowledge is required. Another randomised pilot trial investigated the use of an ERIGO® tilt-table in the ICU setting on patients with severe acquired brain injury [91]. We included this trial in our systematic review. Interestingly they found no adverse events during their trial, which is in contrast to our feasibility trial (paper III). They did, on the other hand, experience deaths in both groups, which resembles the number and distribution of deaths in our feasibility trial and they found a significant benefit on functional outcome and consciousness. However, this trial and our trial were of approximately the same sample size with similar initial GCS.

The relative reliability (ICC) of the nMxa index has been investigated in other studies showing comparable values as in our study [154,155]. The study by Mahdi et al. investigated a group of healthy participants and found an increase in ICC when standing up instead of sitting. This manoeuvre increased the ICC from zero to over 0.7, indicating good reliability [155]. Whether the manipulation of blood pressure is needed to detect impaired cerebral autoregulation has been an ongoing discussion [163, 164]. On the downside, the study did not reveal details on how the nMxa was calculated in terms of block sizes, but the results did resemble our 5-second analysis. It could be problematic to have a method which in a healthy population has an ICC of zero as were found in the study by Mahdi et al. in the seated position [155]. Also, this is in contrast to studies showing

that more extended measurement periods are necessary to get stable measurements of dynamic autoregulation [151,152]. In our reliability study, we found a limit of agreement of 0.35 during HUT, indicating that on the individual level, a subtle change in dCA would be challenging to detect. Mahdi et al. also stated that standing doubled the coefficient of variation, which could be the reason for the increased ICC as this tends to increase with the increased variation of the measured outcome, but they also shortened the number of measurements by a factor five, which could explain the larger SDs [193].

We have not found any other studies that have tested dynamic cerebral autoregulation in patients with severe traumatic brain injury in the standing position as early as we did in our trial (paper VI). A study in the early phase after traumatic brain injury retrospectively examined the nMxa in the supine position and found a nMxa of 0.21, with measurements performed from day 1 to 14 after the injury [194]. The relative observed drop in MCAv during HUT was similar to that found in healthy male persons in other studies [101,195,196]. As the patients in our study furthermore presented with an increase in both MAP, HR, and CVR it may be justified to assume that the patients had preserved systemic haemodynamic reactivity to protect cerebral perfusion, at least at a level corresponding to that of healthy persons.

8.2 Strengths and limitations

The decision to design our feasibility trial as a randomised trial can be an advantage as well as a disadvantage. Randomisation meant that the possibility of not being included in the intervention group and thereby only receiving additional examinations is reflected in the inclusion proportion; one of our feasibility outcomes. Furthermore, for investigating harms, we needed a formal control group. On the downside, we could have increased the power of the other feasibility data by assessing the intervention on all the patients, although such power comes with a cost of getting heterogeneity introduced if the effect of the intervention differs between patients.

Our feasibility trial was successful on all three predetermined specifications for claiming that the trial was feasible. Nevertheless, emphasis should be done in striving for even higher inclusion rate, intervention rate and minimising adverse events, if possible. The high percentage of patients lost to follow-up is an explicit limitation of the feasibility trial and an essential place for improvement

in future trials. We were limited by the number of hospitals involved in the trial, as patients were moved to other hospitals between admission to the ICU and the rehabilitation unit.

Our feasibility trial did not reach the predetermined sample size, and therefore we had a lower power and precision of our estimates. Nevertheless, as a feasibility trial with no prior trials to base our estimation on, we used clinical judgement as our best guess. Furthermore, it has been pointed out that external feasibility trials should not form the basis of larger definitive trials. Future trials should have an internal feasibility trial (e.g. the first 70 patients included) to truly calculate the sample size of a given outcome of interest [162]. Our feasibility trial identified a broad range of adverse events of different degrees. Patients with severe traumatic brain injury are at high risk of experiencing a large variety of adverse events. Nevertheless, the identification of these adverse events should be taken into consideration when estimating the sample size of a larger trial to identify any harms from this intervention [70].

One of the major strengths of our systematic review is the pre-planned and up-loaded protocol to PROSPERO. Furthermore, we took a thorough and inclusive approach to the literature-search to ensure that we would decrease our chances of missing relevant trials because mobilisation is still a poorly defined concept in the literature. We included four trials of differing quality, but our sub-group analysis on methodology did not show any significant difference between trials at low risk of bias and high risk of bias. Furthermore, using the TSA for controlling type II error was a strength in our design.

The number of trials was a limitation to our systematic review as illustrated by all the TSA showing that the required information size was far from reached, except for quality of life. The selection of trial design may also have limited our chances of discovering some harms from the treatment. Randomised clinical trials are historically known for underreporting adverse events due either to design with strict protocols or the length of reporting [197]. This is especially evident in long-term harms which are more commonly reported in observational cohort studies [198].

As the AVERT III trial represented 86% of the patients in this review, our ability to extrapolate data to other types of brain injury than stroke is limited. The different aetiology, age, and the number of comorbidities between the stroke population and the often much younger traumatic brain injury population could result in different outcomes.

Our systematic review is limited in the heterogeneity of the included studies and patients. As mentioned earlier, trials must focus on a more homogeneous patient group. On the other hand, this heterogeneity was not evident in our analysis, as I^2 were often at 0%. However, this finding does not preclude that heterogeneity may increase in the future.

The analysis of cerebral autoregulation in our trial on patients with a severe traumatic brain injury was explorative by design and is likely to be underpowered to draw firm conclusions. The missing data at follow-up was as in our feasibility trial, a clear limitation for drawing a conclusion. On a positive note, nearly all patients were assessed at baseline, giving a valuable dataset in the somewhat earlier stage after traumatic brain injury. One of the downsides of using the nMxa during a HUT test is the amount of data that is lost in patients with orthostatic intolerance. Patients with orthostatic intolerance will as soon as the blood pressure drops or the HR increases to a predetermined degree, be returned to the supine position, which then will result in a shortening of the amount of data recorded. The patients with the most significant haemodynamic challenge will then be the patients with the least reliable data. Furthermore, all studies using transcranial Doppler are limited to measuring a few areas of blood flow. As explained earlier (chapter 5), cerebral autoregulation is different in various regions of the brain, and not all of the brain's autoregulation is affected by the large arteries such as the middle cerebral artery that we measured in our trial.

Several studies have pointed out that the mechanical stepping of the ERIGO® tilt-table counteracts orthostatic reactions and thus increases the exercise time [9,86]. For a frail patient population with potentially impaired cerebral autoregulation utilising this mechanism seems reasonable. On the other hand, for a sustainable change in the cardiovascular regulation of blood pressure and cardiac output, the neuroendocrine response may need to be further challenged. In this regard, studies have shown that HUT increases renin, angiotensin and aldosterone in healthy people [199,200].

The small study population limited our reliability study of the nMxa. A larger group of healthy persons could potentially have a more substantial variety of the nMxa, which in consequence would return a higher ICC estimate as this is highly sensitive to variation in data [193]. Nevertheless, it did illustrate some critical issues on the precision of this method.

Chapter 9

The final chapter will summarise the main conclusions of this thesis and bring some future perspectives of directions for future research.

9.0 Conclusions

We were not able to find any evidence of the effects of early mobilisation compared to standard care on acquired brain injury through the systematic literature review. Too few studies limited our ability to draw firm conclusions. We found evidence that early mobilisation does not improve long term quality of life, although the certainty was low, and this was only in trials, including patients with stroke.

Based on the results from this thesis, there is still equipoise on early mobilisation given that it may be beneficial or harmful for patients with severe acquired brain injury and even more particularly in patients with traumatic brain injury. We did find the intervention feasible, and our feasibility trial did not indicate that our treatment protocol further harmed patients. Neither did our analysis indicate that early orthostatic exercise affects systemic or cerebral haemodynamics during a four-week mobilisation period starting 13 days after injury.

Researchers or clinicians using the nMxa index must carefully consider which method is used for calculation. We found better reliability when using 3-second blocks than 5- or 10-second blocks.

9.1 Future perspectives

The potential of early mobilisation to counteract the adverse effects of bed rest, increase arousal and improve functional outcome is still not thoroughly investigated. More extensive trials in patients with severe traumatic brain injury are needed to examine the effects of an early mobilisation intervention with a focus on both benefits and harms and different intensities.

More specific knowledge on the mechanisms of intensive bed rest and how it affects glucose level, arterial blood gases, and arousal in these patients during their stay at the ICU is also of great interest and whether any of the adverse effects from bed rest can be reversed or abolished through early

daily mobilisation could benefit patients on the long run. The aetiology behind orthostatic reactions is still unclear and needs further investigation. Therefore, future studies focusing on the mechanisms behind orthostatic reactions and the prediction of orthostatic reactions could be helpful.

Finally, adverse events, as were found in abundance in our clinical trial, should be of high focus and interest to researchers and clinicians. Emphasis on investigating adverse events is important, as some of these may be the result of the prolonged bed rest and some could be the result of mobilisation.

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Notes

Papers

Attached are the full text version of the included papers:

I. **Early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury – Protocol for a randomised clinical feasibility trial.** *Christian Gunge Riberholt, Jane Lindschou, Christian Gluud, Jesper Mehlsen and Kirsten Møller.* Trials 2018 Nov. 8; 19(1):612. DOI: 10.1186/s13063-018-3004-x

II. **Statistical analysis plan for: Early mobilization by head-up tilt with stepping versus standard care after severe traumatic brain injury.** *Christian Gunge Riberholt, Christian Gluud, Christian Ovesen, Janus Jakobsen, Jesper Mehlsen and Kirsten Møller.*
Brain Injury 2020, June 1, submitted for publication

III. **Early orthostatic exercise by head-up tilt with stepping versus standard care after severe traumatic brain injury. A feasibility randomised clinical trial.** *Christian Gunge Riberholt, Markus Harboe Olsen, Christian Baastrup Søndergaard, Christian Gluud, Christian Ovesen, Janus Christian Jakobsen, Jesper Mehlsen and Kirsten Møller.*
Neurorehabilitation and Neural Repair 2020, May 15, submitted for publication

IV. **Early head up mobilisation versus standard care for patients with severe acquired brain injury: a systematic review with meta-analysis and Trial Sequential Analysis.** *Christian Gunge Riberholt, Vibeke Wagner, Jane Lindschou, Christian Gluud, Jesper Mehlsen, Kirsten Møller.*
PLoS One 2020, May 7, submitted for publication

V. **Reliability of the transcranial Doppler ultrasound-derived mean flow index for assessing dynamic cerebral autoregulation in healthy volunteers.** *Christian Gunge Riberholt, Markus Harboe Olsen, Lene Theil Skovgaard, Ronan MG Berg, Kirsten Møller, Jesper Mehlsen.* Scientific Reports 2020, January 16, submitted for publication.

VI. **Dynamic cerebral autoregulation during early orthostatic exercise in patients with severe traumatic brain injury: results from a randomised clinical feasibility trial.** *Christian Gunge Riberholt, Markus Harboe Olsen, Ronan Berg, Jesper Mehlsen, Kirsten Møller.*
Journal of Head Trauma Rehabilitation 2020, May 28, submitted for publication.

Paper I

Riberholt et al. Trials (2018) 19:612
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Trials

STUDY PROTOCOL Open Access

Early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury – Protocol for a randomised clinical feasibility trial

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Abstract

Background: Intensive rehabilitation of patients with severe traumatic brain injury is generally applied in the subacute stages of the hospital stay. Few studies have assessed the association between early and intensive physical rehabilitation and functional outcomes. The aim of this trial is to assess the feasibility of an intensive physical rehabilitation intervention focusing on mobilisation to the upright position, starting as early as clinically possible versus standard care in the intensive care unit. The feasibility study is intended to inform a subsequent randomised clinical trial that will investigate benefits and harms of the intervention.

Methods: This randomised clinical feasibility trial with a follow-up period of 1 year will use blinded outcome assessors for the Coma Recovery Scale–Revised. A maximum of 60 patients admitted to the neurointensive care unit at Rigshospitalet, Denmark, with traumatic brain injury (age of at least 18 years), a low level of consciousness, and stable intracranial pressure will be included in the trial. Patients will be randomly assigned to experimental intervention versus standard care (1:1) stratified according to their Glasgow Coma Score. The intervention group will receive daily mobilisation in a tilt table with an integrated stepping device (ERIGO®). Feasibility is declared if more than 60% (the lower 95% confidence interval of the proportion) of eligible patients are included in the trial and more than 52% (the lower 95% confidence interval of the proportion) of patients in the intervention group receive more than 60% of the planned interventions. Safety is assessed by the occurrence of adverse events and adverse reactions. Exploratory clinical outcomes consist of cerebral haemodynamics (blood flow velocity and pressure autoregulation) and baroreceptor sensitivity in the early phase as well as functional outcomes (Coma Recovery Scale–Revised, Early Functional Ability scale, and Functional Independence Measure).

Discussion: Our findings will inform a future, larger-scale randomised clinical trial on early mobilisation using a tilt table early after severe traumatic brain injury.

Trial registration: ClinicalTrials.gov identifier: NCT02924649. Registered on 3 October 2016.

Keywords: Brain injury, Randomised feasibility trial, Cerebral autoregulation of blood flow, Rehabilitation, Tilt-table therapy

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Background

Patients with severe acquired brain injury (ABI) may benefit from early and intensive rehabilitation, which partly consists of physical exercise [1]. Thus, observational studies have found an association between higher-level physical activities and better final outcome in these patients [1, 2]. However, such exercise poses an orthostatic challenge and requires that the patient be able to compensate for this challenge. Accordingly, for patients with severe ABI and a low level of consciousness, mobilisation to the upright position on a tilt table is an important first step. Several beneficial effects are hypothesised to result from this type of activity. In a recent observational study, we showed that patients with impaired consciousness open their eyes for longer periods of time in the upright compared with the lying position, indicating increased arousal [3]; other authors have confirmed this finding [4, 5] and reported that head-up tilt (HUT) also reduced the risk of ankle contractures (range of motion) and improved lung function [6, 7].

On the other hand, mobilisation to the upright position may trigger haemodynamic problems, including hypotension and syncope, and may also pose a risk of extubation in intubated patients, dislodgement of indwelling catheters, and falls. About 40% of patients with severe ABI have orthostatic intolerance that limits their chance of achieving an upright position [3]. Neither the physiological mechanisms causing orthostatic hypotension nor those that enable recovery from this phenomenon have been thoroughly investigated. Considering analysis of electrocardiography (ECG) signals obtained from ABI patients during HUT, we suggested that impairment of baroreceptor sensitivity may be involved [8]. Whether the impairment is caused by the brain lesion per se or prolonged immobilisation or both remains to be investigated. However, in other patient populations with neurally mediated syncope or orthostatic hypotension, intensive tilt-table training has been shown to be beneficial for regaining neurovascular control [9, 10]. In addition, recent studies including a large number of patients with ABI have found an association between impaired cerebral autoregulation measured the first days after injury and an unfavourable outcome [11, 12]. In line with these results, we have shown impaired autoregulation during HUT in patients with severe ABI as late as 40 days after injury [8]. Thus, it is possible that autoregulation and baroreceptor sensitivity are progressively impaired with prolonged immobilisation and that this further restricts attempts at mobilisation in some of these patients, ultimately leading to an impaired functional outcome.

Even though Andelic et al. found a beneficial effect of early rehabilitation in patients with traumatic brain injury (TBI) in their quasi-randomised trial [13], the net effect of early mobilisation in patients with TBI remains unclear. Also, mobilisation of patients with severe ABI is usually not initiated in the acute stage after injury, during the intensive care stay, but rather at a later, subacute stage (weeks), after stabilisation and transfer for rehabilitation [14]. A recent small study conducted in four patients with acute severe TBI and disorders of consciousness suggested that early mobilisation is feasible and safe using a tilt table with integrated stepping that increases the venous return of blood to the heart [15] but these data warrant replication in larger studies.

In February 2017, we conducted a thorough search of the literature in relevant databases (MEDLINE, CINAHL, EMBASE, CENTRAL, and Web of Science) on early out-of-bed mobilisation in patients with TBI by using Medical Subject Headings (MeSH) terms (brain injuries, traumatic AND rehabilitation). The search showed that no randomised trials have yet been performed in this field.

Therefore, we wish to assess the feasibility of an early HUT protocol in patients with severe TBI, in terms not only of the number of patients who are successfully mobilised but also of the number of adverse events (AEs) and adverse reactions (ARs). In exploratory analyses, we will assess clinical outcomes at 3 months and 1 year. Furthermore, we wish to explore physiological variables during ongoing mobilisation in the early phase and their possible association with the patients' clinical outcome. Finally, as an exploratory part of this trial, we wish to investigate the occurrence and time to recovery of orthostatic tolerance and cerebral autoregulation in patients with severe TBI who receive early and intense mobilisation and their relation to the functional outcome.

Methods/Design

This trial is a randomised clinical feasibility trial comparing an early HUT protocol versus standard care in a neurointensive care unit (NICU) and a specialised neurorehabilitation department. The protocol was developed in accordance with the guidelines and checklists for Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Additional file 1) [16]. Results will be reported as stated in the Consolidated Standards of Reporting Trials (CONSORT) statement [17]. Randomisation will be conducted centrally by the Copenhagen Trial Unit using a web-based randomisation system. The allocation sequence will be computer-generated using block sizes of varying length concealed for the investigators. The allocation ratio is 1:1. Because consciousness measured by the Glasgow Coma Scale (GCS) score can be partly a predictor of outcome [18], the allocation sequence will be stratified for GCS score at the time of inclusion (3–6 points compared with 7–10 points). All included patients will be followed from inclusion until 1 year after injury. All baseline assessments will be conducted before

randomisation and start of intervention (time point – 1). Cerebral blood flow autoregulation will be studied after 2 and 4 weeks. Functional assessments will be conducted after 4 weeks, 3 months and 1 year (Fig. 1).

Blinding

It is not possible to blind the intervention for the treating physical therapists or the participant. However, outcome assessment using the Coma Recovery Scale–Revised (CRS-R) will be conducted by assessors who are blinded to the intervention. Data are entered in a validated Microsoft Excel spreadsheet by the primary investigator (CGR) and will be checked for correctness against the source data by a colleague otherwise not involved in the trial. Furthermore, the person analysing the data will be blinded to the patient's randomisation, and concealed allocation will be revealed only after all analyses have been completed and two conclusions drawn [19].

Recruitment and informed consent

Patients admitted to the NICU will be screened for eligibility on a daily basis by the principal investigator (CGR). The nearest relative to the patient acts as proxy (next of kin) and is given written information about participation in the trial. The relative is then invited to an information meeting. The relatives are informed that they can withdraw their consent at any time. If consent is given, a medical doctor not involved in the trial but acting as trial guardian is asked to give consent as well. Written informed consent must be obtained from the patient himself or herself if he or she regains consciousness and decision-making capability during the trial period.

Participants

Participants included in this trial must be admitted to the NICU at Rigshospitalet, Copenhagen, Denmark, with severe TBI, be at least 18 years old, and have a clinical presentation that does not exclude a later diagnosis of vegetative state or minimally conscious state or a GCS score of lower than 11 points during wake-up call, and stable intracranial pressure of less than 20 mm Hg for 24 h, and informed consent from the nearest relative and trial guardian must be in place. Patients with unstable fractures or other injuries that contraindicate mobilisation, patients with spinal cord injury, or patients without relevant informed consent are excluded from the trial.

Time schedule

We will include patients until January 1, 2019 or until a maximum of 60 patients have been included, whichever

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	-1	0	2w	4w	3m	1y
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Early mobilisation		←	—	→		
Standard care						
ASSESSMENTS:						
Age, gender, time since injury, comorbidity, surgical procedures, functional status prior to injury, GCS	X					
Feasibility outcome		←	—	→		
FIM, CRS-R, EFA,	X		X	X	X	X
Five days ECG monitoring	X					
HUT-test (blood pressure, cerebral blood flow velocity, ECG, $PaCO_2$,	X		X	X		
LOS, Time with tilt-table exercise, PTA,						X

Fig. 1 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) table of enrollment, intervention, and assessments

occurs first. For a detailed flowchart on patient inclusion, please refer to Fig. 2. Data analysis will commence 3 months after (April 1, 2019). At this time, the 1-year follow-up will most likely not be complete for all patients. This variable will remain blinded until all data are gathered (January 1, 2020). A full statistical analysis plan will be developed before April 1, 2019.

Early daily mobilisation (experimental intervention group)
In addition to standard care (see below), the experimental intervention group is subjected to an early and daily mobilisation protocol with HUT during their stay in the intensive care unit and throughout the early stages of rehabilitation. Mobilisation will be conducted using a tilt table with an integrated stepping device, which activates the venous pump and counteracts pooling of blood in the lower extremities (ERIGO®, Hocoma, Volketswil, Switzerland). The tilt-table intervention is applied once daily, 5 days per week for 4 weeks during the stay in the NICU. The duration of upright positioning is 20 min per session. Within each session, the patient will be moved to the tilt table and secured with straps and harness. The patient is then mobilised stepwise to 30°, 50°, and 70° HUT at 1-minute intervals while blood pressure (BP), heart rate (HR), respiratory rate, and peripheral oxygen saturation are closely monitored. Cerebral perfusion pressure (CPP) and intracranial pressure (ICP) are monitored as clinically indicated. If at any time our predetermined safety limits for BP, CPP, ICP, or HR (Table 1) are crossed, the patient is lowered to 0° tilt. When the values have returned within the safety limits, the procedure is resumed until the patient has been in the

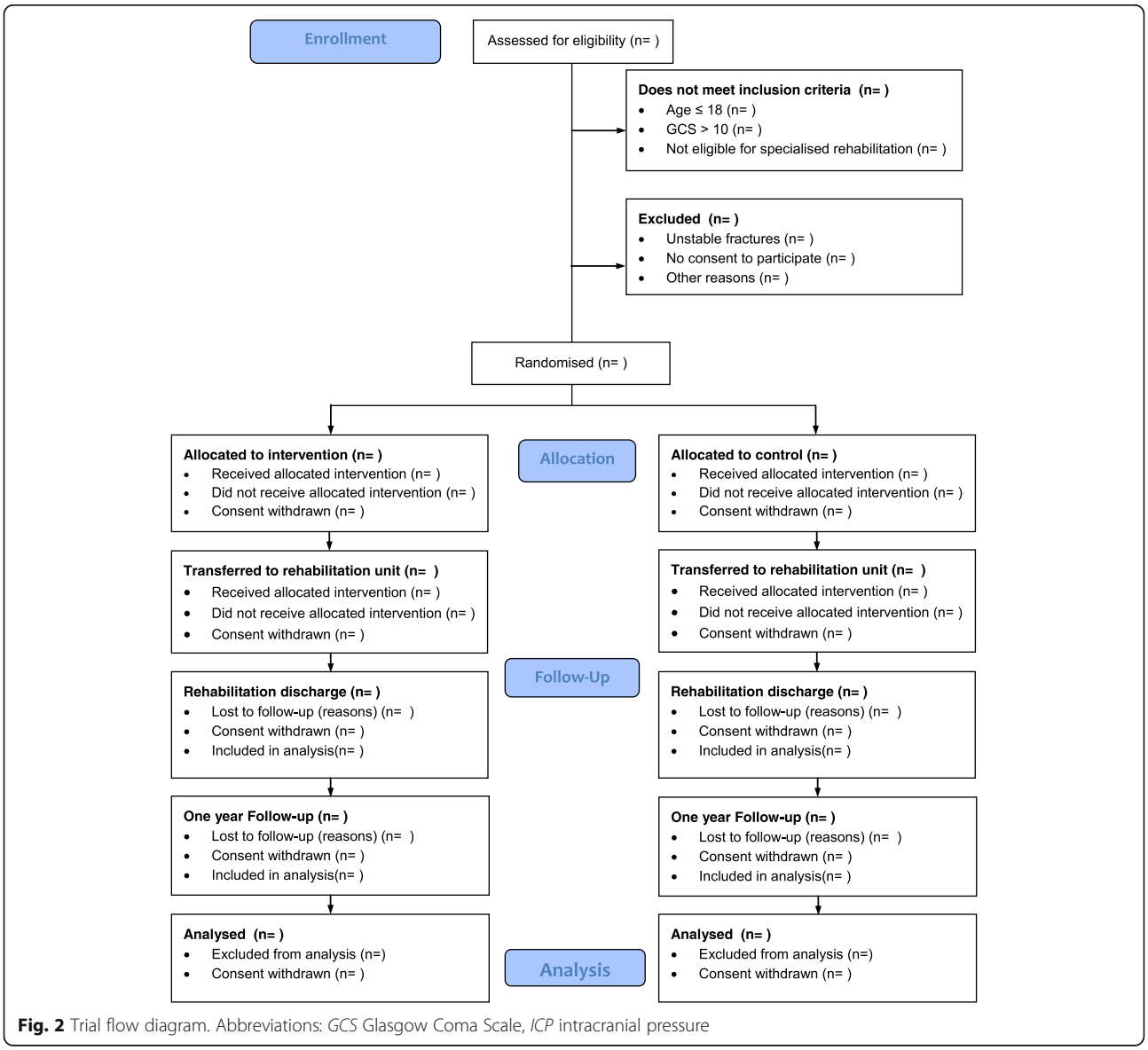

Fig. 2 Trial flow diagram. Abbreviations: *GCS* Glasgow Coma Scale, *ICP* intracranial pressure

Table 1 Predetermined safety limits during head-up tilt

Absolute	Systolic/Diastolic BP	>80/50 mm Hg
	CPP	>50 mm Hg
	HR	<180 bpm
	ICP	<25 mm Hg
Relative	Permitted decrease from baseline systolic/diastolic BP	<30/15 mm Hg
	Permitted increase in HR from baseline	<30 bpm

Abbreviations: *BP* blood pressure, *CPP* cerebral perfusion pressure, *HR* heart rate, *ICP* intracranial pressure

upright position for a maximum of 20 min or until a total duration of 40 min for the HUT session has been reached, whichever occurs first.

If the patient is discharged from the NICU to the department of neurorehabilitation/TBI unit before the 4-week intervention period has ended, training will continue at the latter institution with a prespecified tilt-table protocol consisting of mobilisation twice a day on a similar tilt table. Patients who show functional improvement beyond the scope of tilt-table training (for example, are able to stand from a chair) before the trial period has ended will have their experimental intervention withdrawn and their final evaluation performed immediately hereafter; subsequently, the standard rehabilitation regimen will be continued.

Some patients will be discharged from the NICU to a temporary stay at another intensive care unit in the Capital Region of Copenhagen. In that case, the mobilisation and assessments will be continued using a standard tilt table (without the stepping device).

Standard care (experimental and control groups)

The experimental and control groups receive standard rehabilitation as decided in collaboration between doctors, nurses, and physiotherapists and will be monitored during the trial. Only a small amount of time is used on mobilising the patient to either the edge of the bed or to a wheelchair whilst admitted to the NICU. The physiotherapists' main focus is on respiratory function and positioning to avoid bedsores. The patients in the control group do not receive physical therapy on a daily basis.

Trial duration

The trial intervention will consist of 4 weeks of mobilisation corresponding to 20 mobilisation sessions (Fig. 1). The patients included will be followed until end of in-hospital rehabilitation and again 1 year after injury.

Data collection

Information on patient characteristics (age, sex, diagnosis, comorbidities, functional status prior to this injury, time since injury, and surgical procedures) is retrieved from the patient charts. For patients receiving the experimental intervention, the number of training sessions during the 4-week intervention period is recorded.

Outcomes are described below. There are two types of outcomes: feasibility outcomes and exploratory clinical outcomes.

Feasibility outcomes

The primary objective of this trial is to assess feasibility. First, we will evaluate the number of patients we are able to include in the trial during the 2-year inclusion period, and a proportion of 60% or more of TBI patients who are eligible for the trial is acceptable. Second, we will evaluate the number of sessions applied in the experimental intervention group. The intervention will be considered to be feasible if at least 60% of the intended sessions (maximum of two per weekday in the trial for 4 weeks after randomisation, for a maximum of 20 sessions in total) are given to at least 52% of the patients in the intervention group. If a patient is transferred to another department and it is not possible to apply the intervention, we will count sessions as missing. If a patient dies, the number of applied and missing sessions is recorded at the time of death. Both feasibility outcomes are based on clinical judgement from the staff at the department and the trial investigators.

AEs, serious AEs (SAEs), ARs, serious ARs (SARs), and suspected unexpected SARs will be monitored during the trial counting the number of occurrences. Causality of AR will be assessed daily.

For a larger trial to be deemed feasible, both feasibility outcomes need to be attained, meaning that more than 60% of eligible patients will participate and at least 52% of the intervention group will receive more than 60% of the intended interventions.

Exploratory clinical outcomes

The exploratory clinical outcomes are the CRS-R [20], the Early Functional Ability (EFA) [21], and the Functional Independence Measure (FIM) [22]. The CRS-R [20] evaluates changes in consciousness. It is hierarchically ordered and composed of six categories evaluating auditory, visual, motor, oromotor–verbal function, communication, and arousal. The scale ranges from 0 to 23 points, and a higher score indicates a higher level of function [20]. The evaluation will be carried out by two assessors who are experienced at using the scale. These assessors will be blinded to the patient's treatment allocation. To obtain a complete evaluation of the patient's progress, the EFA scale is included. The EFA scale is constructed to fill the evaluation gap between the GCS and FIM. The scale comprises 20 items, including measures of wakefulness, activities of daily living and cognitive

abilities [21]; again, a higher score (range from 20 to 100 points) indicates a higher level of function. The FIM consists of 18 items highlighting motor function, ability to do activities of daily living and higher cognitive functions ranging from 18 to 126 points, and a higher score indicates a higher level of function. Scoring will be conducted by the staff at the two departments. It is not possible to blind these assessors to the randomisation procedure. The FIM has been thoroughly investigated in patients with TBI and has been shown to be valid and reliable and have established measures for detecting the minimal clinically important difference [23, 24]. The FIM was chosen as an outcome to track patient improvements over a long period of time. Owing to the initial low levels of consciousness in patients with severe TBI, combining the EFA and FIM has been recommended for a more complete assessment [25]. Preferably, the patient will be tested by CRS-R at the same time of day. The FIM and the EFA will be scored at the NICU by one tester with experience from the department of neurorehabilitation, who will gather necessary information from the multidisciplinary team treating the patient. Assessment of the patients at the department of neurorehabilitation will be performed by members of the clinical staff, who are experienced at using the two scales. The FIM, EFA, and CRS-R will be applied at baseline, at 4 weeks and 3 months after the baseline assessment, and at 1 year after the initial injury (Fig. 1).

Furthermore, length of stay at the two departments, time until tilt-table training is no longer relevant, and the duration of post-traumatic amnesia, as defined by time from injury and until the patient regains coherent day-to-day memory [26] are also registered. During the trial, the total amount of physical therapy sessions allocated to the patients is measured in both groups.

To address the haemodynamic changes during the transition from the supine position to HUT, we will measure non-invasive blood pressure by beat-to-beat photopletysmography and HR by ECG (ADInstruments, Oxford, UK), cerebral blood flow velocity (transcranial Doppler, Multi-Dop® T digital, Compumedics Germany/DWL, Singen, Germany), and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) (ABL800, Radiometer, Copenhagen, Denmark). The HUT test will take place at baseline, after 2 weeks and after 4 weeks, or at the end of the intervention period. The data are used to investigate orthostatic tolerance and cerebral autoregulation as well as the patient's baroreceptor sensitivity (beat-to-beat variation). Furthermore, ECG will be recorded continuously for 5 days, immediately after the patient has been included in the trial (ePatch, BioTelemetry Technology Aps, Hørsholm, Denmark).

Statistical analyses

The primary feasibility outcome is the ratio between patients included and eligible patients. Eligible patients are those who fulfil the inclusion criteria of our trial. For example, if the number of randomly assigned participants is 44 out of 60 eligible patients, then the proportion will be 0.73 with a 95% confidence interval (CI) between 0.60 and 0.84. A proportion of 0.60 (the lower CI of the proportion) or more randomly assigned patients will be acceptable for a future larger-scale trial. We strive for having as large a proportion of eligible patients as participants to make the latter as representative of the former as possible and have arbitrarily set the acceptable lower 95% CI to be 60% or above. We will include a maximum of 60 participants or as many as possible during the 24-month recruitment period.

The second feasibility outcome is defined as the number of HUT sessions applied during the 4-week intervention period. In our clinical judgement, we believe that it is satisfactory to be able to apply more than 60% of the daily HUT sessions on weekdays for more than 70% or at least 52% (the lower CI of the proportion) of the patients. Since a maximum of 30 patients will be randomly assigned to the intervention, a binominal distribution is calculated from the proportion of 70%, which gives a lower 95% CI of 52%.

The number of patients with at least one AE or SAE during the intervention period will be analysed as exploratory feasibility outcomes using logistic regression adjusted for the protocol-specified stratification variable. Moreover, we will compare the proportions and severity in the two intervention groups.

Baseline data will be used to describe the population. Data will be analysed by using SAS Enterprise version 7.11 (SAS Institute Inc., Cary, NC, USA). A binominal distribution will be used to calculate the 95% CI for our primary feasibility outcome as the proportion of randomly assigned patients from the eligible patients.

The clinical exploratory outcomes will not undergo traditional statistical testing, as this is a small feasibility trial with large risks of random errors. However, in order to test the feasibility of the analyses and for exploratory purposes, outcomes will be analysed and *P* values will be presented. *P* values of any size will not be interpreted as "significant".

The CRS-R, FIM, and EFA as well as the physiological measures of mean arterial pressure, HR, cerebral blood flow, and the dynamic autoregulation index contain multiple measurement points and will be analysed accordingly with analysis of variance or other linear regression models for repeated measures. Missing data will be treated with the multiple imputation method.

Dynamic cerebral blood flow autoregulation is analysed as the ratio between mean arterial pressure and

cerebral blood flow velocity. For this, a Pearson correlation coefficient of 30 mean values of mean arterial pressure and cerebral blood flow each consisting of 10 s of measurements are correlated in the supine position and during maximum HUT [12, 27]. This gives two values of the so-called Mx index per tilt test. Baroreceptor regulation is assessed by using data from the ECG waves to conduct a power spectral analysis of the RR intervals. The purpose is to analyse the low-frequency content (0.05 to 0.15 Hz), which is assumed to reflect the baroreceptor activity, as well as the high-frequency content (0.15 to 0.35 Hz), which is related mainly to parasympathetic activity [28].

All analyses will be intention-to-treat using multiple imputations to account for missing data as described by Jakobsen et al. [29]. Analyses will be conducted blinded with the two intervention groups coded as, for example, 0 and 1. After the drawing of conclusions, the blinding will be broken.

Discussion

Early physical rehabilitation has previously been associated with improved outcome in patients with TBI in a cohort study [13]. The pilot study published by Frazzitta et al. showed promising results when starting physical rehabilitation early in 31 patients with ABI, of whom 12 were affected by TBI [30]. Nevertheless, there is a lack of studies investigating the causal relationship between early physical rehabilitation and long-term outcome. Andelic et al. conducted a quasi-randomised cohort study on the effects of early rehabilitation at the intensive care unit in patients with TBI [13]. Although the consistency of the rehabilitation paradigm was unspecified, they did observe a benefit of this intervention as measured by the Glasgow Outcome Scale Extended and the Disability Rating Scale after 12 months [13]. This trial intends to lay the foundation for a larger-scale multicentre randomised clinical trial, investigating whether the patients are able to tolerate HUT, whether the intervention is practically feasible, and whether the outcomes are improved. A trial comparing short- and long-term functional outcomes after standard care compared with early mobilisation should also assess the effects of mobilisation on haemodynamic regulation which has previously been associated with poor outcome or death [11, 12], in an attempt to identify potential predictors of long-term recovery. The trial is designed aiming for a low risk of bias using centralised randomisation, blinded outcome assessors where possible, and blinded statistical analyses [31–33]. However, it is not possible to blind the patients or care givers, which may lead to risk of bias. Furthermore, given the small sample size and the heterogeneous trial population, any differences we find between groups may be due to selection bias or random errors or both [33–35]. Therefore, any result should be interpreted with great caution.

Investigating AEs and ARs is with limitations. Whether or not there is a direct causal relation between an incidence and an AE and the intervention can in many ways be subjective and hard to determine. Nevertheless, we feel confident that the experienced staff can provide support in informing when in doubt. We believe it is important to do this feasibility trial as a randomised clinical trial since it is likely to affect the decision of entering the trial. Whether the mobilisation intervention is feasible could have been answered in a classic observational study.

It is difficult to provide sufficient evidence for the general assumptions presented in this protocol that longer periods of bed rest may influence the baroreceptor sensitivity and that early mobilisation may re-establish it. Using HR variability to assess regulation of the autonomic nerve system has been the subject of debate but is a relatively simple, non-invasive tool, even though more sophisticated and invasive measures could be used for measuring sympathetic nerve activity, such as direct recording of single-fibre muscle sympathetic nerve activity.

If a larger multicentre randomised clinical trial is deemed feasible, the data gathered in the present trial should be of great use. The required sample size of a larger randomised clinical trial shall be calculated on the basis of the data from the likely effects from the present trial as well as evidence from updated systematic reviews of randomised clinical trials. Moreover, the financial estimates of conducting a larger trial will be clearer from estimates of time consumption based on the present feasibility trial.

Trial status

Enrolment commenced on January 2, 2017. At present, 34 patients have been randomly assigned. We will continue including patients until January 1, 2019 or until 60 patients are included, whichever occurs first, and will complete the last 1-year follow-up assessment in December 2019.

Additional file

Additional file 1: SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*. (DOC 122 kb)

Abbreviations

ABI: Acquired brain injury; AE: Adverse event; AR: Adverse reaction; BP: Blood pressure; CI: Confidence interval; CPP: Cerebral perfusion pressure; CRS-R: Coma Recovery Scale–Revised; ECG: Electrocardiography; EFA: Early Functional Ability; FIM: Functional Independence Measure; GCS: Glasgow Coma Scale; HR: Heart rate; HUT: Head-up tilt; ICP: Intracranial pressure; NICU: Neurointensive care unit; SAE: Severe adverse event; SAR: Severe adverse reaction; TBI: Traumatic brain injury

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Availability of data and materials
Not applicable.

Authors' contributions
The initial protocol was developed by CGR. JM, JL, CG, and KM contributed to the optimisation of the protocol. CGR prepared the initial manuscript. JM, JL, CG, and KM revised the manuscript critically for important intellectual content. The final version of the manuscript was read and approved by all authors.

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Ethics approval and consent to participate
This trial has been approved by the Scientific-Ethics Committee of the Capital Region (H-16041794) and is registered at www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02924649). After a patient is found to be eligible for the trial, informed consent from the proxy and a trial guardian (a physician not involved in the trial) is obtained by CGR. CGR is the project manager and is responsible for collecting and storing data and all correspondence.
The trial is carried out in accordance with the principles of the Helsinki Declaration. The project manager is responsible for informing the Scientific-Ethics Committee of the Capital Region in Denmark of any critical adverse event or major changes of the protocol or both. All correspondence will be filed by the project manager.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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Paper II

Statistical analysis plan: Early mobilization by head-up tilt with stepping versus standard care after severe traumatic brain injury

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Trial registration: ClinicalTrials.gov identifier: NCT02924649. Registered on the 3rd of October 2016.

SAP revision history

SAP version	Action	Changes made	Timing of SAP	Date changed
1.0	Submitted for Trials	Original first submission	Before the last three-month follow-up and before starting analysis	12th of March 2019
1.1	Editorial revision	Added information to the manuscript and submitted checklist	Last three-month follow-up and analysis completed	11th of June 2019
1.2	First revision	Changes made in response to reviewer comments	All analysis finished according to protocol except per-protocol analysis.	23rd of December 2019
1.3	Rejected	The reviewer pointed out unclarity in the definition of the feasibility outcomes and lacked specification in the analysis of the data.	All analysis finished according to the statistical analysis plan	19th of April 2020
1.4	Submitted for Brain Injury	Changes made in response to the unclarity pointed out by the reviewer	All analysis finished according to the statistical analysis plan	1st of June 2020

Word count: 2,698

Abstract

Background: Early mobilization on a tilt table with stepping versus standard care may be beneficial for patients with severe brain injury, but data from randomized clinical trials are lacking. This detailed statistical analysis plan describes the analyses of data collected in a randomized clinical feasibility trial for early mobilization by head-up tilt with stepping versus standard care after severe traumatic brain injury.

Methods: Primary feasibility outcomes are the proportion of included participants who were randomized out of all screened patients; the proportion of participants allocated to the experimental intervention who received at least 60% of the planned exercise sessions; and safety outcomes such as adverse events and reactions and serious adverse events and reactions. Exploratory clinical outcomes are suspected unexpected serious adverse reactions; and functional outcomes as assessed by the Coma Recovery Scale-Revised at four weeks; Early Functional Ability Scale and Functional Independence Measure at three months. The description includes the statistical analysis plan, including the use of multiple imputations and Trial Sequential Analysis.

Keywords: Statistical analysis plan; Early mobilization; Trial sequential analysis; Traumatic brain injury

Introduction

The early mobilization by head-up tilt with stepping versus standard care after severe traumatic brain injury (HUT-TBI) trial is a randomized clinical trial assessing the feasibility of using a tilt-table with integrated stepping for early mobilization to the upright position in the neuro-intensive care unit [1]. The possible negative effects of bed rest on human physiology have been investigated for decades [2–4]. With the possibility of counteracting the adverse effects of prolonged bed rest, it might be beneficial for the patients to undergo early mobilization, whereby they are moved to the upright position using a tilt table. The simultaneous stepping is intended to counteract orthostatic hypotension in the standing position.

Early rehabilitation of patients with a severe traumatic brain injury has hitherto been subject to few studies, in which the interventions have been incompletely described [5,6]. Nonetheless, the available studies indicate that early mobilization may improve functional outcome after traumatic brain injury. However, a large randomized clinical trial, the AVERT trial, showed no benefit of early and intensive mobilization on functional outcomes measured three months after stroke [7]. Moreover, a systematic review with a meta-analysis found no impact of early active mobilization and rehabilitation on mortality at discharge from the intensive care unit (ICU) in a large variety of non-neurological ICU patients. However, the intervention did increase muscle strength, walking ability, and the number of days alive and out of the hospital at six months [8].

The present trial assessed if using a tilt table for early orthostatic exercise was feasible in a group of patients with severe traumatic brain injury [1]. Here we report the detailed statistical analysis plan for the HUT-TBI trial [1], which has been updated and finalized during the data collection period. Besides the primary outcomes related to feasibility, the analysis plan also addresses the statistical handling of exploratory clinical outcomes.

Methods

Ethical approval

This randomized clinical feasibility trial was approved by the Scientific-Ethics Committee of the Capital Region (H-16041794) and is registered on www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02924649); the trial protocol has been published in Trials [1]. The project manager (CGR) is responsible for collecting and storing data and all correspondence. After a patient was found to be eligible for the trial, informed consent from the proxy and a trial guardian (a physician not involved in the trial) was obtained by CGR. The trial was carried out following the principles of the Helsinki Declaration [9].

Primary research questions

Is an early head-up tilt protocol feasible in patients with severe traumatic brain injury, in terms of the number of participants who are successfully included, the number of exercise sessions performed in the experimental group, and the number of patients with serious adverse events (SAE) and non-serious adverse events (AE) and serious adverse reactions (SAR) and non-serious adverse reactions (AR)?

Exploratory research questions

- Does early head-up tilt with stepping reduce the number of AE, AR, SAE, and SAR compared with standard care after severe traumatic brain injury?
- Does early head-up tilt with stepping improve the level of consciousness (Coma Recovery Scale-Revised) after four weeks, early functional abilities (Early Functional Ability scale) after three months, or functional independence (Functional Independence Measure) after three months, compared with standard care after severe traumatic brain injury?
- Does head-up tilt with stepping improve the level of consciousness (Coma Recovery Scale-Revised), early functional abilities (Early Functional Ability scale), or functional independence (Functional Independence Measure) after one year compared with standard care in patients with severe traumatic brain injury?

Main trial design

The present statistical analysis plan describes our planned analyses for the feasibility trial, investigating head-up tilt with stepping versus standard care in patients with severe traumatic brain injury. As described in the published protocol, the sample size (n=60)) has been chosen as a realistic number to reach for this feasibility trial [1].

The trial is a randomized clinical feasibility trial with a pragmatic stratification according to the Glasgow Coma Score at inclusion (3-6 compared to 7-10 points). The patients are randomized in a 1:1 ratio by the Copenhagen Trial Unit using a central web-based randomization system.

Besides standard care, the experimental intervention group received daily (Monday to Friday) mobilization on a tilt-table to the standing position for up to 20 minutes per session. This orthostatic exercise continued for four weeks from randomization or until the patient could stand from a chair or bed with assistance. The tilt-table has a build-in stepping device that increases the venous return of blood to the heart and thereby counteracts orthostatic hypotension and increases standing time [10,11]. The control group received standard care. Standard care was decided in collaboration between doctors, nurses, and physiotherapists and was monitored
during the trial. The standard care group used little time on mobilizing the patient to the edge of the bed or chair while admitted to the neurologic ICU. The focus of the physiotherapist is on respiratory function and in bed positioning to avoid bedsores.

Primary feasibility outcomes

Our primary feasibility outcomes are as follows:

The lower limit of the confidence interval of the inclusion ratio (the proportion of included participants randomized compared to all eligible patients). For example, if 44 of 60 eligible patients agree to participate, then the proportion will be 73% with a 95% confidence interval (95% CI) between 60% and 84%. The lower limit for this feasibility outcome is set at 60%; if the lower limit of the confidence interval of the gathered data of the HUT-TBI Trial is at 60% or higher, then the trial is successful in terms of inclusion. This is equivalent to a one-sided test (please see the statistical section below).

The lower limit of the confidence interval of the intervention success rate defined as the proportion of participants allocated to the experimental intervention who received at least 60% of the planned exercise sessions. For example, if 21 of 30 participants (70%) randomized to the experimental intervention group receive 60% of the exercise sessions, the lower limit of the confidence interval will be 52%. Accordingly, if the lower limit of the confidence interval of the gathered data of the HUT-TBI Trial is at or above 52%, the trial will be successful in terms of exercise completeness. Both the inclusion ratio and the intervention success rate limits are arbitrary limits decided together with the clinical staff at the department. It, therefore, emphasizes clinical reality on the validity of the data.

Our safety outcomes are defined as either proportion of participants with either an SAE, SAR, AE, or AR not considered serious [12]. SAEs are defined as any undesirable event that results in death, is life-threatening, requires prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or requires intervention to prevent permanent impairment or damage, whether considered related to the trial intervention or not [12]. AEs are defined as any undesirable event not considered serious occurring to a participant during the trial. The proportion of participants with at least one SAE, SAR, AR, or AE during the intervention period will be compared between the two intervention groups (please see the statistical section below).

Exploratory clinical outcomes

For the exploratory clinical outcomes, we have chosen three outcomes: The Coma Recovery Scale-Revised (CRS-R) [13], the Early Functional Ability scale (EFA) [14,15], and the Functional Independence Measure (FIM) [16,17], all of which are scored at baseline and after four-weeks, three-months and one-year. The CRS-R reflects changes in consciousness and will be analyzed at the four-week time point (end of the intervention period) comparing the two intervention groups and was scored by assessors blinded to the intervention allocation. The EFA evaluates early functional changes, and the FIM evaluates the ability to perform functions and activities of daily living independently. Both were evaluated at the three-month time point. Secondly, the data for all three exploratory clinical outcomes will be presented as longitudinal data in a figure (error bar plot) showing the mean and the 95% CI for each group. At the one-year follow-up, the same three outcome scales are used and supplemented by the Glasgow Outcome Scale – Extended (GOSE); the latter is used routinely at the department for the one-year follow-up.

Statistical analyses

Statistical analysis will be handled using STATA (StataCorp, College Station, Texas, USA).

All baseline characteristics will be presented for each intervention group. Continuous variables will be summarized using means and standard deviations or medians and interquartile range depending on the distribution of data. Discrete variables will be presented as frequencies, proportions, and percentages.

The timing of outcome assessments can be found in the published protocol in figure 1 [1].

Regarding the feasibility outcome, we will not adjust for multiplicity since all three outcomes should be achieved for the trial to be considered feasible. That is, the inclusion ratio and exercise success rate should be above the decided limits, and the adverse events should not be significantly different in favor of the standard care group. We have decided to use a one-sided test for the feasibility outcomes corresponding to the description above. In these analyses, a significance level of 2.5% will be used.

All our analyses will primarily be intention-to-treat, i.e., all randomized participants will be included in the primary analyses and analyzed as randomized. We will secondly perform per-

protocol analyses, including the participants allocated to the intervention who received at least 60% of the planned exercise sessions compared to the patients in the standard care group.

If we do not reach the desired number of participants in the trial, we will consider analyzing our data using Trial Sequential Analysis [19,20]. In this case, we will use the pre-specified standard deviations and minimal relevant differences described in supplementary table 1 for the continuous outcome and the proportion in the control group for dichotomized outcomes. The calculations will be based on an alpha of 5% and a beta of 10%. Trial Sequential Analysis reduces the risk of type I and type II errors due to small sample size and multiple outcome testing [20].

The analysis will start after the last three-month follow-up has been collected and after submission of this statistical analysis plan (end of March 2019). The analysis of the one-year follow-up data will start after data from the last patient has been collected in late December 2019.

Feasibility outcomes

The first two primary feasibility outcomes will be derived from the trial with the above-mentioned lower limits of the proportions. For the intervention to be feasible, both feasibility outcomes should be achieved, and the early orthostatic intervention group should not have an overrepresentation of SAE, AE, SAR, AR, or suspected unexpected serious adverse reactions (SUSAR).

All analyses described below using general linear regression, logistic regression, or mixed-model linear regression will be adjusted for the protocol specified stratification variable (high or low GCS).

We will use the inspection of data (descriptive analysis) to evaluate adverse events due to the low power. Secondly, the proportions of participants with one or more SAEs, SARs, ARs, and AEs between the two groups will be examined using Fisher's exact test [1]. Accordingly, we will use an alpha of 5%. Each patient with at least one SUSAR during the intervention period will be analyzed as an exploratory feasibility outcome, also using logistic regression analysis. Where appropriate, we will present data with a 95% CI.

Exploratory clinical outcomes

All exploratory clinical outcomes and physiological outcomes are on a continuous interval scale.

The exploratory clinical outcomes will primarily be compared between allocation groups at specified time points. The CRS-R will be analyzed at the four-week time point, and EFA and FIM will be analyzed at the three-month time point using general linear regression analysis.

Each outcome, with the corresponding minimal relevant difference, standard deviation, and power level, can be found in Supplementary Table 1. The one-year follow up data for CRS-R, EFA, and FIM will be analyzed in the same way. Furthermore, for the one-year analysis, the Glasgow outcome scale extended will be compared between groups using general linear regression and adjusting for stratification-specific variables.

In case the regression models described above (linear regression and mixed model) cannot be fitted due to breach of their underlying assumptions (e.g., skewed distribution of data/residuals), non-parametric methods (e.g., Van Elteren's test) taking the stratified randomization into account will be employed. The analysis will, in all cases, be conducted at the pre-specified time points as stipulated above. As described in our protocol, we have still reported that all results will be interpreted as hypothesis-generating.

Missing data

Trials conducted in the ICU are at high risk of missing data alone on account of the patient´s condition [21]. If data are missing, we will consider using multiple imputations according to the recommendations by Jakobsen and colleagues [22]. These recommendations state that up to 40% of missing data can be imputed, but the method of choice depends on the outcomes, whether the dependent variable has missing data only at baseline, etc. [22]. If multiple imputations are used, the following variables will be incorporated in the analysis: baseline value of the dependent variable, stratification variable (GCS), end of post-traumatic amnesia, and days to the first mobilization. For all continuous clinical outcomes, we will analyze survivors, and in a sensitivity analysis, impute the lowest possible value for participants who died or dropped out as well as the best possible value. We will present the results of both analyses.

Trial status and profile

The inclusion period ended in December 2018, with only 38 patients included for two years. The end of the three-month follow-up period will be in March 2019, and the one-year follow up will be in December 2019. The flow of patients will be presented in a CONSORT diagram, as reported in the protocol [1]. We will report the number of screened patients, the number of included patients, and the main reason for the exclusion of eligible patients. Furthermore, we will present the number of patients who died within the four-week intervention period, within the first three months from randomization, and within the first year.

Presentation of results in tables and figures

For the presentation of tables and figures, please see additional file 2.

Discussion

This statistical analysis plan for the feasibility trial of conducting early orthostatic exercise in patients with severe traumatic brain injury is published to minimize outcome reporting bias and data-driven results. From the total data gathered in the trial, the primary outcomes are feasibility outcomes, but we have also described assessments of our exploratory outcomes.

Our statistical analysis plan is based on considerations to secure unbiased data handling and analyses without getting inspired by the collected data, i.e., *P*-hacking [19].

The use of Trial Sequential analysis for the exploratory clinical outcomes will help establish sample size estimation for a larger trial. One objective of the present trial would direct which outcome to choose. Assessing the functional outcome in patients with a severe traumatic brain injury throughout illness is challenging since they may present with a reduced level of consciousness in the early stage but may eventually return to work. Hence, the scale must encompass many outcomes. The alternative would be to use a scale such as the Glasgow Outcome Scale Extended. This scale is cruder than other scales, and its validity, while the patient is admitted to a hospital department, may be limited. For future trials, our trial results may inspire the initial sample size calculation, which can then be adjusted as data from more trials are added.

Our statistical analysis plan has some limitations. The analysis plan was finished before we began the data analysis. Due to several unforeseen events, the original analysis plan was not published immediately, which would have been optimal. We did, however, manage to make the original analysis plan publicly available. Furthermore, multiple imputations for missing data assumes that these are missing at random; however, this assumption may be incorrect. For example, data completeness may differ between patients in the intervention and the standard care group.

Conclusions

The HUT-TBI trial investigates the feasibility of early orthostatic exercise versus usual care. With the present pre-specified statistical analysis plan, we hope to minimize analytic bias. On the larger scale, we hope that the feasibility outcomes and the exploratory outcomes may inform and enable the generation of hypotheses for a larger multicenter trial investigating the benefits and harms of early orthostatic exercise.

Abbreviations

AE: adverse event; AR: adverse reaction; CG: Control group; 95% CI: 95% confidence interval; CRS-R: Coma Recovery Scale-Revised; EFA: Early Functional Ability; EOE: Early orthostatic exercise; FIM: Functional Independence Measure; GCS: Glasgow coma scale; ICU: Intensive care unit; SAE: serious adverse event; SAR: serious adverse reaction; SD: standard deviation; SUSAR: suspected unexpected adverse reaction;

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Availability of data and materials

The datasets analyzed during the current study are not publicly available due to the small sample size but are available from the corresponding author on request.

Authors' contributions

All authors were involved in the conception of the statistical analysis plan. CGR drafted the statistical analysis plan. CGR, JCJ, CO, JM, and KM provided input for drafting and finalizing the statistical analysis plan. JCJ acted as a senior statistician and CO as a co-statistician. JCJ and CO did the analysis independently. KM is the chief investigator of the trial. All authors read and approved the manuscript for publication.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no known competing interests.

Data management plan and standard operating procedure

The data management plan and standard operating procedure are kept at the Copenhagen Trial Unit.

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Paper III

Early orthostatic exercise by head-up tilt with stepping versus standard care after severe traumatic brain injury. A randomized clinical feasibility trial

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Abstract

Background: Intensive rehabilitation of patients after severe traumatic brain injury aims to improve functional outcome. The effect of initiating rehabilitation in the early phase, in the form of head-up mobilization, is unclear.

Objective: To assess whether early mobilization is feasible and safe in patients with traumatic brain injury admitted to a neurointensive care unit.

Methods: This was a parallel-group, randomized clinical trial, including patients with severe traumatic brain injury (Glasgow coma scale < 11 and admission to the neurointensive care unit). The intervention consisted of daily mobilization on a tilt-table for four weeks. The control group received standard care. Outcomes were the number of included patients relative to all patients with traumatic brain injury who were approached for inclusion, the number of conducted mobilization sessions relative to all planned sessions, as well as adverse events and reactions. Information on clinical outcome was collected for exploratory purposes.

Results: Thirty-eight participants were included (19 in each group), corresponding to 76% of all approached patients [95% confidence interval (95% CI) 63% to 86%]. In the intervention group, 74% [95% CI 52% to 89%] of planned sessions were carried out. There was no difference in the number of adverse events, serious adverse events, or adverse reactions between the groups.

Conclusions: Early head-up mobilization is feasible in patients with severe traumatic brain injury. Larger randomized clinical trials are needed to explore potential benefits and harms of such an intervention.

Trial registration: ClinicalTrials.gov identifier: NCT02924649. Registered on 3rd October 2016

Keywords: Early mobilization; traumatic brain injury; head-up tilt; feasibility trial.

Introduction

Patients with severe traumatic brain injury need extensive rehabilitation reaching from in-hospital stay at neurocritical care units to rehabilitation out of hospital[1]. Early mobilization seems to be associated with positive effects on delirium, days on a ventilator, amount of sedation needed, and on functional outcome in a variety of patients in the critical care unit[2]. Mobilization using a tilt table in patients with impaired consciousness is typically offered as an intervention modality during rehabilitation to increase arousal and prevent secondary complications such as contractures of weight-bearing joints[3–6].

Orthostatic hypotension is often found in patients with acute brain injury and could complicate the use of a tilt table for mobilization[7,8]. The pathophysiology of orthostatic hypotension is considered to be multifactorial and comprise, e.g., impaired baroreflex sensitivity, cardiovascular deconditioning, and lack of fluid retention due to neuroendocrine impairment[7,9]. Immobilization during hospitalization and the brain injury itself will facilitate the development of orthostatic hypotension[2]. This will potentially hamper the recovery, either by depriving the brain of a sufficient oxygen supply during orthostatic episodes or by reducing the amount of rehabilitation offered to the patient[7]. Conversely, the early orthostatic challenge may potentially prevent deconditioning by activating protective cardiovascular and neuroendocrine responses[10–12].

In the present trial, we investigated the feasibility of using early orthostatic exercise by a head-up tilt with stepping to mobilize to the upright position, compared to standard care in patients, who had been admitted to the neurointensive care unit with severe traumatic brain injury. We randomized participants after their brain injury had

subsided to a point where head-up tilt was deemed by the clinicians to be safe, e.g. without provoking intracranial pressure surges. Feasibility was assessed by whether patients could be recruited for the study and undergo the planned exercise sessions, as well as by adverse events and reactions.

Methods

The trial protocol has previously been published[13]; the statistical analysis plan was planned before the study ended (Riberholt CG et al. “Statistical analysis plan for early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury – a randomised clinical feasibility trial”, submitted. DOI: 10.21203/rs.2.468/v3). This study was approved by the Regional Ethics Committee of the Capital Region in Denmark (H-16041794) and registered at clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02924649). Patients admitted to the neurocritical care unit at University Hospital of Copenhagen - Rigshospitalet, Denmark, between January 2017 and December 2018 were screened daily by the primary investigator (CGR) and a physiotherapist. After a patient was deemed eligible for participation, informed written consent from the next-of-kin and a trial guardian (a physician not involved in the study) was obtained by a member of the trial staff.

Participants

Patients with severe traumatic brain injury were eligible for inclusion. Severe traumatic brain injury is commonly defined as a Glasgow Coma Score (GCS) < 9. In this trial, we defined severe traumatic brain injury as a GCS < 11 because patients with a clinical presentation that would not exclude a later diagnosis of vegetative state or minimally conscious state can have a higher score on the GCS. Inclusion criteria, therefore, included a GCS < 11 and stable intracranial pressure for 24 hours < 20 mmHg at the time of inclusion. Patients were excluded if they had spinal cord injury or fractures of the lower extremities that prohibited weight-bearing, or if no informed consent was obtained. All participants were tested hemodynamically on a tilt table by tilting to the

standing position (70 degrees) before randomization to ensure hemodynamic stability. This trial did not prohibit other interventions.

Randomization and masking

After measurements at baseline, participants were randomly assigned (1:1) to the intervention group or the control group using a central web-based computer-generated block randomization procedure. Block sizes were randomly assigned with either 4, 6, or 8 participants in each block. We stratified the randomization according to the GCS at the time of inclusion (low GCS 3 to 6 compared to high GCS 7 to 10). The randomization procedure was set up by an independent statistician at the Copenhagen Trial Unit. None of the investigators involved in the recruitment, data collection, or data analysis had access to the allocation sequence or block sizes.

Due to the nature of the intervention (tilt-table), it was not possible to mask the investigators, the staff at the department, or the patient. The outcome assessors assessing the *Coma Recovery Scale-Revised* and adverse and serious adverse events were blinded to the allocation of the participant, but the *Early Functional Ability Scale* and the *Functional Independence Measure* were assessed by the department staff without any masking.

Interventions

The intervention group underwent early orthostatic exercise and otherwise received the same treatment throughout as the control group. The early orthostatic exercise consisted of daily (Monday to Friday) exercise on an ERIGO® tilt-table (Hocoma AG, Switzerland) to 70 degrees head-up tilt for 20 minutes administered by two

physiotherapists and a nurse. The ERIGO® has a built-in robotic stepping device intended to counteract a drop in blood pressure during standing[8]. The robotic stepping frequency was set at 50-60 steps per minute. If reduction in blood pressure, cerebral perfusion pressure or increase in heart rate and intracranial pressure beyond predetermined limits[13] were observed, the participants were moved to the supine position until stable and then returned to head-up tilt. Time spent in the supine position did not count in the duration of the daily exercise session. The orthostatic exercise sessions were terminated if participants regained the ability to stand up by themselves, but they remained in their assigned group.

The control group received standard treatment at the department, as decided by the treating physicians, nurses, and therapists. This treatment followed recommendations from the Brain Trauma Foundation[14]. Standard treatment did potentially involve mobilization but to a much smaller scale, and the focus was primarily on respiratory function and re-positioning to avoid bedsores.

Outcomes

The primary outcome focused on the feasibility of the study and consisted of a combination of the following three measures of feasibility and safety: 1. The number of included participants relative to the total number of the eligible patients. For the study to be feasible, we required that the lower 95% confidence limit of this number was at least 60%. 2. The number of exercise sessions we were able to perform relative to the planned number. For feasibility, the lower 95% confidence limit of this measure was required to be at least 52%. These limits correspond to a one-sided significance test of 0.025. 3. The total number of serious adverse events and reactions as well as adverse events and reactions in each group at the end of the four-week intervention

period. For acceptable safety, the number in the intervention group was required not to exceed that in the control group. Thus, the study was successful if all three requirements were fulfilled, as also stated in the statistical analysis plan.

As exploratory clinical outcomes, we registered any suspected unexpected serious adverse reactions and measured the Coma Recovery Scale-Revised, Early Functional Ability Scale and Functional Independence Measure. All exploratory clinical outcomes were assessed at baseline, and after four weeks, three months, and one year.

If patients were transferred to other departments within the hospital, they were followed up until one year after the original injury.

Statistical analysis

We estimated the trial power pragmatically to include 60 participants[13]. However, we did not reach this number, resulting in an inadvertently lower power for our trial.

Continuous baseline characteristics are presented as either means and standard deviations (SD) for normally distributed data or medians and interquartile ranges (IQR) for non-normally distributed data. Ordinal variables are presented as medians and interquartile ranges. Discrete variables are presented as frequencies, proportions, and percentages.

The ratio of the two feasibility outcomes was calculated as Wilsons interval, and Jeffreys interval with a 95% confidence interval (95% CI) as these are recommended for proportions from small populations [15]. The Jeffrey interval is based on a Bayesian distribution of 0.5 and the Wilson interval on a normal distribution [15]. If there is a large

difference between the two, the most conservative lower confidence interval was used to determine if the trial procedure was feasible. Adverse events, serious adverse events and adverse reactions were analyzed between groups using Fisher's exact test. We did not use the originally planned logistic regressions analysis due to splitting in data and a high proportion of participants with one or more events. A descriptive analysis of the most common serious adverse events and adverse events not considered serious are presented as frequencies and percentages by each group.

For the exploratory outcomes, the analysis was primarily intention-to-treat using the van Elteren's test for non-normally distributed data, stratified for GCS. As a sensitivity analysis, we did a per-protocol analysis using the participants in the early orthostatic exercise group that completed at least 60% of the intended interventions. Trial Sequential Analysis was used to quantify the reliability of the statistical analysis and determine the required information sizes (Trial Sequential Analysis. Copenhagen Trial Unit, 2011)[16–18]. All statistical analyses were carried out in Stata 15 (StataCorp, TX, USA).

Results

During the intervention period, 50 patients were eligible to be included in the trial. Three declined to participate; for 47 patients, the next of kin provided informed consent. This gave a consent proportion of 94% (95% CI 84% to 98%). Nine of the 47 patients were not able to be included due to improvement in neurological status (n=5), death (n=1), cessation of active care (n=1), continuous unstable intracranial pressure (n=1) between the time of consent and randomization, or fractures discovered after consent

was given (n=1) (**Figure 1**). Therefore, 38 participants were included with a mean (SD) delay of 13 (5) days after injury (19 participants in the intervention group and 19 in the standard care group) (**Table 1**). Thus, 76% of all eligible patients eventually participated in the study (95% CI 63% to 86%) (**Table 2**).

Of the 19 participants in the early orthostatic intervention group, 14 (74% [95% CI 51.6% to 89.2%], Jeffreys interval) participants received at least 60% of the intended exercise sessions (**Table 2**).

Of the 38 included participants, four were transferred out of the participating hospital within the four-week intervention period (critical care units, rehabilitation units or psychiatric wards) to hospitals that were not participating in the trial; they were lost to follow-up. Furthermore, two participants died, and another two participants had their active care stopped due to an expected poor prognosis. None of the participants withdrew their consent to participate during the trial period.

In the intervention group, a total of 203 exercise sessions were completed corresponding to an average of 11 sessions per patient (**Table 2**). We observed 2 (median; IQR, 0 to 3) orthostatic reactions per patient during all exercise sessions. Eight of the 19 participants experienced no orthostatic reactions.

During the four-week intervention period, we registered 202 adverse events or reactions, with 46 determined to be serious adverse events and seven categorized as adverse reactions during the tilt-table intervention or test. **Table 3** shows the distribution of adverse events and reactions in the two groups. For a complete list of serious and non-serious adverse events, please refer to **Supplementary Table 3**. We found no statistically significant difference between participants in the two groups

experiencing at least one adverse event, serious adverse event, or an adverse reaction (**Table 3**). There were no serious adverse reactions during the study period.

The Trial Sequential Analysis on serious adverse events and adverse events showed that a required information size of 628 and 243 participants would be needed to reach the required information size, respectively (**Supplementary figure 1A and B**). The risk of serious adverse events and adverse events in the intervention group did not differ from that of the control group; the confidence interval for the relative risk of the intervention group ranged from 0.2 to 5.7 for serious adverse events and from 0.5 to 2.0 for adverse events, respectively, as calculated using diversity-adjusted Trial Sequential Analysis.

Exploratory outcomes

No suspected unexpected serious adverse reactions were registered during the trial.

After four weeks, there was a trend towards less functional improvement for the intervention group (end of intervention) (Coma Recovery Scale-Revised median score, 13 (IQR 7 to 9) points) compared to the control group (21 (IQR 14 to 23) points) (P = 0.07) (**Figure 2**). At three months, the intervention group had an Early Functional Ability score of 84 (IQR 55 to 93) points compared to the control group (96 (IQR: 44 to 98) points) ((P=0.24). Also, at three months, the intervention group achieved a Functional Independence Measure score (median 36 [IQR 20 to 88] points) that did not differ compared to the control group (median 68 [IQR 18 to 116] points) (P=0.19). The Glasgow Outcome Scale Extended at one-year follow-up showed no between-group differences (**Supplementary Table 1**). Per protocol analysis (participants with more

than 60% completed exercises) showed no difference in any of the outcomes (**Supplementary Table 2**).

Diversity-adjusted Trial Sequential Analysis of data from the Coma Recovery Scale-Revised at four weeks suggested that 266 participants with severe traumatic brain injury were needed to reach the required information size. As Trial Sequential Analysis can assess a more realistic CI, a mean difference of 1.1 points was found between groups, and the Trial Sequential Analysis-adjusted CI showed a range from -16.0 to 24.4 points (**Supplementary Figure 1C**). In contrast, it was not possible to carry out Trial Sequential Analysis on Early Functional Ability scale or Functional Independence Measure because of too little information and a large variance in the data.

Discussion

To our knowledge, this is the first trial investigating both feasibility, safety, and clinical outcomes from early orthostatic exercise in participants with severe traumatic brain injury. We managed to deliver 74% of the intended interventions with the lower confidence limit at 51.6%. The trial was accepted by relatives to the participants at a high percentage (94%), and 76% were randomized. We found no differences between groups with respect to adverse events or reactions.

The lower confidence limits of the feasibility outcomes may inform future trials on what to expect regarding inclusion rate and successful delivery of exercises. A lower boundary in future trials of successfully delivered interventions down to 50% may not be an acceptable rate. In the present study, the main reason for not completing exercises was patient transfer to departments that were not included in the study. This challenge obviously depends on how healthcare is organized in the catchment area; similar studies may benefit from careful preceding analysis of patient flow and contingency planning to ensure a high patient retention rate, which not only is critical to the resulting power of the study but also helps avoid attrition bias.

The present trial suggests that early head-up mobilization does not increase the risk of harm. This may be at odds with the largest trial so far on mobilization of patients with acute stroke (N=2,104), which found that early mobilization decreased the odds ratio of reaching a favorable outcome (OR 0.73; 95% CI 0.59 to 0.90)[19], although a prespecified dose-response analysis showed an improved outcome after three months if participants initiated early rehabilitation with higher frequency but shorter duration of sessions[20]. Nonetheless, these patients are not immediately comparable with the patients included in the present study, as the latter were, in general, deeply sedated

for many days before undergoing mobilization; in the former study, patients were generally not sedated and started mobilization within the first few 24 hours.

Apart from this study, trials investigating early mobilization in participants with acute brain injury have generally reported diverting results. A previous pilot study on patients with acute brain injury (stroke, traumatic brain injury, etc.) mobilized participants 12 (mean; SD: 7) days after injury using the same technique[21]. The authors included 20 participants in both the intervention and the control group and reported no adverse events; five participants in the intervention group and four in the control group died[21]. The study found a significant beneficial effect of early mobilization on the Coma Recovery Scale-Revised and the Disability Rating Scale after one month and approximately four months[21]. A quasi-randomized study of 61 patients with traumatic brain injury also reported a clinical benefit of starting mobilization in the intensive care unit, although selection bias cannot be ruled out[22]. Finally, two trials focusing on early mobilization conducted in the intensive care unit showed improved functional outcome at hospital discharge[2,23], albeit only a few of these participants had a traumatic brain injury. Although at first sight the findings of these smaller studies differ from that of the present study, these as well as the present trial should be considered underpowered to draw any conclusion on effectiveness. Thus, the Trial Sequential Analysis in the present study of patients with traumatic brain injury indicated that a total number of up to 600 participants would be needed for firm conclusions on harms or benefits from early mobilization. A systematic review of the benefits and harms may be a logical next step to guide clinicians and inform future trials on early mobilization. We have made a protocol publicly available for such a review (PROSPERO: CRD42018088790).

The present trial has several limitations. We did not reach the desired number of participants as recruitment was stopped at the end of the planned inclusion period (two years). The recruitment rate was lower than expected, which could be partly explained using rather narrow limits for the Glasgow Coma Scale at the time of inclusion. At any rate, the sample size estimate was pragmatic. Furthermore, patients in the intervention group tended to be older than those in the control group; because lower age is associated with better outcome[24], this may have skewed the data towards more favorable outcomes in the control group. In addition, our control group was mobilized earlier than the intervention group, although this was not significantly different. This could be an expression of a more stable condition in the control group as we used the intracranial pressure measurements as an indicator for when to initiate the intervention. There was a large amount of missing data on the clinical outcome, which was mostly due to death or transfer to other departments. We elected not to use multiple imputation in the exploratory outcomes, as we consider these results as hypothesis-generating only. Finally, as tools for functional outcome assessment, we elected to use the Coma Recovery Scale-Revised, The Early Functional Ability scale and the Functional Independence Measure; although remote scoring could be considered for patients that were transferred out of participating hospitals, such scores were deemed insufficient as they would provide only a rough estimate of the patient's ability to function independently. While the Coma Recovery Scale-Revised seems only useful for measuring shorter-term outcomes (four weeks), the Early Functional Abilities Scale and the Functional Independence Measure measured changes at three months without reaching a maximum score limit.

Conclusion

Early orthostatic exercise is feasible in participants with severe traumatic brain injury. Larger randomized clinical trials are needed to analyze potential benefits and harms of such an intervention.

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Declaration of conflicting interests

The authors have no conflicts of interest to declare.

Author contributions

CGR, JM, KM and CG designed the trial. CGR, MHO and CBS collected the data, and CGR, CO and JCJ analyzed the data under the supervision of CG. All authors were

involved in the interpretation of the results. CGR drafted the manuscript and all authors revised it critically. The manuscript was approved by all the authors.

Availability of data and materials

The datasets analyzed during the current study are not publicly available due to the small sample size but are available from the corresponding author on reasonable request.

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Table 1. Baseline characteristics of included participants

	Early orthostatic exercise (n=19)	Standard care group (n=19)
Age (years) – median (IQR)	49.0 (31.0 to 63.0)	37.0 (27.0 to 54.0)
Male – n (%)	13 (68%)	14 (74%)
Brain injury (initial CT-scan) – n (%)		
Traumatic subarachnoid hematoma	10 (53%)	17 (89%)
Acute subdural hematoma	14 (74%)	17 (89%)
Chronic subdural hematoma	1 (5%)	2 (11%)
Epidural hematoma	3 (16%)	3 (16%)
Intraventricular hematoma	10 (53%)	3 (16%)
Contusion	12 (63%)	11 (58%)
Mechanism of injury – n (%)		
Traffic	7 (37%)	9 (47%)
Fall	8 (42%)	6 (32%)
Blunt force	1 (5%)	4 (21%)
Suicide attempt	2 (11%)	-
Unknown	1 (5%)	-
Secondary injury – n (%)		
1 fracture of extremities or trunk	4 (21%)	4 (21%)
> 1 fracture of extremities or trunk	6 (32%)	4 (21%)
No fractures	9 (47%)	11 (58%)
Comorbidities – n (%)		
Diabetes (type II)	1 (5%)	-
Pulmonary heart disease	1 (5%)	-
Hypertension	-	1 (5%)
Schizophrenia	2 (11%)	-
Chronic obstructive lung disease	1 (5%)	1 (5%)
Atrial fibrillation	1 (5%)	1 (5%)
None	16 (84%)	17 (95%)
Neurosurgical procedures performed – n (%)		

Evacuation of hematoma	8 (42%)	7 (37%)
Craniotomy	9 (47%)	9 (47%)
Craniectomy	4 (21%)	6 (32%)
External ventricular drain	13 (68%)	14 (74%)
Ventriculoperitoneal shunt	3 (16%)	1 (5%)
First measured GCS – median (IQR)	6 (3 to 9)	6 (3 to 9)
GCS at inclusion - n (%)	6.0 (4.0 to 7.0)	6.0 (4.0 to 9.0)
Low GCS (3 to 6)	10 (53%)	10 (53%)
High GCS (7 to 10)	9 (47%)	9 (47%)
Sedated at randomization – n (%)	6 (32%)	6 (32%)
RASS– median (IQR)	-3 (-4 to -3)	-5 (-5 to -3)
Days from injury to randomization – median (IQR)	15 (11 to 16)	10 (7 to 14)
Days to first mobilization - median (IQR)	15 (11 to 16)	12 (10 to 18)*
Days at the Neuro Critical Care Unit – median (IQR)	32 (22 to 40)	25 (18 to 34)
Days at the RU – median (IQR)	72 (37 to 99)	67 (46 to 79)
End of PTA (days) – median (IQR)	81 (53 to 101)	67 (39 to 99)

Legend: * One patient in the standard care group never received mobilization; There were no significant differences between the groups in any of the variables; SD: Standard deviation; n: number; GCS: Glasgow coma score; IQR: Interquartile range; RASS: Richmond agitation sedation scale; RU: Rehabilitation unit; PTA: Posttraumatic amnesia;

Table 2. Feasibility outcome

	n/N (% [95% CI]) *(Wilson intervals)*	n/N (% [95% CI]) *(Jeffreys interval)*
Included patients	38/50 (76.0% [62.6 to 85.7%])	38/50 (76.0% [62.9 to 86.2%])
Patients with >60% completed exercises	14/19 (73.7% [51.2 to 88.2%])	14/19 (73.7% [51.6 to 89.2%])
	Early orthostatic exercise (n=19)	Standard care group (n=19)
Orthostatic exercise sessions – mean (±SD)	10.7 (5.9)	-
Additional mobilizations – median (IQR)*	3 (0 to 9)	8 (3 to 16)
Additional mobilizations by nurses - median (IQR) †	0 (0;0)	0 (0;1)

Legend: *In the standard care group, two patients had more than 70 mobilizations during the intervention period. † In the standard care group, five patients were mobilized between 1 and 15 times, and in the intervention group, one patient was mobilized 9 times during the intervention period. N: All patients; 95%CI: 95% confidence interval; SD: standard deviation; IQR: interquartile range;

Table 3. Adverse events and reactions after the intervention period (4 weeks)

	Early orthostatic exercise (n=19)	Standard care group (n=19)
Number of events		
Adverse events – n (%)	73 (49)	76 (51)
Serious adverse events – n (%)	24 (52)	22 (48)
Adverse reactions – n (%)	4 (57)	3 (43)
Serious adverse reactions - n	-	-
SUSAR - n	-	-
Patients experiencing at least one		
Adverse events – n (%)	17 (89) *	17 (89)
Serious adverse events – n	14 (74) *	13 (68)
Adverse reactions – n	1 (5) †	3 (16)
Serious adverse reactions - n	-	-
SUSAR - n	-	-

Legend: n: number; SUSAR: Suspected unexpected serious adverse reaction;

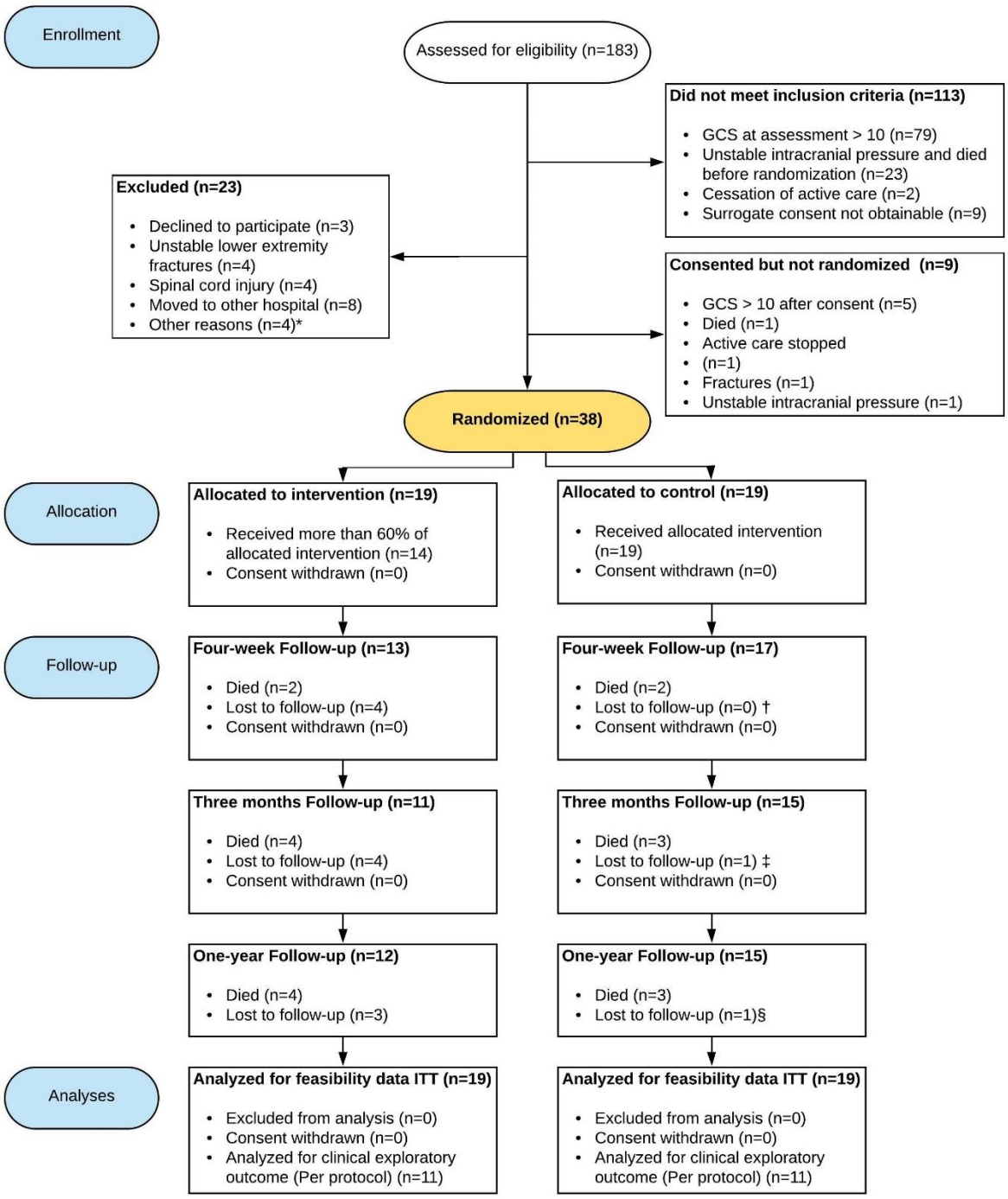
*Fisher's exact test between-group comparison P=1.000; †Fisher's exact test between-group comparison P=0.604;

Table 4. Adverse events and reactions after the intervention period (4 weeks) – Per protocol analysis

	Early orthostatic exercise (n=14)	Usual care group (n=19)
Number of events		
Adverse events – n (%)	58 (43)	76 (57)
Serious adverse events – n	19 (46)	22 (54)
Adverse reactions – n	4 (57)	3 (43)
Serious adverse reactions - n	-	-
SUSAR - n	-	-
Patients experiencing at least one		
Adverse events – n (%)	13 (93%) *	17 (89%)
Serious adverse events – n	11 (79%) †	13 (68%)
Adverse reactions – n	1 (7%) ‡	3 (16%)
Serious adverse reactions - n	-	-
SUSAR - n	-	-

Legend: n: number; AE: Adverse event; SAE: Serious adverse event; AR: adverse reaction; SAR: Serious adverse reaction; SUSAR: Suspected unexpected serious adverse reaction; *Fisher's exact test between-group comparison P =1.000; †Fisher's exact test between-group comparison P = 0.698; ‡ Fisher's exact test between-group comparison P = 0.620;

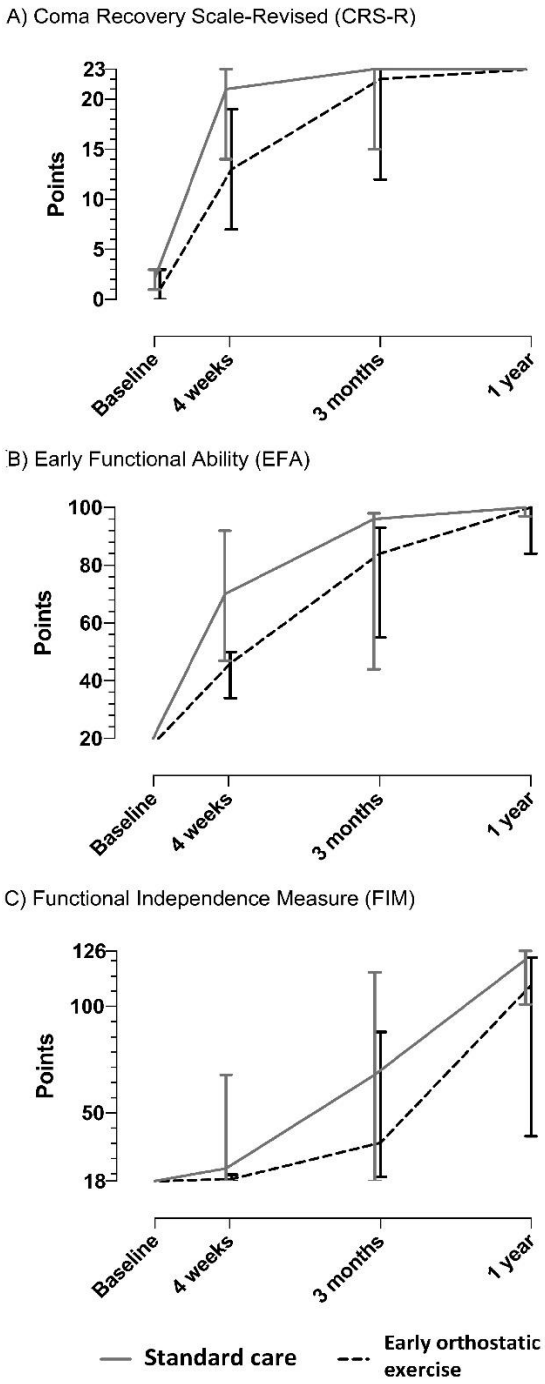
Figure 1. Flow of patients through the trial



Legend: GCS: Glasgow coma score; *Other reasons include: High frequency of dialysis, waiting for a pacemaker, obesity; †CRS-R (n=16) one patient discharged before the test; ‡ Early discharge from the rehabilitation department before

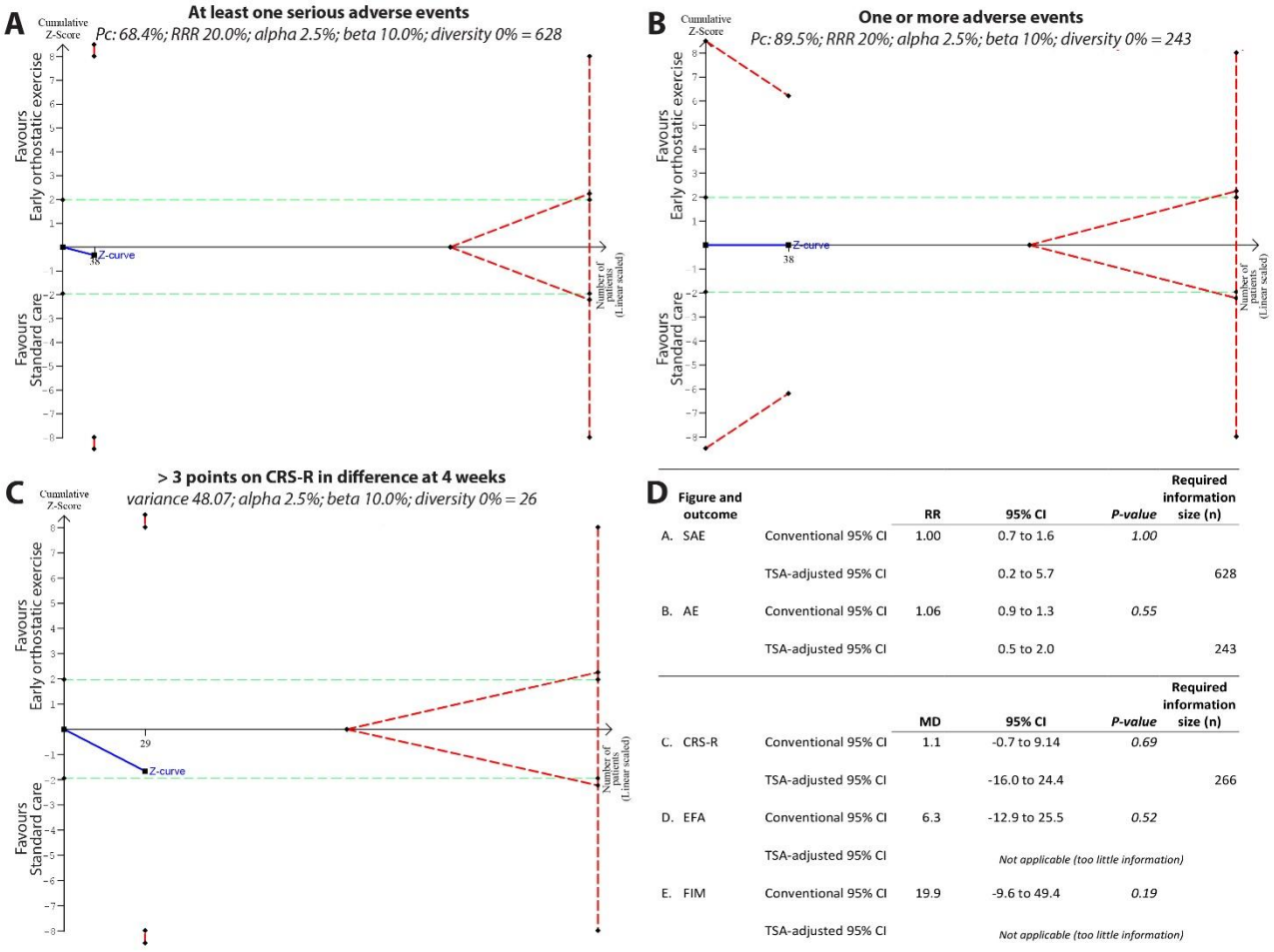
assessments (n=1); § In the intervention group one patient was not assessed with CRS-R and EFA and in the standard care group one patient was not assessed with CRS-R. Due to the nature of GOSE (one equals death), all participants were scored in the standard care group. In the intervention group, three were lost to follow-up.

Figure 2. Exploratory outcomes



Legend: The figure displays the median score (± IQR) obtained within the two treatment groups at baseline, after 4 weeks, 3 months and, one-year (raw data is presented in **Supplementary Table 1**).

Supplementary figure 1. Trial Sequential Analysis.



D

Figure and outcome		RR	95% CI	*P-value*	Required information size (n)
A. SAE	Conventional 95% CI	1.00	0.7 to 1.6	*1.00*	
	TSA-adjusted 95% CI		0.2 to 5.7		628
B. AE	Conventional 95% CI	1.06	0.9 to 1.3	*0.55*	
	TSA-adjusted 95% CI		0.5 to 2.0		243

		MD	95% CI	*P-value*	Required information size (n)
C. CRS-R	Conventional 95% CI	1.1	-0.7 to 9.14	*0.69*	
	TSA-adjusted 95% CI		-16.0 to 24.4		266
D. EFA	Conventional 95% CI	6.3	-12.9 to 25.5	*0.52*	
	TSA-adjusted 95% CI		*Not applicable (too little information)*		
E. FIM	Conventional 95% CI	19.9	-9.6 to 49.4	*0.19*	
	TSA-adjusted 95% CI		*Not applicable (too little information)*		

Legend: Post-hoc Trial Sequential Analysis of the trial results after 4 weeks (SAE, AE or AR and Coma Recovery Scale-Revised). A and B: Shows that 38 participants were assessed for having at least one SAE or at least one AE during the treatment period. The required information size of 628 participants is calculated based on the incidence in the standard care group of 68.4% (A) and 243, with an incidence of 89.5% (B). A type I error of 2.5%, a beta of 10% (power of 90%), and a relative risk reduction of 20% was used. C: shows that 29 participants were tested with the CRS-R after 4 weeks. The required information size of 266 participants is calculated based on a minimal relevant mean difference of 3 points and a standard deviation of 6

points. The analysis was based on a type I error of 2.5% and a beta of 10% (power of 90%). The cumulated Z-curves (blue curve) do not cross the trial sequential boundaries (red inner sloping lines) implying that there is a risk of random error (either due to sparse data or repetitive testing) in the estimate of a beneficial effect of early orthostatic exercise compared with standard care. Furthermore, the Trial Sequential Analysis- adjusted 95% CI (E) shows a wide range for all outcomes.

Supplementary Table 1. Exploratory clinical outcome for baseline, end of the intervention, three months and one year – Intention-to-treat

	Early orthostatic exercise				Usual care group			
	Baseline	End of intervention	Three months	One-year follow-up	Baseline	End of intervention	Three months	One-year follow-up
CRS-R (N)	19	13	11	11	19	16	15	14
Median	1	13	22	23	2	21	23	23
(IQR)	(0 to 3)	(7 to 19) *	(12 to 23)	(23 to 23)	(1 to 3)	(14 to 23) *	(15 to 23)	(23 to 23)
EFA (N)	19	13	11	12	19	17	15	15
Median	20	46	84	100	20	70	96	100
(IQR)	(20 to 20)	(34 to 50)	(55 to 93) †	(84 to 100)	(20 to 20)	(47 to 92)	(44 to 98) †	(97 to 100)
FIM (N)	19	13	11	11	19	17	15	15
Median	18	19	36	110	18	24	68	122
(IQR)	(18 to 18)	(18 to 21)	(20 to 88) ‡	(39 to 123)	(18 to 18)	(18 to 68)	(18 to 116) ‡	(101 to 126)
GOSE (N)				16				19
Median				3				3
(IQR)				(1 to 5) ‡				(3 to 6) ‡

CRS-R: Coma recovery scale - revised; EFA: Early Functional Ability; FIM: Functional independence measure; GOS-E: Glasgow outcome scale - extended; N: number of participants in the analysis; IQR: Interquartile range; For analysis Van Elteren' s test have been used adjusted for stratification variable (Glasgow Coma Score high or low at randomization):
* P=0.07; † P=0.24; ‡ P=0.19;

Supplementary Table 2. Exploratory clinical outcome for baseline, end of the intervention, three months and one year – Per protocol

	Early orthostatic exercise				Usual care group			
	Baseline	End of intervention	Three months	One-year follow-up	Baseline	End of intervention	Three months	One-year follow-up
CRS-R (N)	14	12	9	9	19	16	15	14
Median	2	13	22	23	2	21	23	23
(IQR)	(0 to 4)	(7 to 18) *	(12 to 23)	(23 to 23)	(1 to 3)	(14 to 23) *	(15 to 23)	(23 to 23)
EFA (N)	14	12	9	10	19	17	15	15
Median	20	45	86	100	20	70	96	100
(IQR)	(20 to 20)	(34 to 52)	(56 to 93) †	(92 to 100)	(20 to 20)	(47 to 92)	(44 to 98) †	(97 to 100)
FIM (N)	14	12	9	9	19	17	15	15
Median	18	19	36	110	18	24	68	122
(IQR)	(18 to 18)	(18 to 21)	(20 to 88) ‡	(64 to 123)	(18 to 18)	(18 to 68)	(18 to 116) ‡	(101 to 126)
GOSE (N)				13				19
Median				3				3
(IQR)				(1 to 5) §				(3 to 6) §

CRS-R: Coma recovery scale - revised; EFA: Early Functional Ability; FIM: Functional independence measure; GOS-E: Glasgow outcome scale - extended; N: number of participants in the analysis; IQR: Interquartile range; For analysis Van Elteren' s test have been used adjusted for stratification variable (Glasgow Coma Score high or low at randomization): * P=0.06; † P=0.30; ‡ P=0.26; § P=0.27

Supplementary Table 3. Specification of serious adverse events and adverse events

	Early orthostatic exercise	Usual care group	Total
Serious adverse events			
Pneumonia	9	7	16
Delirium	1	4	5
Death	2	2	4
Sepsis	4	1	5
Blocked tracheal tube	2	1	3
Seizure	2	0	2
Pleural effusion	0	2	2
Ventriculitis	1	0	1
Paroxysmal sympathetic hyperactivity	0	1	1
Desaturation	1	0	1
Respiratory secretion (atelectasis)	1	0	1
Urinary tract infection	0	1	1
Agitated	0	1	1
Other infections	0	1	1
Progression of subdural hematoma	0	1	1
Sudden high intracranial pressure	1	0	1
Total	**24**	**22**	**46**
Adverse events not considered serious	**Early orthostatic exercise**	**Usual care group**	**Total**
Removal of nasogastric tube	6	7	13
Pressure ulcer	6	3	9
Urinary tract infection	3	5	8
Vomiting	3	5	8
Other infections	3	5	8
Paroxysmal sympathetic hyperactivity	3	3	6
Withdrawal symptoms	5	1	6
Anemia	2	3	5
Diarrhea	2	3	5
Oral mycosis	2	2	4
Wounds	3	1	4
Hyponatremia	1	3	4
Hypokalemia	3	1	4
Fall	1	2	3

Tachycardia	1	2	3
Confusion	3	0	3
Conjunctivitis	2	1	3
Bleeding from a surgical wound	1	2	3
Blocked tracheal tube	0	2	2
Ventriculitis	0	2	2
Removal of venous or arterial catheter	0	2	2
Restless	0	2	2
Hypertension	2	0	2
hypercapnia	1	1	2
Hypernatremia	1	1	2
Hyperkalemia	2	0	2
Rash	0	2	2
Tongue biting	1	1	2
Desaturation	0	1	1
Respiratory secretion (atelectasis)	1	0	1
Hypotension	0	1	1
Agitated	0	1	1
Removal of wound dressing	0	1	1
Calf pain	0	1	1
Bleeding urethra	1	0	1
Removal of tracheotomy	1	0	1
Alkalosis	1	0	1
Hypermagnesemia	1	0	1
Hyperglycemia	1	0	1
Subcutaneous emphysema	0	1	1
Heart murmur	0	1	1
Displacement of fracture	0	1	1
Epidermolysis arm	0	1	1
Fever without origin	0	1	1
Increased saliva	0	1	1
Obstipation	0	1	1
Sleep apnea	0	1	1
Gastrointestinal bleeding	0	1	1
Acute Tubulointerstitial Nephropathy	1	0	1
Thrombocytosis	1	0	1
broken tooth	1	0	1
Loose external ventricular drain screw	1	0	1
Dysfunctional arterial catheter	1	0	1
Distended anal sphincter	1	0	1

Pancreatitis	1	0	1
Nose bleeding	1	0	1
Hematoma lower extremity	1	0	1
Joint swelling	1	0	1
Total	**73**	**76**	**149**

Supplementary material (Statistical analysis)

Retrospective changes to the dataset

Post-hoc changes in the dataset after blinded assessors had gone through medical records.

- Patient 3 was diagnosed with sepsis which initially was categorized as an adverse event not considered serious. This was changed to a serious adverse event.
- Patient 5, 8 and 28 had a missing SAE as they were moved from the department and died afterwards all within the 4-week period. One SAE was added to each patient.
- Patient 24 was diagnosed with pneumonia which initially was categorized as an adverse event not considered serious. This was changed to a serious adverse event.

Statistical analysis workflow

First version of the statistical analysis plan was submitted to Trials on the 20th March 2019, the second version on 14th of June 2019 and the third on 23rd of December 2019. Alas, the statistical analysis plan was rejected for publication. Since March 2019 it has been given a digital object identifying (DOI) number (10.21203/rs.2.468/v3). The last 3 months follow-up was gathered on the 28th of March 2019 and the last one-year follow-up on the 10th of November 2019. The first data analysis of the feasibility outcomes and the exploratory clinical outcomes (including the 3-month follow-up) was done on the 7th of May 2019. Final analysis of data including the one-year follow-up was done on the 28th of January 2020. On the 28th of February a meeting was held between the primary Investigator and the two statistical analysts (JCJ and CO), where differences in the methods used in the analysis was resolved and agreement on relevant changes to the dataset was made (see section on "Retrospective changes to the dataset").

Final and published analysis were made on the 10th of March 2020 by CO (approved by JCJ).

Comments to statistical analysis reports

The original plan to do logistic regression or regression and further imputation of missing data was done according to our statistical analysis plan by CO. JCJ was uncertain that the analysis would be valid due to the missing data and low numbers (patients with no adverse events), risk of splitting in the data and, therefore, used a Fischer's exact test for testing differences between groups. This was accepted at the meeting on the 28th of February 2020. The imputation of data was likewise discussed by the group, since CO had followed the statistical analysis plan and made imputations as worst case and best case and JCJ found that these imputations were not fair to the data. First edition of the analysis by both statisticians can be found below.

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	5-6
	2b	Specific objectives or research questions for pilot trial	6
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
	4c	How participants were identified and consented	6-7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	8-9
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	9
Sample size	7a	Rationale for numbers in the pilot trial	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7-8
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	11 and Figure 1.
	13b	For each group, losses and exclusions after randomisation, together with reasons	11 and Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the pilot trial ended or was stopped	16
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Table 2
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Table 2 and 3, supplementary tables, page 11 and 12
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Supplementary tables
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11-12 and table 3
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	16
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	15
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	17
Other information			

Registration	23	Registration number for pilot trial and name of trial registry	3
Protocol	24	Where the pilot trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17
	26	Ethical approval or approval by research review committee, confirmed with reference number	6

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Paper IV

Early head-up mobilisation versus standard care for patients with severe acquired brain injury: a systematic review with meta-analysis and Trial Sequential Analysis

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Review version: 1.0

Date: 05.05.2020

Protocol uploaded to PROSPERO: April 2018 with revision October 2018, CRD42018088790

Abstract

Background

There is increasing focus on earlier rehabilitation in patients with traumatic or hypoxic brain injury or stroke. This systematic review evaluates the benefits and harms of early head-up mobilisation versus standard care in patients with severe acquired brain injury.

Methods

We searched Medline, CENTRAL, EMBASE, CINAHL, PsycINFO, Web of Science, PEDro, and selected clinical trial registries until April 2020. Eligible randomised clinical trials compared early head-up mobilisation versus standard care in patients with severe acquired brain injury and were analysed conducting random- and fixed-effects meta-analyses and Trial Sequential Analysis (TSA). Certainty of evidence was assessed by GRADE.

Main results

We identified four randomised clinical trials (total n=385 patients) with severe acquired brain injury (stroke 86% and traumatic brain injury 13%). Two trials were at low risk and two at high risk of bias. We found no evidence for a difference in mortality or poor functional outcome neither at the end of the intervention (relative risk (RR), early mobilisation vs. standard care, 1.19, 95% CI 0.93 to 1.53; I^2 0%; low certainty) nor at maximal follow-up (RR 1.03, 95% CI 0.89 to 1.21; I^2 0%; low certainty). We found evidence against an effect on quality of life at maximal follow-up. The proportion of patients with at least one serious adverse event did not differ at end of intervention or at maximal follow-up. For most comparisons, TSA suggested that further trials are needed.

Conclusions

We found no evidence of a difference between early mobilisation compared with standard care for patients with severe acquired brain injury regarding mortality, poor functional outcome, or

serious adverse events. Early mobilisation appeared not to exert a major impact on quality of life. This systematic review highlights the insufficient evidence in patients with severe brain injury, and no firm conclusions can be drawn from these data.

Keywords: Early mobilisation; severe acquired brain injury; severe stroke; severe traumatic brain injury; meta-analyses; Trial Sequential Analysis;

Background

Severe acquired brain injury is brain damage that occurs after birth and is unrelated to congenital or degenerative conditions [1]. The World Health Organization considers acquired brain injury a major public health problem [2]. It affects people of all ages and infers a large burden on quality of life and health economics [2]. The severity of acquired brain injury is defined in a variety of ways depending on the aetiology. Severe stroke is often defined by a National Institute of Health Stroke Scale score > 16 [3], whereas severe traumatic or anoxic brain injury is characterised by a low Glasgow Coma Score (≤ 8) [4] or for traumatic injury a post-traumatic amnesia period of more than 28 days [5–7].

During recent years, increased focus has been given to early physical intervention within many subspecialties of neurorehabilitation [5,8,9]. Early mobilisation intends to counteract the adverse effects of prolonged bed rest on primarily the cardiovascular and musculoskeletal systems, the internal organs, as well as arousal in patients with chronic disorders of consciousness [10–14]. On the other hand, concerns have been voiced that mobilising the patient head up may reduce cerebral blood flow and/or intracranial pressure, thus negatively impacting functional level [15]. These concerns were not supported by the cluster randomised trial by Anderson et al., who showed no difference in functional outcome after three months when elevating the head of the bed early to 30 degrees compared to participants lying flat in supine positioning [16].

Many clinical guidelines recommend mobilisation of patients with stroke started within the first 48 hours from ictus [17,18]. The effect of early mobilisation in patients with stroke was investigated in the AVERT II trial [19], which suggested that early mobilisation lead to earlier return to walking [20]. The subsequent AVERT III trial, however, showed less positive results [5], finding an odds ratio of a favourable outcome for early mobilisation compared with standard care as measured by the modified Rankin scale at three months of 0.73 (95% confidence interval (CI) 0.59 to 0.90) (3). However, some criticism was raised towards this trial. Thus, most of the patients were with mild rather than severe stroke, with around 40% being able to walk independently after disease onset [21]. Also, a secondary analysis of the AVERT III trial suggested another conclusion, i.e. that early but shorter and more frequent mobilisation after stroke seemed to be beneficial when controlling for stroke severity and age [22]. Importantly, such subgroup analyses should only be considered hypothesis-generating and further research is warranted [23].

Guidelines on the management of severe traumatic brain injury do not have recommendations on the use or timing of mobilisation after severe brain injury [24–26]. In a quasi-randomised study on patients with traumatic brain injury, Andelic et al. found less 12-months disability when comparing an unspecified early rehabilitation regime in the intensive care unit to delayed treatment [8]. However, such non-randomised studies are known to overestimate intervention effects [27]. The beneficial or harmful effects of early mobilisation thus remain incompletely explored in patients with severe acquired brain injury.

Objectives

This systematic review aimed to assess benefits and harms of early head-up mobilisation, with the head and torso elevated more than 50 degrees above the horizontal level, compared with standard care in patients with severe acquired brain injury.

Methods

The protocol for this systematic review was submitted to the PROSPERO-database (CRD42018088790) in April 2018 and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (**S4 Table**) [28].

Criteria for considering studies for this review

Types of studies

Randomised clinical trials aiming at evaluating benefits and harms of early head-up mobilisation regardless of language, publication date, publication type, or publication status were included. We did not directly search for quasi-randomised studies or observational studies, but such studies were included and analysed separately for the analysis of harms when encountered during our searches, as they may provide information on rare or late occurring adverse events [29]. We are aware that the decision not to search systematically for all observational studies may have biased our review towards the assessment of benefits and may overlook certain harms, such as late or rare harms.

Types of participants

We included patients with severe acquired brain injury. Broadly defined, this is an acute injury that is not caused by degenerative processes and was not present at birth. For the present systematic review, acquired brain injury was specifically defined as a direct brain injury caused by one of the following mechanisms:

- major stroke: interruption of blood supply to the brain usually caused by one or more bursting blood vessels (haemorrhagic) or because of blockage of one or more vessels (ischaemic) [30] and associated with a National Institute of Health Stroke Scale (NIHSS) score > 16 [5], *or*

- severe traumatic brain injury: injury resulting from trauma to the head and any coinciding or subsequent complications, including hypoxia, hypotension, intracranial haemorrhage, and raised intracranial pressure [6] and with a duration of post-traumatic amnesia of more than 28 days or Glasgow Coma Score < 9, or

- severe diffuse hypoxic brain injury: diffuse damage arising from trauma due to a range of other acute incidents including hypoxia (e.g. resulting from drowning, electrocution, anaesthetic accident) [6] and with a duration of post-injury amnesia of more than 28 days or Glasgow Coma Score < 9.

Types of interventions

The characteristic of the intervention of interest was defined as any intervention comparing an early intervention of head and torso mobilisation to at least 50 degrees and comparing this with a control intervention of mobilisation to less than 50 degrees.

Types of outcomes

All outcomes were assessed at the end of the intervention (as defined by the trials; primary outcome) and at the last follow-up.

Primary outcomes

- Mortality or poor functional outcome: This was defined as a poor functional outcome measured on any scale. For the modified Rankin scale (mRS), a poor functional outcome was recorded if the score was from 5 to 6, with 5 being severe disability and 6 being death. For the Disability Rating Scale (DRS), we defined poor outcome as a score from 12 to 30. The DRS has a highest score of 30 (equalling death, with 29 equalling an extreme vegetative state). Finally, for the Functional Independence Measure, we defined a poor outcome as an improvement of less than 0.5 standard deviations derived from the study data.
- Quality of life: This was defined as any variable recording quality of life continuously such as the Australian quality of life (AQoL(4D)) scale, which is a validated measure of quality of life. The score ranges from 1 (best possible quality of life) to 0 (death) to –0.04 (state worse

than death) [31]. For this review, we analysed outcome on a continuous scale using mean, standard deviation (SD) and the mean difference between the intervention groups.

- The proportion of participants with serious adverse events, defined as any untoward medical complication that resulted in death; was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability; or jeopardised the patient [32].

Secondary outcomes

- The proportion of participants with one or more adverse events not considered serious [32].
- The level of consciousness as measured by the Coma Recovery Scale-Revised [33] or other relevant scales as defined in the individual trial.

Exploratory outcomes

- Individual serious adverse events.
- Individual adverse events not considered serious.

Search methods for identification of studies

We aimed at identifying all relevant randomised clinical trials, regardless of language or publication status. Selected articles were translated if required.

All reports were uploaded to the Covidence© database for further management [34]. The Covidence© database removed duplicates and managed the selection process, risk of bias assessments, and extraction of data (please see below).

Database search: published reports

A search strategy for the Medline database was formulated and tested before the first search. The formal search was then performed in Medline (Ovid) (**see S1**) and adjusted to fit the following other databases: Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library); EMBASE (Ovid); CINAHL (EBSCO); PsycINFO; Science Citation Index Expanded on Web of Science; and PEDro. The databases were initially searched in May 2018 and then updated in April 2020. The Boolean search used MeSH terms relating to the condition and the intervention. The intervention term had low specificity in our search as it was our impression that this early intervention is not specifically mentioned in the literature. We used a modified version of the Cochrane sensitivity-maximising clinical trial filter in the Medline search and adopted it to the other databases except for CENTRAL. We did not use any other limitations in our search.

Database search: Unpublished or ongoing studies

We searched for ongoing and un-identified trials on Google Scholar; Database on Research in Stroke (DORIS); The Turning Research into Practice (TRIP) Database; ClinicalTrials.gov; EU Clinical Trial Register; Chinese Clinical Trial Registry (ChiCTR); International Standard Randomised Controlled Trial Number (ISRCTN) registry; Pan African Clinical Trials Registry (PACTR); Australian

New Zealand Clinical Trials Registry (ANZCTR); Clinical Trials Registry - India (CTRI); and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal.

The references of included trials were screened to identify further trials of interest.

Data collection and analysis

Selection of studies

All titles and abstracts were screened by VW and either CGR or JM, using the above-mentioned inclusion criteria. Any disagreement between authors was solved by discussion; if any uncertainty remained, the study was included for full-text assessment. Full-text papers were obtained and read by CGR and VW independently; clinical trials to be included were identified based on study type, types of participants and intervention, and intervention. The studies were then classified as either eligible, not eligible, or uncertain. Studies that both authors had classified as not eligible were excluded and studies classified as eligible were included. Studies classified as uncertain were discussed between CGR and VW, and additional information was retrieved from corresponding authors of the trials. If individual patient data were not already made available, the corresponding authors were asked to supply data for data extraction for those patients with severe brain injury as defined in our inclusion criteria. Multiple publications on the same trial were analysed as one trial.

Data extraction and management

All data extraction was done independently by CGR and VW using a standardised data-extraction checklist set-up in Covidence©. CGR is the first author of one included trial [35]. Therefore, data extraction of this trial was assessed by VW and JL.

We extracted the following data:

- General information: publication status, title, authors' names, source, country, contact address, language of publication, year of publication, duplicate publication; trial characteristics: design and setting.
- Interventions: type of intervention used for mobilisation, dose, duration, type of control intervention; participants: inclusion and exclusion criteria, number of participants randomised in intervention and control groups, participant demographics such as sex and age, and baseline characteristics for patients relevant for subgroup analysis.
- Outcomes: number of patients analysed for each outcome. For details, please see the primary and secondary outcome measures section above.
- Risk of bias: please see the risk of bias (quality) assessment below.
- Data relevant for subgroup and sensitivity analyses; for details, please see "Subgroup analysis and investigation of heterogeneity" below.

After data extraction, the Covidence© extraction form was compared by the two authors to ensure detailed and correct extraction. Subsequently, all information was transferred from Covidence© to Review Manager [36].

Assessment of risk of bias in included studies

Two authors (CGR and VW) assessed all included studies using the Risk of Bias tool ver. 1.0 from The Cochrane Collaboration [37]. CGR is the first author of one included trial [35]. Therefore, the risk of bias of this trial was assessed by VW and JL. We evaluated the following study characteristics: random sequence generation, allocation concealment, blinding of participants and treatment providers, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. Furthermore, the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' were assessed for each outcome result. Finally, the overall risk of bias assessment was dichotomised into high (high or unclear) or low.

Measures of treatment effect

Treatment effects were analysed using the statistical programs Review Manager 5 [36], SAS/STAT software [38], and Trial Sequential Analysis (TSA) [39]. For the primary outcomes and non-serious adverse events, data was dichotomised and analysed as the relative risk (RR) with 95% CI. Individual events reported was presented with a RR and 95% CI. If no event existed for one of the groups a risk difference (RD) and 95% CI was presented. All serious adverse events were reported. As different outcomes measures were used in different trials, we chose to dichotomize these scales and to classify outcomes as either "good" or "poor" (please refer to "Types of outcome measures" section). Level of consciousness was analysed as a continuous outcome using mean difference and minimal clinically relevant differences of 0.5 standard deviations calculated from the observed variance of the trials. The meta-analysis was conducted using random-effects and

fixed-effects models (as sensitivity analysis); the most conservative result was reported, using a *P*-value for the primary outcomes of 2.5% as significant [40].

Trial Sequential Analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and/or multiple testing of accumulating data [37,41–46]. TSA can be applied to control for random errors and assess the risks of imprecision (http://www.ctu.dk/tsa/)[39,40,47]. Similar to a sample size calculation in a randomised clinical trial, TSA calculates the required information size or meta-analytic sample size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect reliably) to control random errors [46,48]. The required information size for a dichotomous outcome takes into account the event proportion in the control group, the assumption of a plausible risk ratio (RR) reduction, and the heterogeneity of the meta-analysis [48,49]. TSA with Lan-DeMets' stopping boundaries enables testing for significance to be conducted each time a new trial is included in the meta-analysis. Based on the required information size, trial sequential monitoring boundaries can be constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size [45,46]. Firm evidence for benefit or harm may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, in which case further trials may turn out to be superfluous. In contrast, if the boundary is not surpassed, one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with TSA. This occurs when the cumulative Z score crosses the trial sequential monitoring boundaries for futility.

For dichotomous outcomes, we estimated the required information size based on the proportion of patients with an outcome in the control group, a relative risk reduction (RRR) of 20%, an alpha of 2.5% for primary outcomes and 3.33% for secondary outcomes, a beta of 10%, and the variance suggested by the trials in a random-effects meta-analysis (diversity-adjusted required information size) [40,48,50]. Additionally, we calculated diversity-adjusted TSA CI. In case there was some evidence of the effect of the intervention, a supplementary TSA was planned based on an anticipated intervention effect equal to the limit of the CI closest to 1.00 [40].

For continuous outcomes, we were unable to identify valid previous data on effect sizes on quality of life, so we chose SD/2 as the anticipated intervention effect [51]. Hence, we estimated the required information size based on the SD observed in the control group of trials at low risk of bias or lower risk of bias and a minimal relevant difference of the observed SD/2, an alpha value of 2.5% for primary outcomes and 3.33% for secondary outcomes, a beta of 10%, and the variance suggested by the trials in a random-effects meta-analysis (diversity-adjusted required information size) [40,48]. Additionally, we calculated the diversity-adjusted TSA CI. In case there was evidence of the effect of the intervention, a supplementary TSA was planned to be used based on an anticipated intervention effect equal to the limit of the CI closest to 0.00 [40].

Assessment of heterogeneity

The statistical heterogeneity was examined between trials using the I^2 statistic. Considerable heterogeneity was defined as an I^2 between 75% and 100%, substantial heterogeneity between

50% and 90%, moderate heterogeneity between 30% and 60%, and no or low heterogeneity (might not be important) between 0% and 40% [37].

Subgroup analysis and investigation of heterogeneity

We categorised the results of included studies according to the following considerations:

Methodological

- Trials at low risk of bias compared to trials at high risk of bias.

Clinical

- Type of injury (stroke patients, traumatic brain injury, or diffuse acquired hypoxic brain injury).
- Type of mobilisation intervention used (tilt-table intervention compared to other experimental interventions).
- Duration of the intervention period (studies with long duration were defined as those with a duration above the median time and were compared to those with a duration below the median time).
- Intensity of the intervention (studies with high intensity were defined as those with an exercise duration of more than one hour per day and were compared to those with a duration of one hour or less per day).
- Frequency of the intervention (studies with a high intensity frequency were defined as those with four or more intervention sessions per day during the intervention period and were compared to those with three or less sessions per day).

- Timing of the intervention (studies in which the intervention was started earlier than 48 hours after brain injury, compared to those in which it was started later than 48 hours after the brain injury).

GRADE

A summary of findings table was produced summarising the results of the trials at overall low risk of bias and for all trials, separately. The quality of the available evidence was downgraded if the risk of bias evaluation found evidence of publication bias, heterogeneity, imprecision, or indirectness (e.g. surrogate outcomes) [52,53]. We compared the imprecision assessed according to GRADE using our plausible parameters with that of TSA (i.e. the diversity-adjusted TSA CI) [54,55].

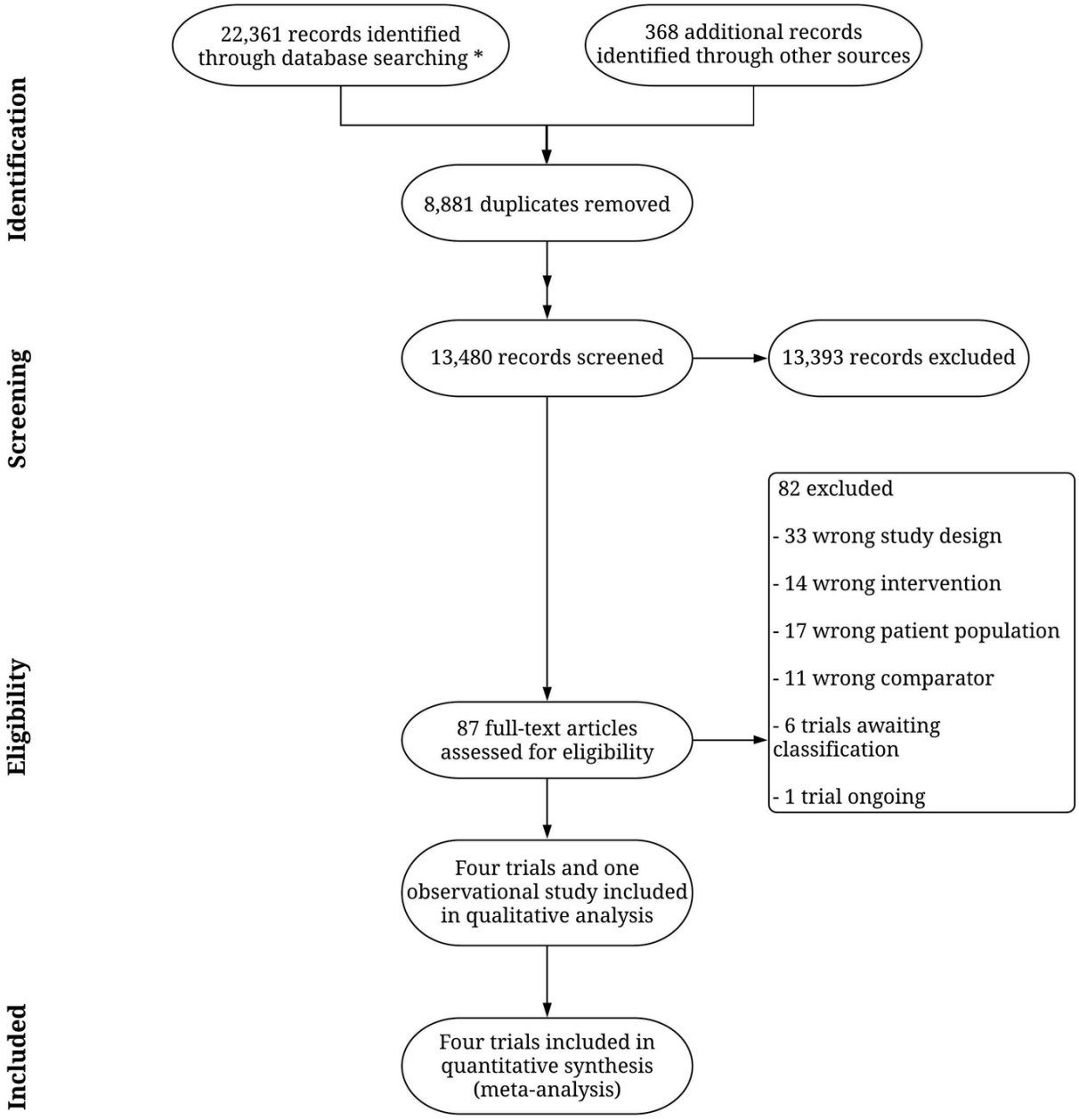
Results

Description of studies

Results of the search

After the removal of duplicates, the initial literature search revealed 13,480 records (for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, please refer to **Fig 1**). 13,393 records were excluded initially because their title or abstract indicated the study was not related to acquired brain injury or the intervention was not within the scope of the present study. Accordingly, a total of 87 full-text articles were retrieved for full-text assessment. Of these, 82 were excluded (**S2 Tabel**). One trial was still ongoing, but it was possible to include data from the trial as the data analysis was finished during the review process [35].

Fig 1. Flow chart



Study flow chart through the systematic review. *Detailed search history can be found in supplement 1 (**S1**).

Of the 87 full-text articles, 17 primary investigators were contacted to verify if their trial suited our inclusion criteria or for further extraction of patient data. Eleven trialists responded, resulting in the conclusion that six of the trials did not fit our inclusion criteria [56–61]. Six trialists and their

affiliated institutions did not respond [62–67]. Therefore, these trials are awaiting classification. We have not been able to retrieve further information from these studies to clarify the eligibility of them and they were not included in the analysis. This left four randomised trials for inclusion in the review [5,19,35,68] and one observational study [69]. Data from the latter study was retrieved from the primary investigator [66].

Included studies

We included four trials with a total of 385 participants [5,19,35,68] (**Table 1**). The included patients had a severe traumatic brain injury (n=50), severe anoxic brain injury (n=3), severe other brain injury (n=1), or severe stroke (n=331). In total, patients with stroke represented 86% of the population in this review. One trial from the latter category was much larger than the remaining trials (n=291) [5]. One trial only included patients with severe traumatic brain injury [35]. These two trials had a maximal follow-up of three months [5] and one-year [19]. The trial including patients with traumatic brain injury had a maximal follow-up of one year [35] and the last trial had a maximal follow-up of approximately 4 to 5 months [68].

Table 1. Characteristics of included randomised clinical trials

Trial	**AVERT II**	**AVERT III**	**Frazzitta et al.**	**Riberholt et al.**
Year	2008	2015	2016	2018
Trial characteristics	RCT	RCT	RCT	RCT
Number of trial sites	2	56	1	1
Intervention used	Out of bed mobilisation	Out of bed mobilisation	Erigo tilt table	Erigo tilt table
Criteria for inclusion	> 18 years. First or recurrent stroke	> 18 years. First or recurrent stroke.	> 18 years. GCS ≤ 8 for ≥ 24h from the event.	> 18 years. GCS < 11 at inclusion.

	Admitted within 24 hours of symptom. Able to react to verbal commands (but did not need to be fully alert). Systolic blood pressure between 120 and 220 mmHg, Oxygen saturation >92%. Heart rate between 40 and 100 beats per minute Temperature 38.5°C.	Admitted within 24 hours of symptom. Treatment with rtPA was allowed.	VS or MCS on third day after injury. Arterial O2 pressure/O2 flux ratio ≥ 250. Stable hemodynamic	Tentative diagnose of prolonged VS or MCS. No fractures in lower extremities. Intracranial pressure < 20 mmHg for 24 hours
Population	Stroke (n=4 haemorrhagic)	Stroke (n=35 haemorrhagic)	Stroke (n=22, 20 haemorrhagic), traumatic brain injury (14), anoxic brain injury (3)	Traumatic brain injury
Participants				
Early mobilisation				
Number of participants	10	147	20	19
Age	78 (SD ±11)	77.1 (IQR: 67.7;82.3)	53 (SD ±15)	47.8 (18.1)
Sex (male)	5	83	9	13
First stroke or head injury	5	129	Not reported	19
Severity	NIHSS 22 (IQR: 19 to 23)	NIHSS 20 (IQR: 18 to 23)	GCS: 7.0 (IQR: 4 to 8)	GCS: 6 (IQR: 4 to 7)
Standard care				
Number of participants	7	144	20	19
Age	76 (±6)	74.6 (IQR: 66.6;82.1)	69 (SD±16)	41.8 (SD ±18.3)
Sex (male)	3	91	11	14
First stroke or head injury	5	115	Not reported	19
Severity	NIHSS 21 (IQR: 18 to 22)	NIHSS 21 (IQR: 18;24)	GCS: 8.5 (IQR: 6.3,10.0)	GCS: 6 (IQR: 4;9)
Interventions				
Degree of elevation	To sitting or standing (90 degrees)	To sitting or standing (90 degrees)	60 degrees	70 degrees

Dose of mobilisation in early mobilisation group	40.9 minutes (±31.2)	186 minutes (IQR: 65;375)	450 minutes (15 sessions of 30 minutes)	10.7 ±5.9 times of 20 minutes sessions
Dose of mobilisation in standard care group	12.3 minutes (±9.2)	102 minutes (IQR: 32;162)	0 minutes	0 minutes
Time to first mobilisation in early mobilisation group	21.5 hours (IQR: 16 to 27)	20 hours (IQR: 13;23)	12.4 days (SD ±7.3)	15 days (IQR: 11;16)
Time to first mobilisation in standard care group	35 hours (IQR: 20 to 95)	29 hours (IQR: 22;43)	25.1 days (SD ±11.2)	12 days (IQR: 10;18)
Outcomes				
Death	mRS	mRS	Incident reported	Incident reported as serious adverse event
Functional outcome	mRS	mRS	DRS	FIM
Quality of life	AqQoL (4D)	AQoL (4D)	Not measured	Not measured
Adverse events	Registered SAE and AE (predefined) for three months	Registered SAE and AE during intervention and IME (predefined) for three months	Registered SAE and AE during intervention	Retrospective analysis of all serious and non-serious adverse events during intervention period
Level of consciousness	Not measured	Not measured	CRS-R	CRS-R

rtPA: recombinant tissue plasminogen activator; GCS: Glasgow Coma Scale; VS: vegetative state; MCS: Minimally conscious state; IQR: inter quartile range; SD: Standard deviation; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; DRS: Disability Rating Scale; FIM: Functional Independence Measure; AQoL(4D): Assessment of quality of life (4D); SAE: Serious adverse event; AE: Adverse event not considered serious; CRS-R: Coma Recovery Scale-Revised

The intervention was categorised as either mobilisation to the edge of the bed and standing/walking [5,19], or tilt-table mobilisation [35,68]. Two trials performed early intensive mobilisation with a high daily frequency of out of bed mobility within 24 hours versus standard care [5,19]. The other two trials mobilised patients in the intervention group on a tilt table daily

starting as early as possible and performed standard mobilisation in the control group [35,68]. In the latter, the experimental intervention was applied at a later stage (mean 14 ± 6 days from injury when studies are combined).

One observational cohort study was included for analysis of harms [69].

Excluded studies

We excluded 84 studies as described in the Characteristics of excluded studies (**S2 Table**). The reasons for exclusion were that the study was not a randomised controlled or observational trial, that the intervention did not include mobilization head up to at least 50 degrees, that the comparator included head up mobilisation to at least 50 degrees (or this could not be ruled out), or that the patient population did not comprise patients with severe acute brain injury. Also, studies, with a broader defined patient population, where less than 10 of the included participants matched our inclusion criteria, were excluded.

Risk of bias in included studies

All four included trials were at risk of bias (**Fig 2 and 3**). Given the exercise nature of the intervention, it was not possible to blind participants nor the persons that delivered the intervention. Some effort at single blinding was done in the AVERT trials; thus, the patients were only informed that they were given one of two rehabilitation approaches without explaining the details of the intervention. Furthermore, all interventions were carried out behind a curtain to avoid unblinding of the remaining investigators, staff, or family [5,19]. The trial by Frazzitta et al.

[68] was registered as having an unknown risk of bias with regard to selective outcome reporting, since the trial was registered in clinicaltrials.org only after patient inclusion was completed. The trial used fixed block sizes of 4 and did not blind patients and personnel to the allocation, which increases the risk of selection bias and performance bias. Finally, differences in age and the occurrence of hypertension between the two groups could directly influence the results of the trial. The trial by Riberholt et al. [35] was at risk of bias regarding lack of blinding for the intervention both for the included patients, the staff, and for outcome assessors for some of the outcomes (functional scales). Furthermore, the study was at risk of attrition bias due to incomplete outcome data at follow-up.

Fig 2. Risk of bias assessment: review authors' judgements about each risk of bias item for each included study

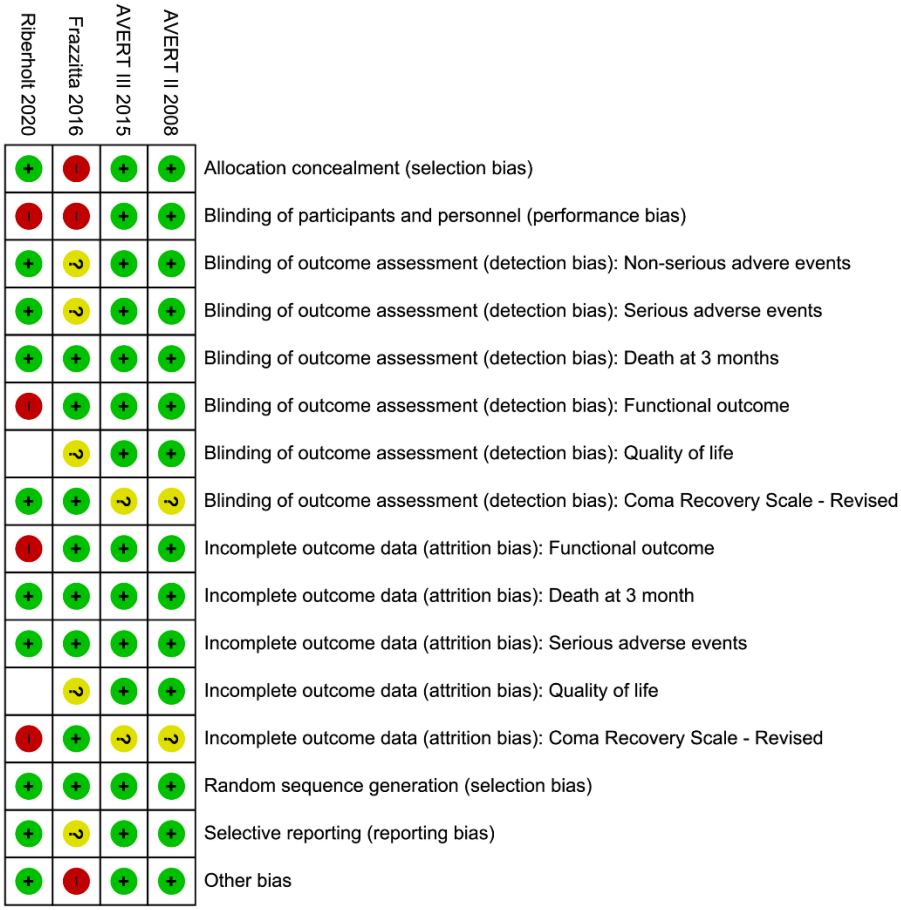


Fig 3. Risk of bias graph: review author's judgements about each risk of bias item presented as percentages across all included studies

Effects of interventions

Primary outcomes

Mortality or poor functional outcome

Three trials reported on mortality and poor functional outcome at the end of intervention [19,35,68] and all four trials reported on mortality and poor functional outcome at maximal follow-up [5,19,35,68]. At the end of the intervention, 36 (80%) patients died or had a poor functional outcome in the early mobilisation group versus 31 (67%) in the standard care group. The fixed-effect meta-analysis showed no difference between groups (RR 1.19, 95% CI 0.93 to 1.53; I^2 0%) (**Fig 4A**) and the diversity-adjusted TSA CI was between 0.43 to 3.29 [GRADE certainty LOW] (**Table 3**). The TSA showed that only 14% of the required information was accrued (**Fig 4C**). At maximal follow-up, 121 (63%) patients died or had a poor functional outcome in the early

mobilisation group compared with 114 (60%) for the standard care group. Fixed-effect meta-analysis showed no difference between the two treatment groups (RR 1.03, 95% CI 0.89 to 1.21; I^2 0%) (**Fig 5A**) and the diversity-adjusted TSA CI was 0.78 to 1.38 [GRADE certainty LOW] (**Table 3**). The accrued information size from the TSA at maximal follow-up was too small to reject a 20% RRR achieved by early mobilisation (**Fig 5C**).

Table 3. Results of Trial Sequential Analysis of early mobilisation versus standard care

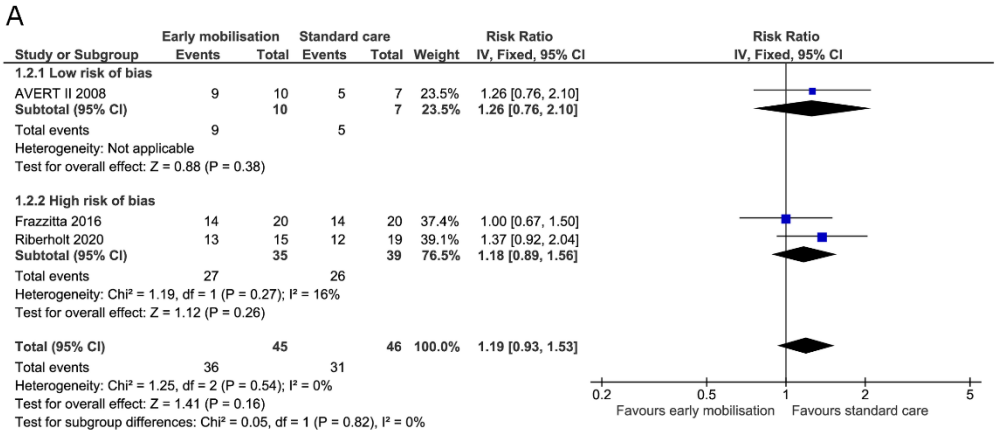
Outcome	No. of trials	Pc	RRR	MIREDIF / variance	D^2	TSARIS*	% of TSARIS obtained	TSA boundaries crossed?		TSA adjusted 95% CI
								Superiority boundaries	Futility boundaries	
Primary outcomes										
Mortality or poor functional outcome at the end of intervention	3	67.4 %	20%	NA	0%	652	14%	No	No	0.43 to 3.29
Mortality	4	17.4 %	20%	NA	0%	5415	7%	No	No	0.25 to 6.89
Poor functional outcome	4	61.5 %	20%	NA	0%	811	9%	No	No	0.32 to 4.41
Mortality or poor functional outcome at the longest follow-up	4	60.3 %	20%	NA	0%	848	45%	No	No	0.78 to 1.38
Mortality	4	26.3 %	20%	NA	0%	3242	12%	No	No	0.36 to 4.47
Poor functional outcome	4	40.3 %	20%	NA	0%	1867	14%	No	No	0.35 to 3.53
QOL at the longest follow-up	2	NA	NA	0.1 / 0.04	0%	199	105%	No	Yes	-0.2 to 0.2

Proportion of participants with at least one SAE at the end of intervention	4	35.8 %	20%	NA	0%	2115	18%	No	No	0.41 to 3.12
Proportion of participants with at least one SAE at the longest follow-up	2	48.3 %	20%	NA	0%	1308	24%	No	No	0.53 to 2.42
Secondary outcomes										
Proportion of participants with at least one AE considered to be non-serious at the end of intervention	4	41.6 %	20%	NA	0%	1574	25%	No	No	0.61 to 1.67
Proportion of participants with at least one AE considered to be non-serious at the longest follow-up	2	39.7 %	20%	NA	0%	3278	9%	No	No	0.39 to 3.20
Level of consciousness CRS-R at the end of intervention	2	NA	NA	3.9 / 60.2	80 %	766	8%	No	No	-33.6 to 33.6
Level of consciousness CRS-R at the longest follow-up	2	NA	NA	3.5 / 50.2	70 %	545	10%	No	No	-21.57 to 22.81

No: number; RRR; assumed relative risk reduction (dichotomous outcomes); Pc: proportion in control group; MIREDIF: minimal relevant difference; SD: standard deviation; D^2: diversity (squared); TSARIS: trial sequential analysis required information size; QOL: quality of life; SAE: serious adverse events; AE: adverse event. *α-level (type 1 error) of 2.5% and β-level (type 2 error) of 90% used in calculation of TSARIS.

Fig 4. Comparison of early mobilisation versus standard care – mortality or poor functional outcome at the end of the intervention

A



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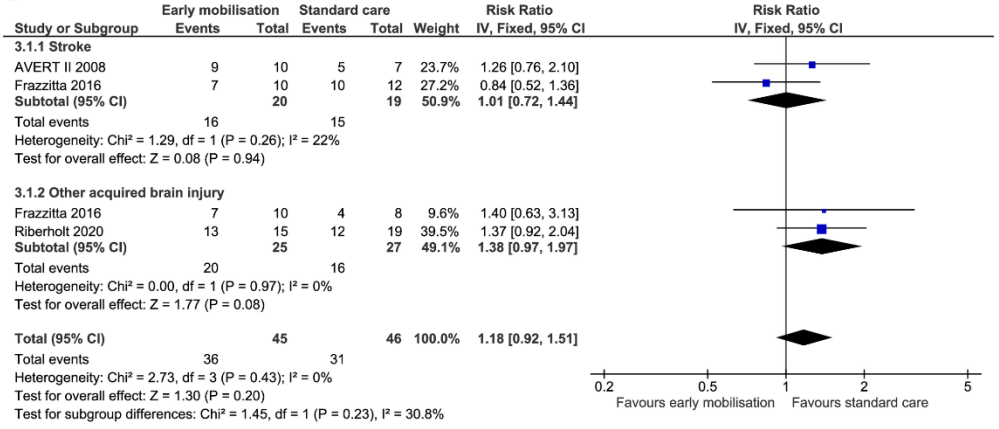

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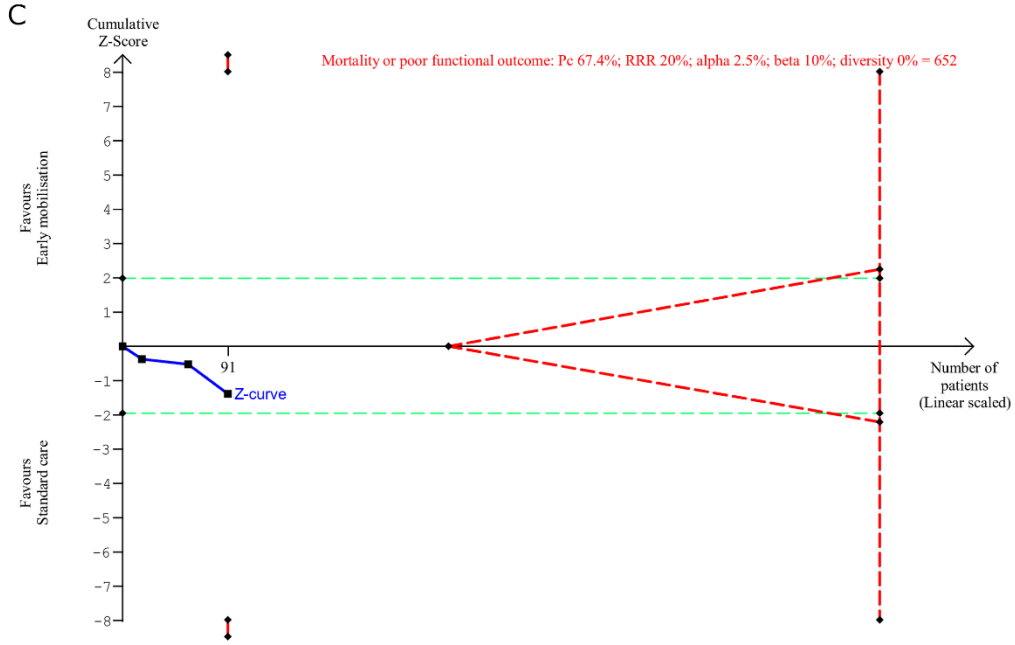
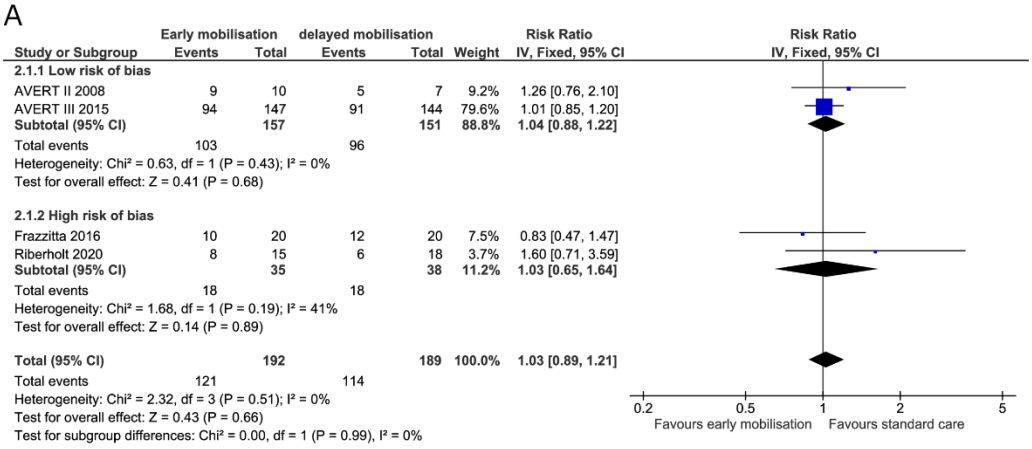


Figure 4 A and B. Forest-plots showing the results from the meta-analysis of the primary composite outcome mortality or poor functional outcome at the end of intervention with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 4 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on mortality or poor functional outcome in patients with severe acquired brain injury is based on a proportion in the control group (Pc) of 67.4%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 652 patients. The cumulative Z-curve (blue) does not pass the boundaries for benefit (upper red line), harm (lower red line), or futility (the two rightmost red lines).

Fig 5. Comparison of early mobilisation versus standard care – mortality or poor functional outcome at maximal follow-up

A



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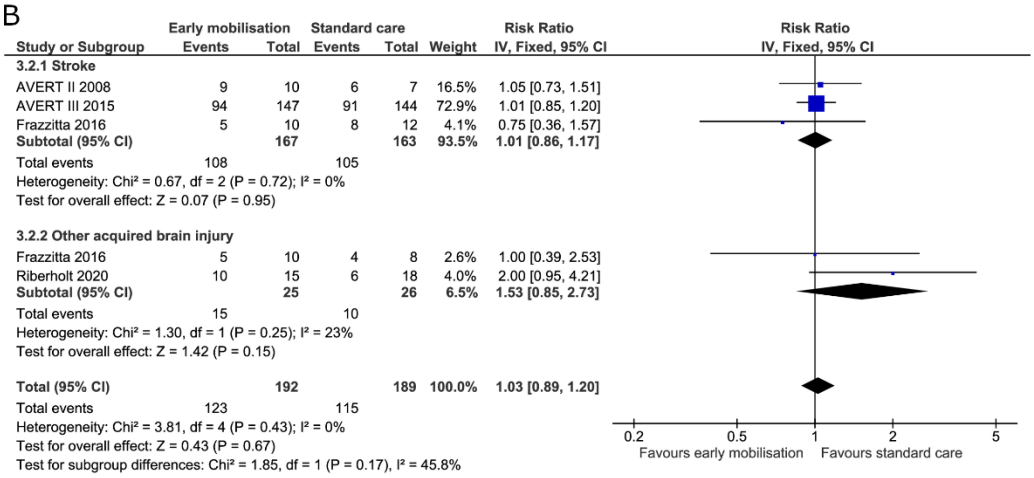

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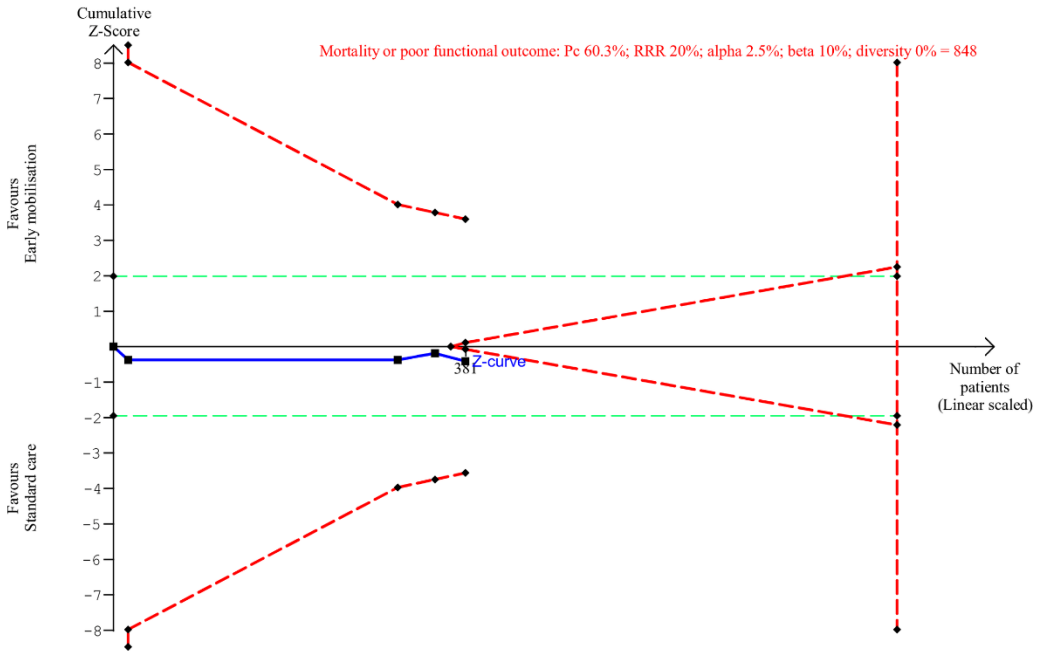


Figure 5 A and B. Forest-plots showing the results from the meta-analysis of the primary composite outcome mortality or poor functional outcome at maximal follow-up with subgroup divided according to risk of bias (A) or diagnosis (B).

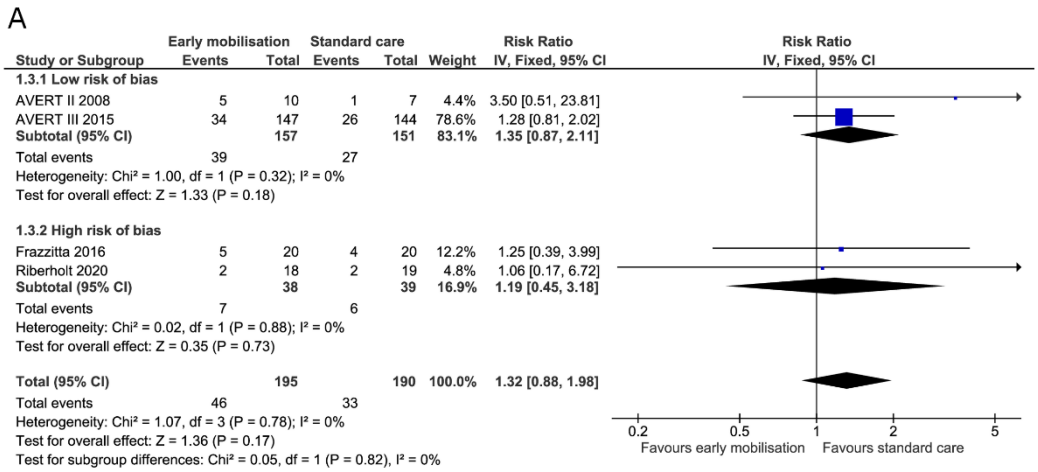
Figure 5 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on mortality or poor functional outcome in patients with severe acquired brain injury is based on a proportion in the control group (Pc) of 60.3%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 848 patients. The cumulative Z-curve (blue) is close to entering the area of futility (the two rightmost red lines) but is far from the barriers of benefit or harm (upper and lower red lines).

Subgroup analysis in patients with stroke alone compared to patients with non-stroke acquired brain injury showed no difference between groups in mortality or poor functional outcome either at the end of the intervention or at maximal follow-up with moderate to low heterogeneity (**Fig 4B and 5B**).

We found no evidence for a difference between the early mobilisation group versus standard care on mortality at the end of the intervention (RR 1.32, 95% CI 0.88 to 1.98; I^2 0%) (**Fig 6A)** with the diversity-adjusted TSA CI from 0.25 to 6.89 (**Table 3**) and severe lack of required information (**Fig 6C**). At maximal follow-up there was no between group difference in mortality (RR 1.26, 95% CI 0.93 to 1.72; I^2 0%) (**Fig 7A**) and the diversity-adjusted TSA CI between 0.36 to 4.47 (**Table 3**). The TSA showed a severe lack of required information at maximal follow-up as more than 3,000 patients were needed (**Fig 7C**). Subgroup analysis on patients with stroke alone or patients with non-stroke acquired brain injury also showed no difference at the end of the intervention or maximal follow-up (**Fig 6B and 7B**).

Fig 6. Comparison of early mobilisation versus standard care – mortality at the end of the intervention

A



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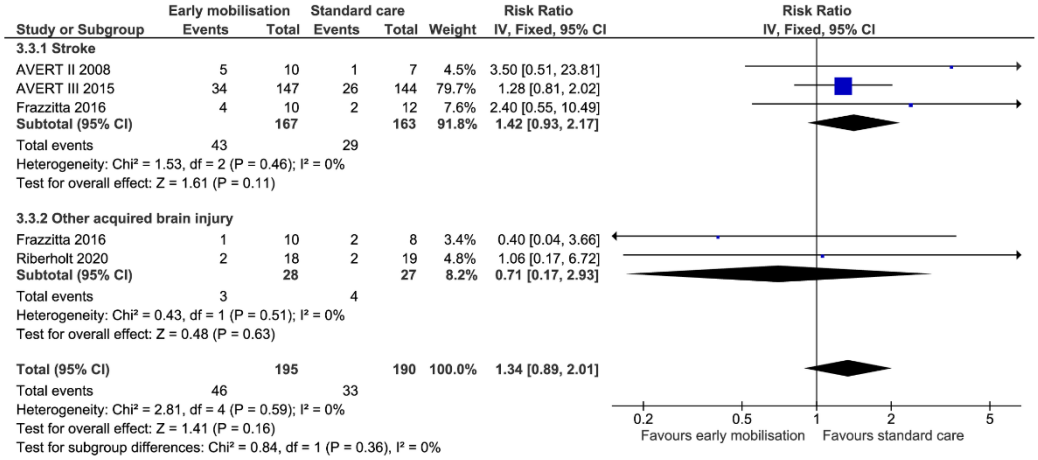

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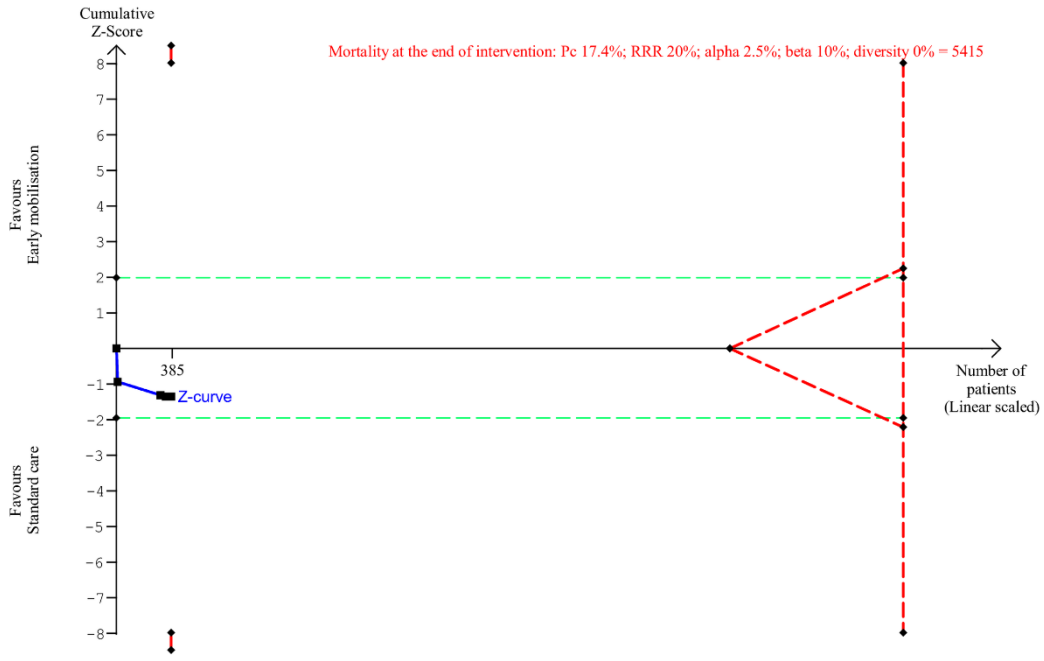
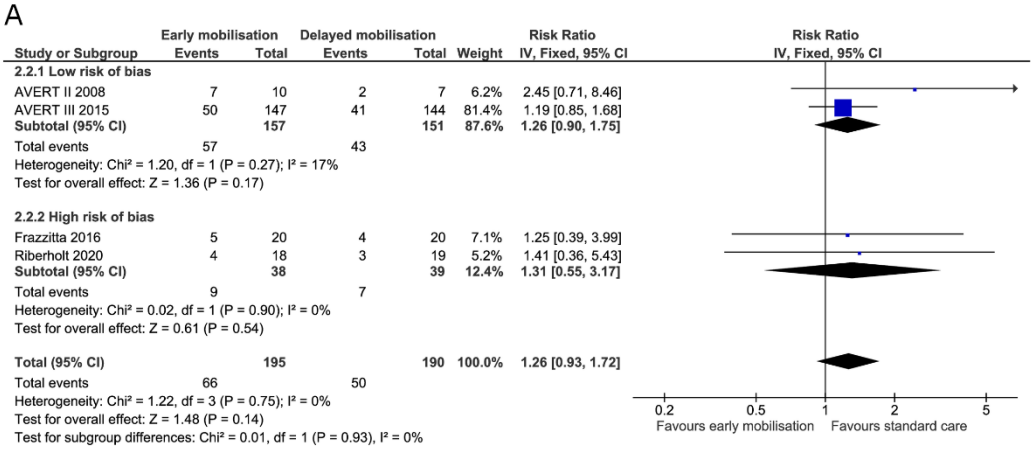


Figure 6 A and B. Forest-plots showing the results from the meta-analysis of the outcome mortality at end of intervention with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 6 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on mortality in patients with severe acquired brain injury is based on a proportion in the control group (Pc) of 17.4%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 5415 patients; The cumulative Z-curve (blue) is far from breaking any boundaries for benefit or harm (upper and lower red lines), or futility (the two rightmost red lines).

Fig 7. Comparison of early mobilisation versus standard care – mortality at maximal follow-up

A



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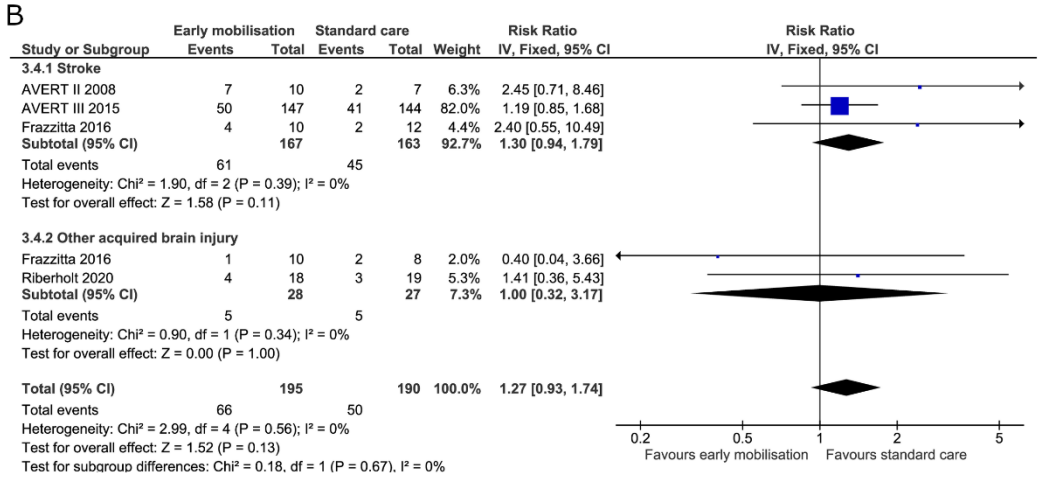

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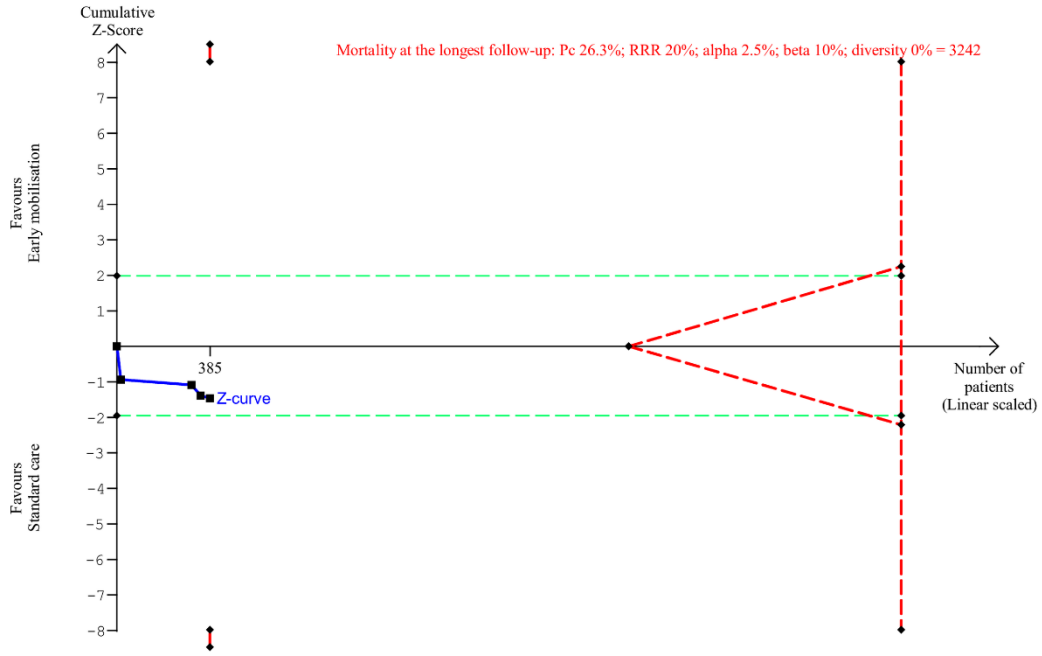


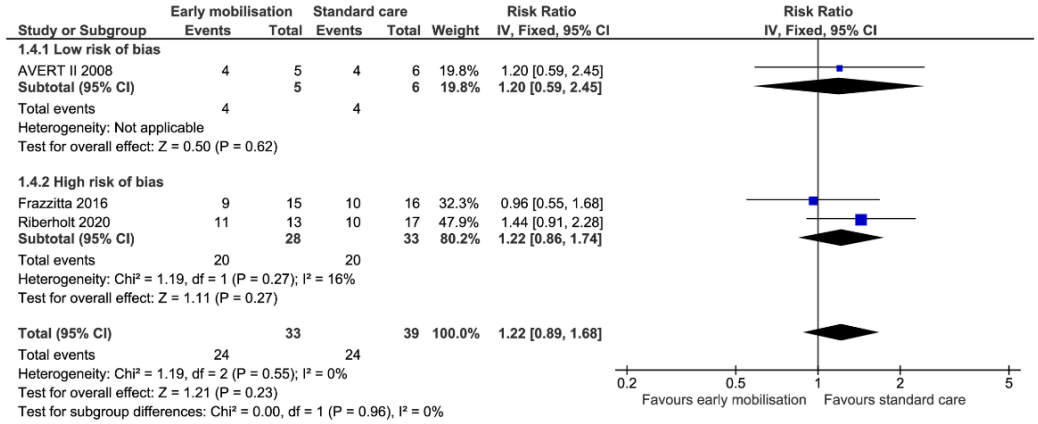
Figure 7 A and B. Forest-plots showing the results from the meta-analysis of the outcome mortality at maximal follow-up with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 7 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on mortality in patients with severe acquired brain injury. The analysis is based on a proportion in the control group (Pc) of 26.3%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 3242 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit, harm (upper and lower red lines), or futility (the two rightmost red lines).

We found no evidence of a difference between the early mobilisation group versus standard care on poor functional outcome (among survivors) at the end of the intervention (RR 1.22, 95% CI 0.89 to 1.68) (**Fig 8A**) and the diversity-adjusted TSA CI was 0.32 to 4.41 (**Table 3**). The TSA estimated an inclusion of 811 patients in the analysis to reach the required information size (**Fig 8C**). Poor functional outcome (among survivors) at maximal follow up had a RR of 1.12 (95% CI 0.84 to 1.49; I^2 0%) (**Fig 9A**) and the diversity-adjusted TSA CI was 0.35 to 3.53 (**Table 3**). Poor functional outcome (among survivors) did not reach futility in the TSA with estimated required information size of 1867 patients at maximal follow-up (**Fig 9C**).

Fig 8. Comparison of early mobilisation versus standard care – Poor functional outcome among survivors at the end of the intervention

A



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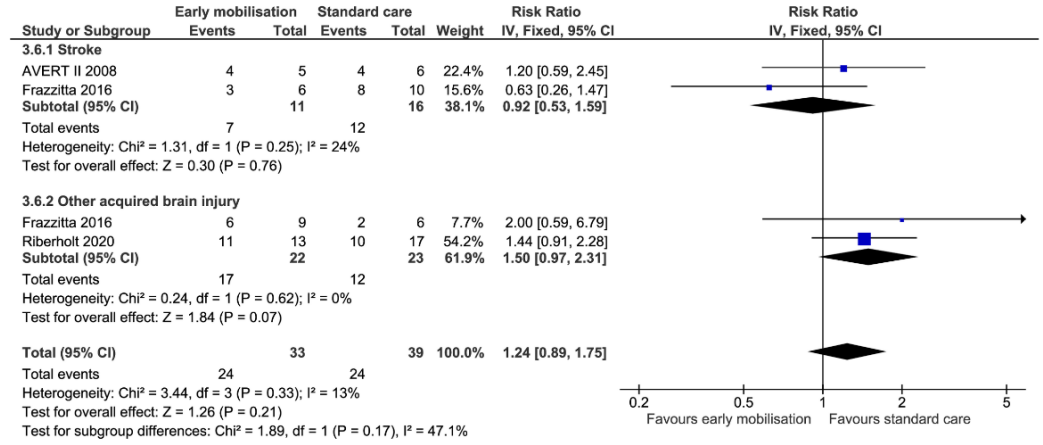

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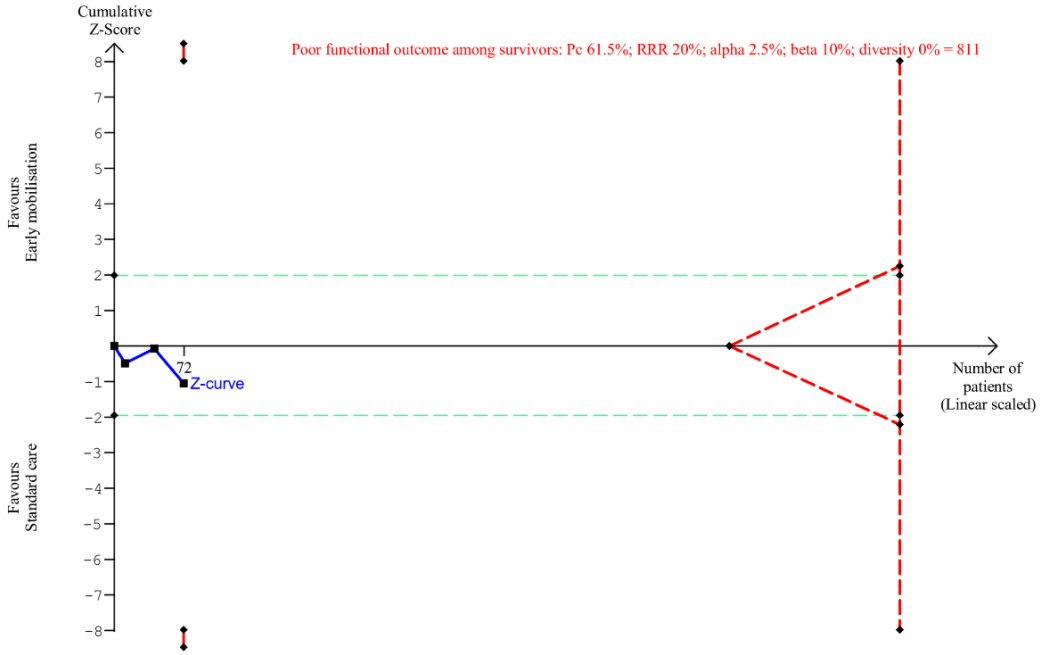
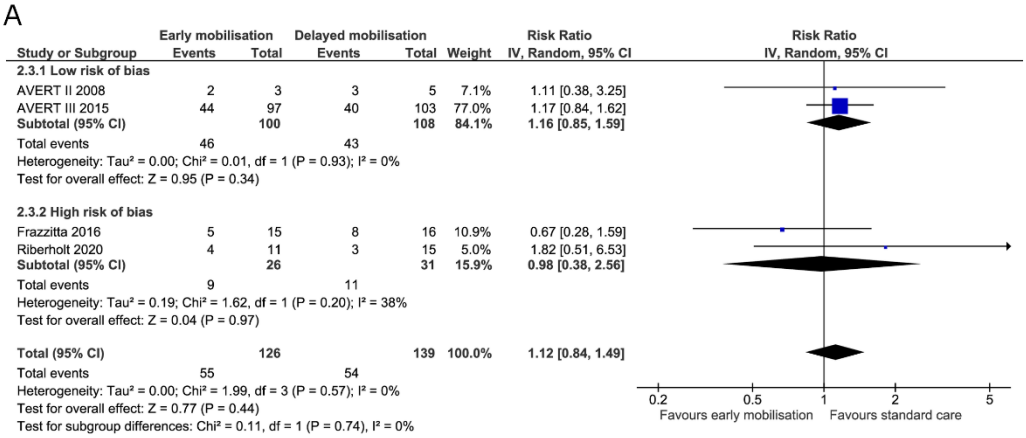


Figure 8 A and B. Forest-plots showing the results from the meta-analysis of the outcome poor function at the end of intervention with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 8 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on poor functional outcome in patients with severe acquired brain injury is based on a proportion in the control group (Pc) of 61.5%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 811 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit, harm (upper and lower red lines), or futility (the two rightmost red lines).

Fig 9. Comparison of early mobilisation versus standard care – Poor functional outcome among survivors at maximal follow-up

A



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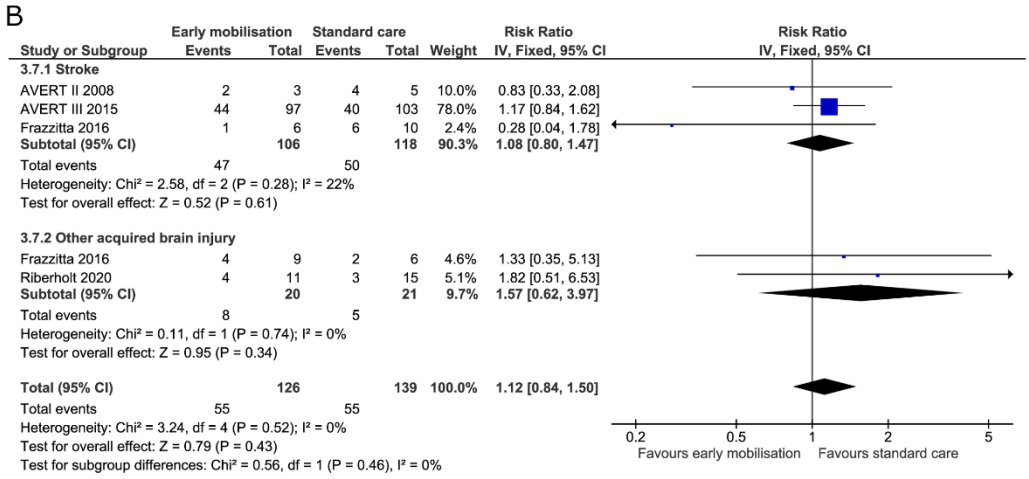

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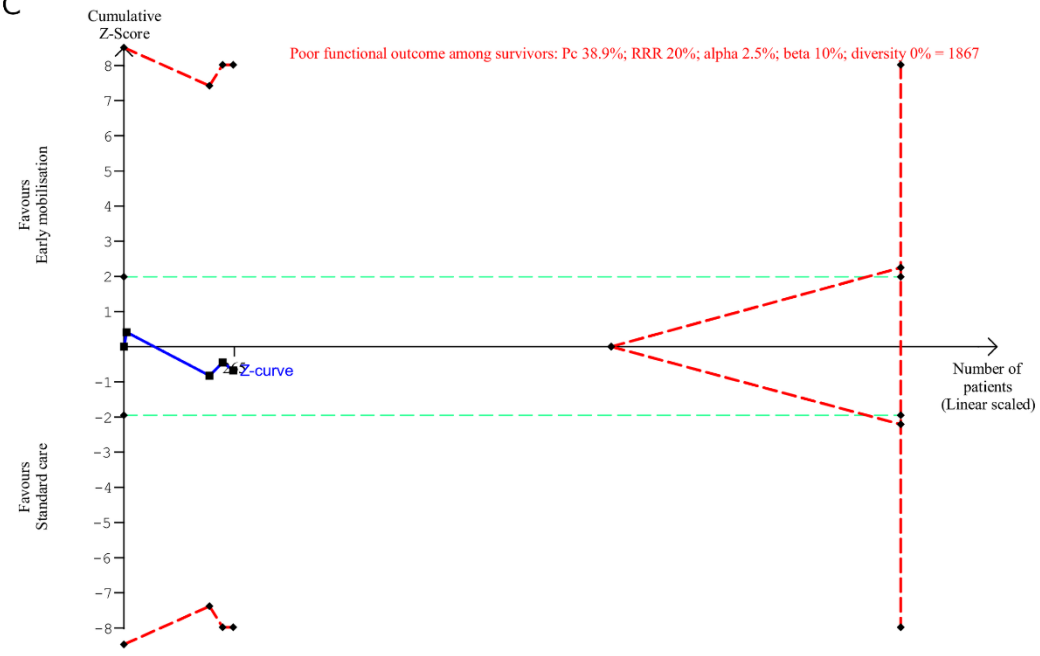


Figure 9 A and B. Forest-plot showing the results from the meta-analysis of the outcome poor functional outcome at the longest follow-up with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 9 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on poor functional outcome among survivors in patients with severe acquired brain injury is based on a proportion in the control group (Pc) of 38.9%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 1867 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit, harm (upper and lower red lines), or futility (the two rightmost red lines).

Quality of life

Two trials reported quality of life at maximal follow-up [5,19]. We found no evidence of a difference between the early mobilisation group versus standard care with a mean difference of 0.0 points (95% CI -0.05 to 0.05; I^2 0%) and the diversity-adjusted TSA CI was -0.2 to 0.2 [GRADE certainty LOW] (**Fig 10A and B**). The TSA reached futility and beyond the required information size indicating that a minimum relevant difference of 0.1 points is not likely to be found.

Fig 10. Comparison of early mobilisation versus standard care – Quality of life at maximal follow-up

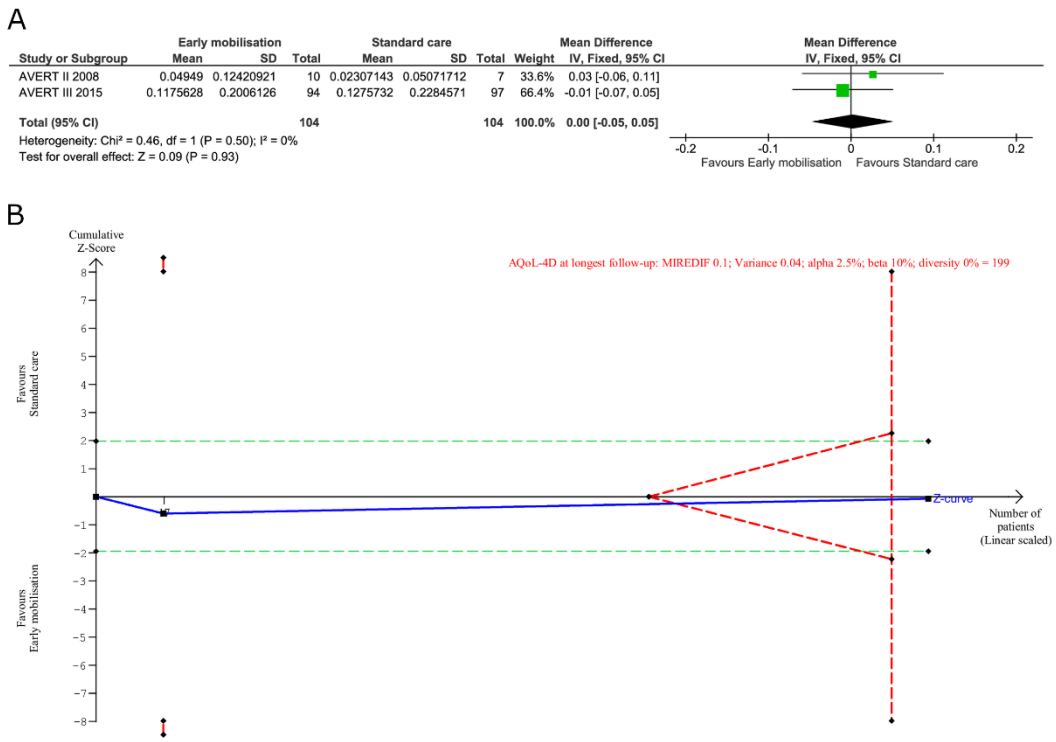


Figure 10 A. Forest-plot showing the results from the meta-analysis of the outcome quality of life at maximal follow-up with subgroup divided according to risk of bias.

Figure 10 B. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on quality of life in patients with severe stroke is based on a minimal relevant difference (MIREDIF) of 0.1 and a variance of 0.04, calculated from the control group data, an alpha of 2.5%, a beta of 10%, and diversity of 0% and equals 199 patients. The cumulative Z-curve (blue) enters the area of futility (the two rightmost red lines) and goes beyond the line of required information size (the red vertical line).

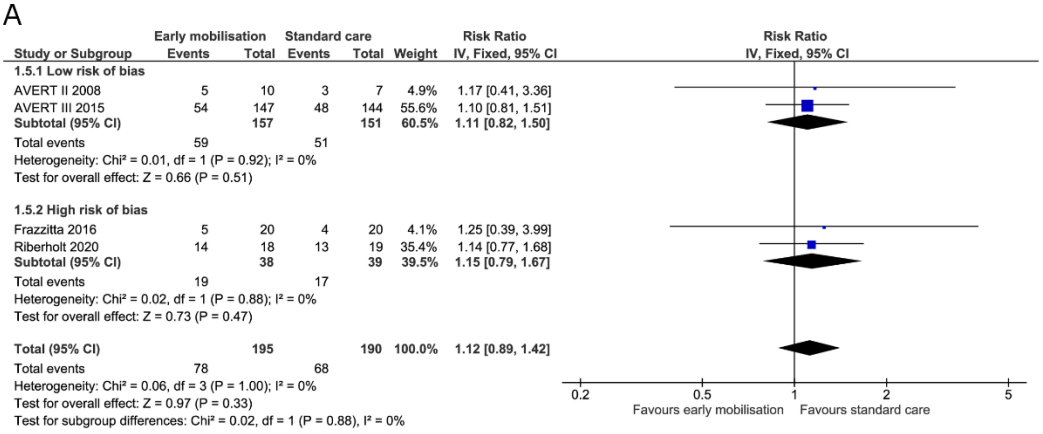
Serious adverse events

All four trials reported serious adverse events at the end of the intervention. The AVERT II trial reported events for three months by categorically searching for prespecified adverse events [19]. The AVERT III trial reported adverse events during the intervention period (14 days) and reported important medical events for the ensuing three months (also prespecified) [5]. Frazzitta et al. reported that they experienced no adverse event during the three-week intervention period in the critical care unit. The trial did, however, report deaths during the intervention period, and we

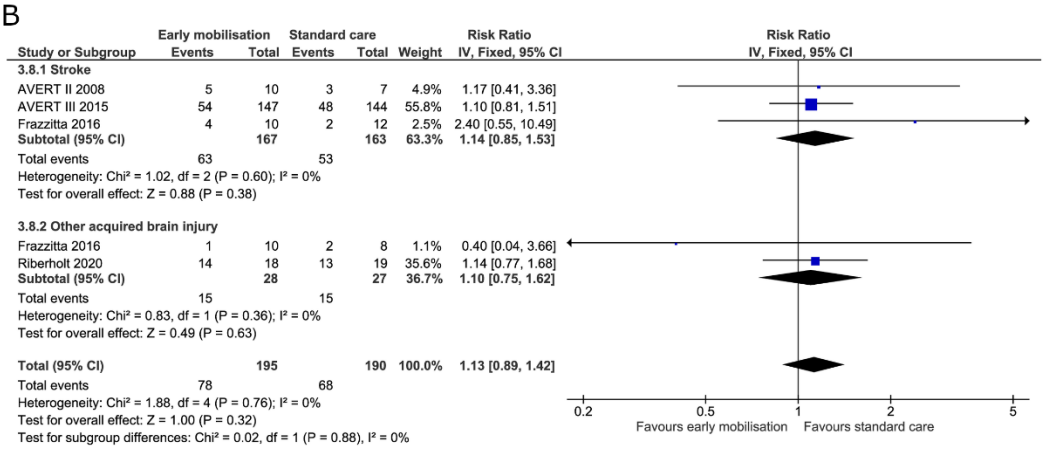
included these as serious adverse events in the analysis [68]. In the trial by Riberholt et al., patient reports were retrospectively screened for serious adverse events by two blinded investigators during the intervention period (up to four weeks) [35]. We found no evidence of a difference between early mobilisation and standard care on serious adverse events at the end of the intervention (RR 1.10, 95% CI 0.86 to 1.39) (**Fig 11A)** with a diversity-adjusted TSA CI from 0.41 to 3.12 [GRADE certainty LOW]. The TSA showed that 18% of the required information size was obtained and the boundaries of benefit or harm were not surpassed (**Fig 11C**). The estimate did not change after subdividing the patients according to diagnosis (**Fig 11B**). For serious adverse events at maximal follow-up, the RR was 1.08 (95% CI 0.87 to 1.35) (**Fig 12A**) and the diversity-adjusted TSA CI was 0.53 to 2.42 [GRADE certainty LOW] (**Fig 12C**). The TSA showed that only 24% of the required information size was obtained and the boundaries of benefit or harm were not surpassed.

Fig 11. Comparison of early mobilisation versus standard care – Serious adverse events at the end of the intervention

A



B



C

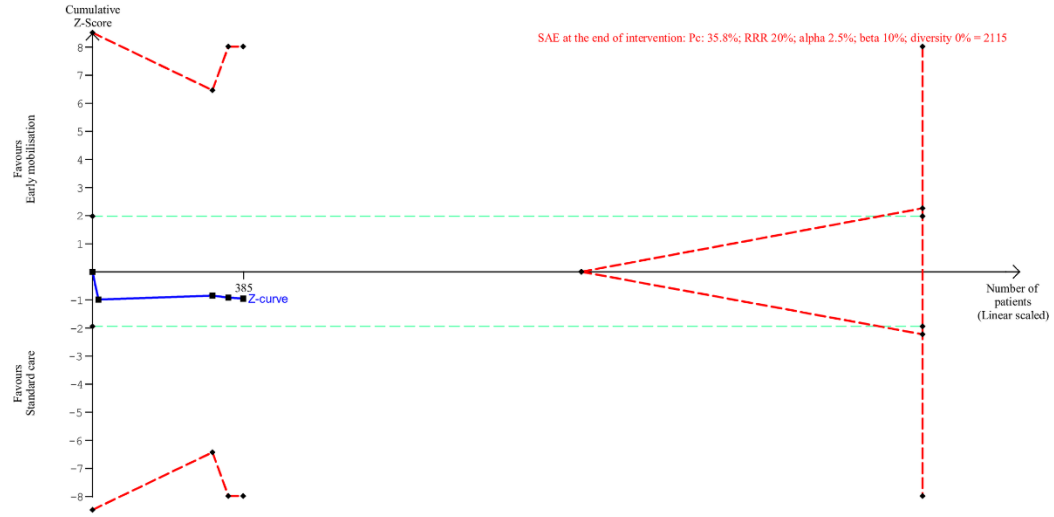


Figure 11 A and B. Forest-plots showing the results from the meta-analysis of the outcome serious adverse events at the end of intervention with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 11 C. Trial Sequential Analysis (C) of the cumulative meta-analysis assessing early mobilisation versus standard care on serious adverse events in patients with severe acquired brain injury is based on a

proportion in the control group (Pc) of 35.8%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 2115 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit, harm (upper and lower red lines), or futility (the two rightmost red lines).

Fig 12. Comparison of early mobilisation versus standard care – Serious adverse events at maximal follow-up

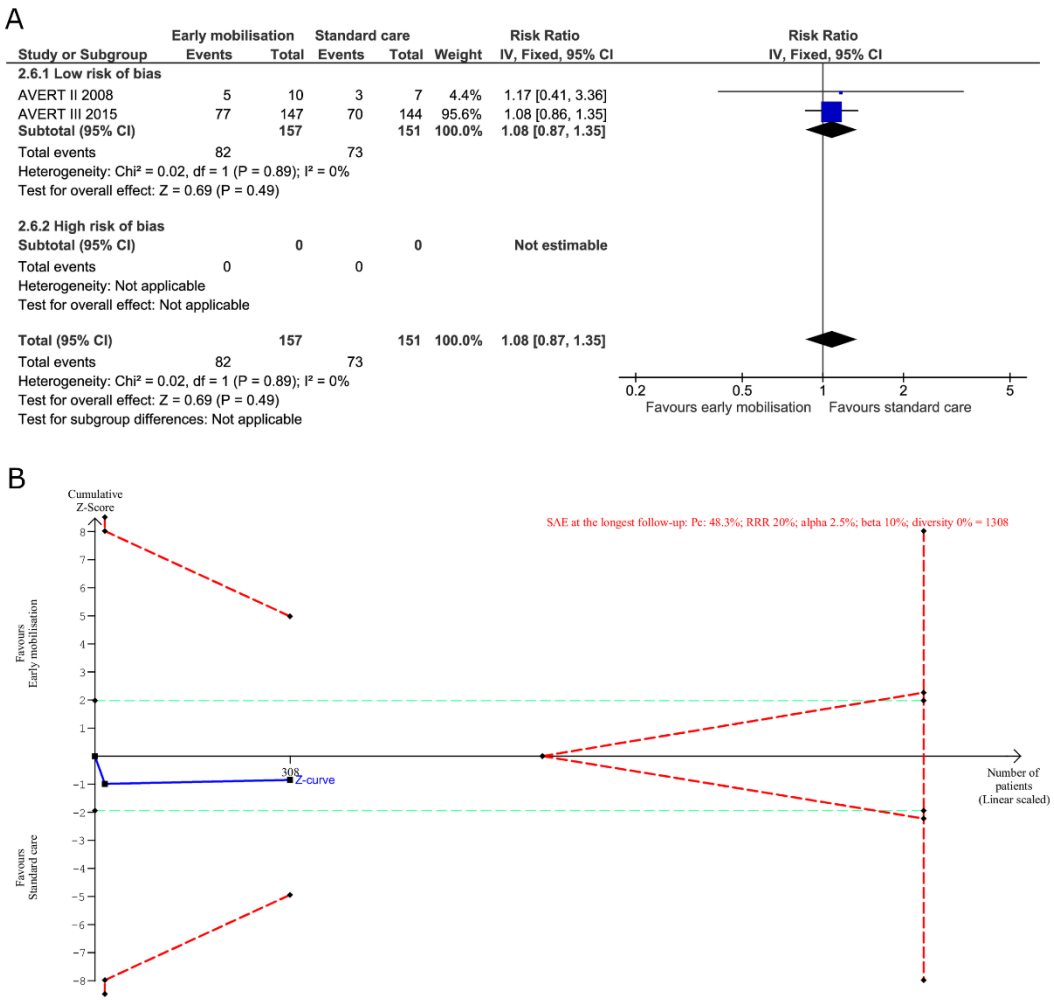


Figure 12 A. Forest-plot showing the results from the meta-analysis of the outcome serious adverse events at the longest follow-up with subgroup divided according to low risk of bias or risk of bias.

Figure 12 B. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on serious adverse events in patients with stroke is based on a proportion in the control group (Pc) of 48.3%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and results in a required information size of 1308 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit, harm (upper and lower red lines), or futility (the two rightmost red lines).

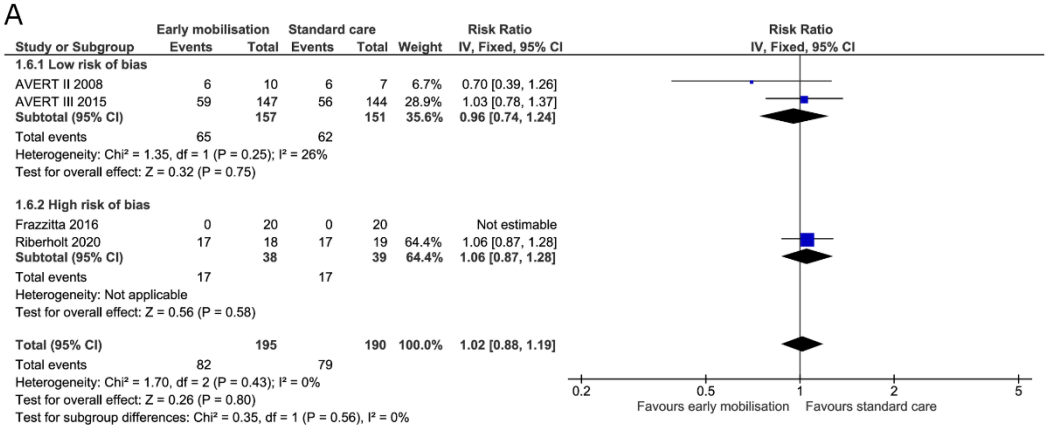
Secondary outcomes

The proportion of participants with one or more adverse events not considered serious

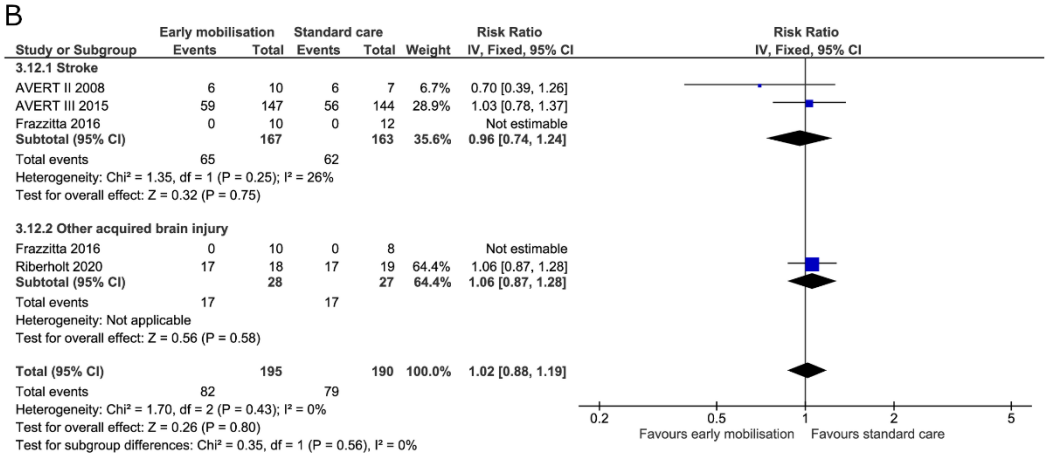
Non-serious adverse events were reported in four trials at the end of the intervention [5,19,35,68]. The fixed-effect meta-analysis revealed no difference between early mobilisation and standard care at the end of the intervention (RR 1.02, 95% CI 0.88 to 1.19; I^2 0%) and no heterogeneity (**Fig 13A and B**). The diversity-adjusted TSA CI ranged from 0.68 to 1.50 (**Table 3**) with the cumulative Z score reaching 23% of the required information size (**Fig 13C**). At the maximal follow-up, only two trials reported data [5,19]. There was no difference between groups at this time (RR 1.07, 95% CI 0.84 to 1.37; I^2 30%) but moderate to low heterogeneity was found (**Fig 14A**). Furthermore, the diversity-adjusted TSA CI for adverse events not considered serious was between 0.39 and 3.20 at maximal follow-up; 9% of the required information size was obtained (**Table 3**).

Fig 13. Comparison of early mobilisation versus standard care – Adverse events not considered serious at the end of the intervention

A



B



C

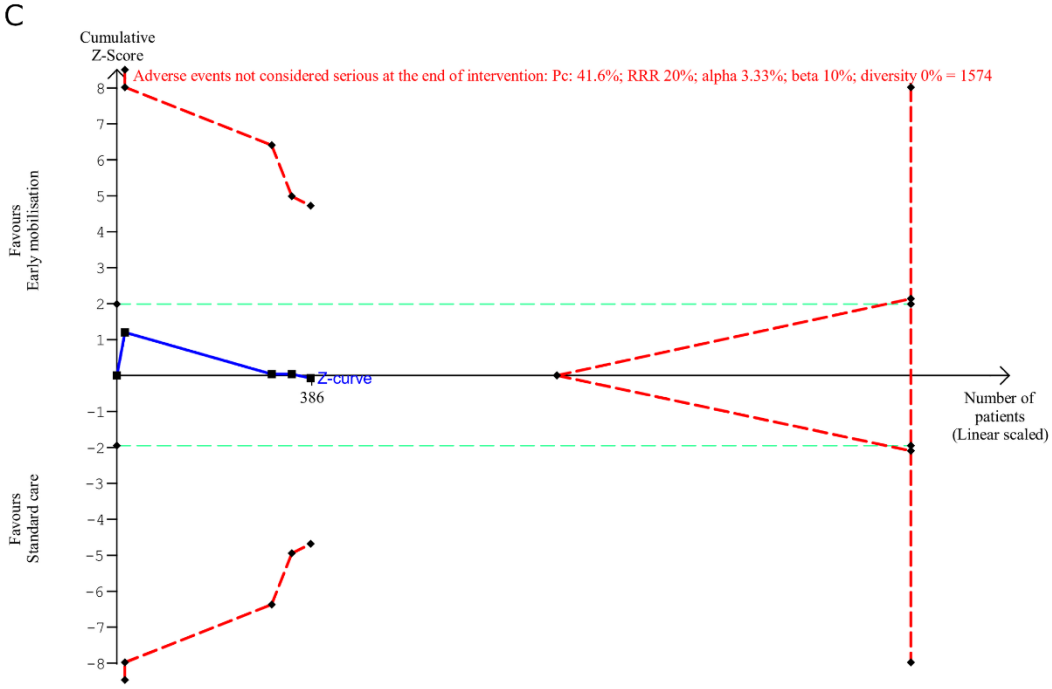
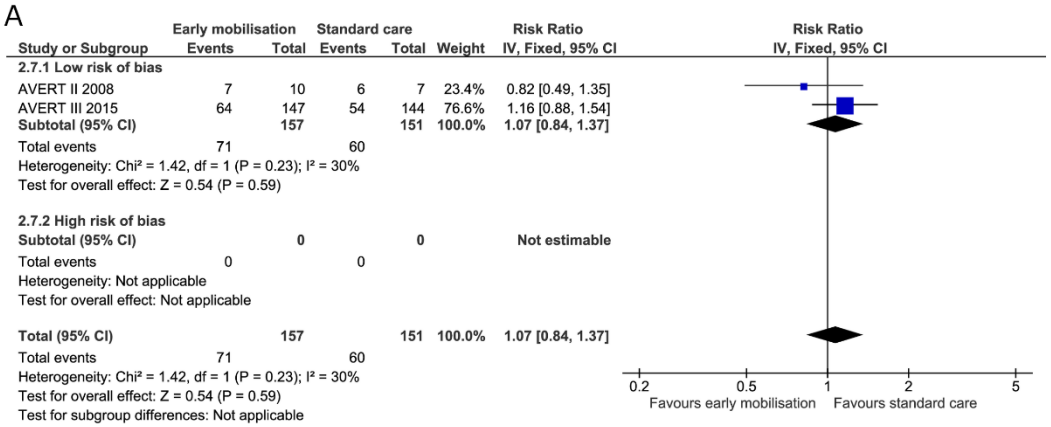


Figure 13 A and B. Forest-plot showing the results from the meta-analysis of the outcome adverse events not considered serious at the end of intervention with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 13 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on adverse events not considered serious in patients with severe acquired brain injury is based on a proportion in the control group (Pc) of 41.6%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and equals 1680 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit or harm (upper and lower red lines), or futility (the two rightmost red lines).

Fig 14. Comparison of early mobilisation versus standard care – Adverse events not considered serious at maximal follow-up

A



B

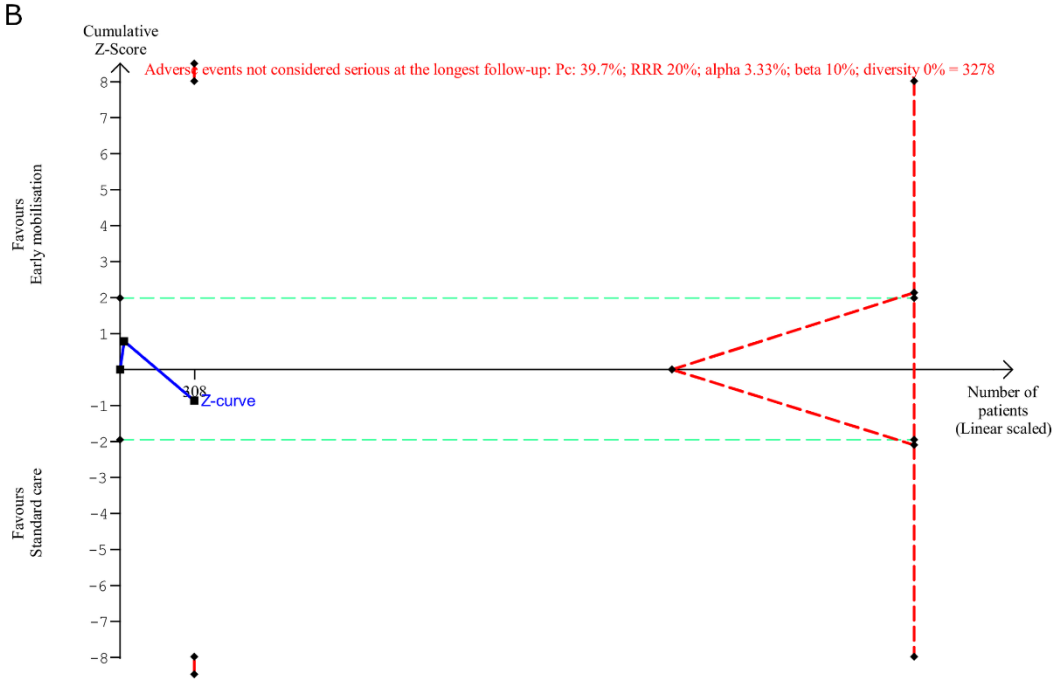


Figure 14 A. Forest-plot showing the results from the meta-analysis of the outcome adverse events not considered serious at the maximal follow-up with subgroup divided according to risk of bias.

Figure 14 B. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on adverse events not considered serious in patients with severe acquired brain injury is based on a proportion in the control group (Pc) of 39.7%, a relative risk reduction (RRR) of 20%, an alpha of 2.5%, a beta of 10%, and diversity of 0% and equals 3499 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit or harm (upper and lower red lines), or futility (the two rightmost red lines).

Consciousness

Two trials measured the level of consciousness using the Coma Recovery Scale-Revised at the end of the intervention and maximal follow-up [35,68]. The I^2 was 80% and 65% at the end of the intervention and maximal follow-up, respectively, indicating moderate to substantial heterogeneity. We found no evidence of a difference between groups at the end of the intervention (mean difference -0.00 points, 95% CI -8.23 to 8.23; I^2 80%) (**Fig 15A**) and a diversity-adjusted TSA CI from -33.60 to 33.60 [GRADE certainty VERY LOW] (**Table 3**). The cumulative Z score did not reach futility and would require an information size of 816 patients (**Fig 15 C**). The subgroup analysis between patients with stroke or other acquired brain injury showed no difference between groups (mean difference 1.38, 95% CI -6.57 to 9.33; I^2 88%) and considerable heterogeneity (**Fig 15B**). At maximal follow-up, a mean difference of 0.62 (95% CI -4.82 to 6.06; I^2 65%) was found (**Fig 16A**) and a diversity-adjusted TSA CI from -21.57 to 22.81 [GRADE certainty VERY LOW]. Only 10% of the TSA required information size was accrued (**Table 3**).

Fig 15. Comparison of early mobilisation versus standard care – Coma Recovery Scale-Revised at the end of the intervention

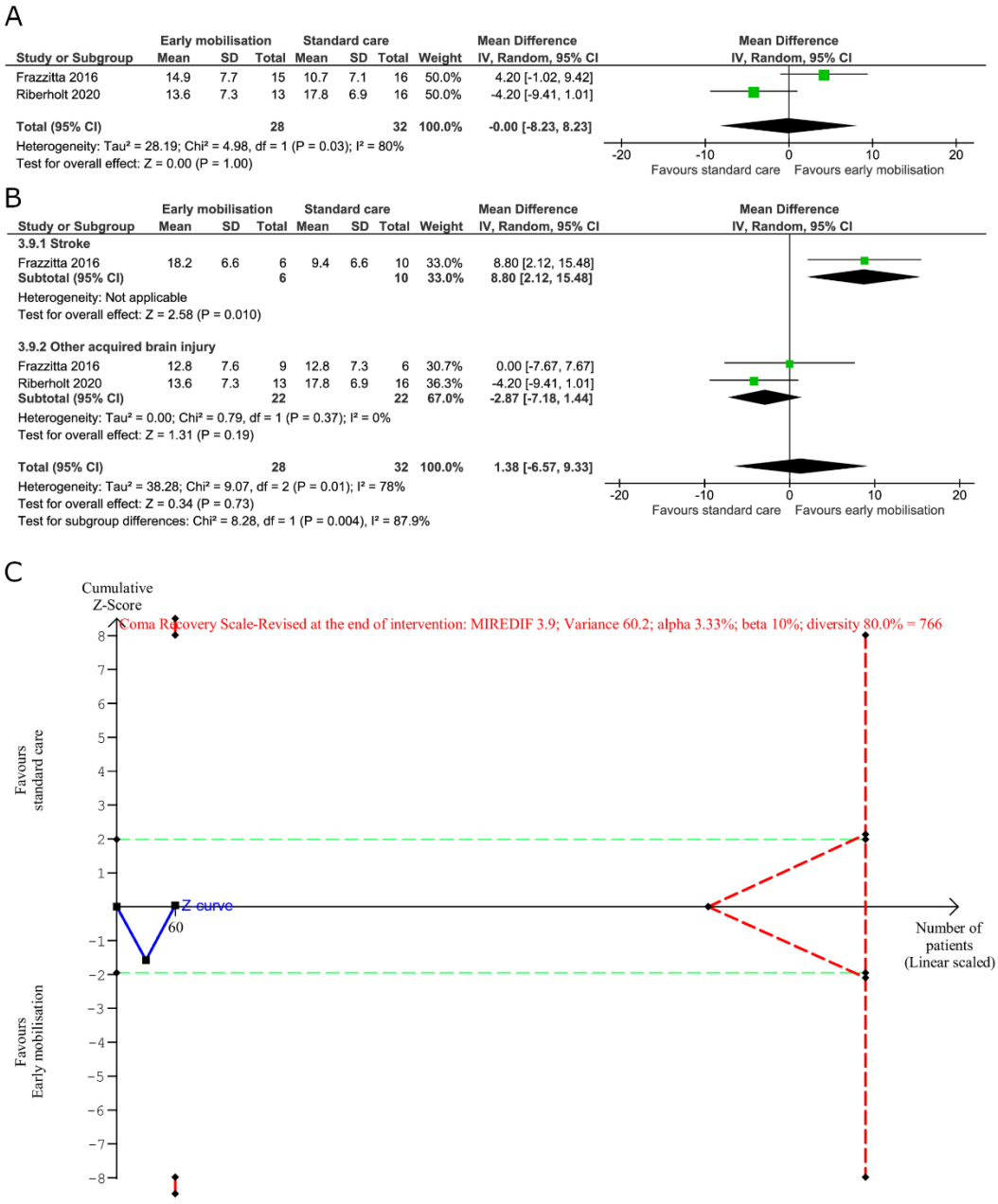
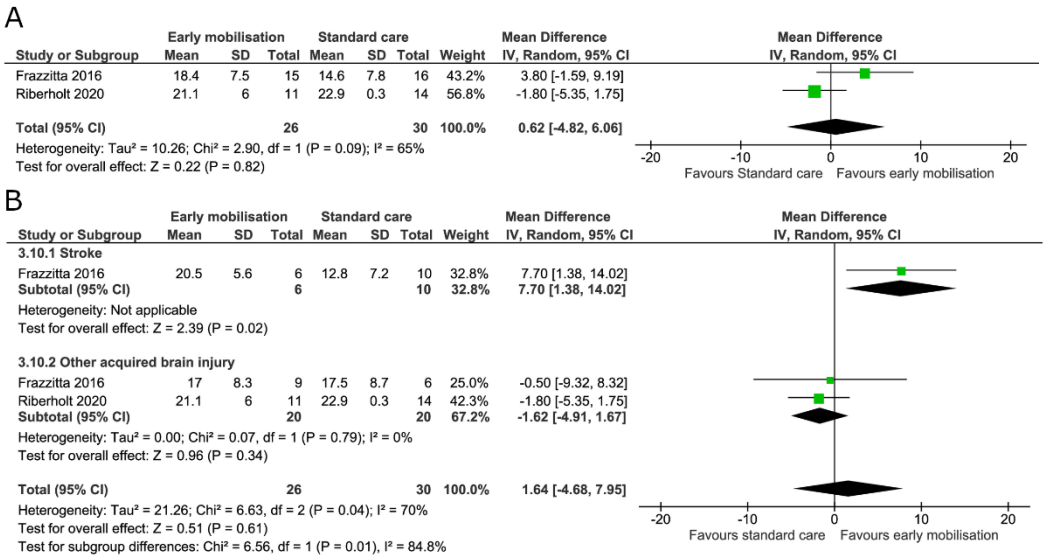


Figure 15 A and B. Forest-plot showing the results from the meta-analysis of the outcome Coma Recovery Scale-Revised at the end of intervention with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 15 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on Coma Recovery Scale-Revised in patients with severe acquired brain injury is based on a minimal relevant difference (MIREDIF) of 3.9 and a variance of 60.2, calculated from the control group data, an alpha of 2.5%, a beta of 10%, and diversity of 80% and equals 816 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit, harm (upper and lower red lines), or futility (the two rightmost red lines).

Fig 16. Comparison of early mobilisation versus standard care – Coma Recovery Scale-Revised at maximal follow-up



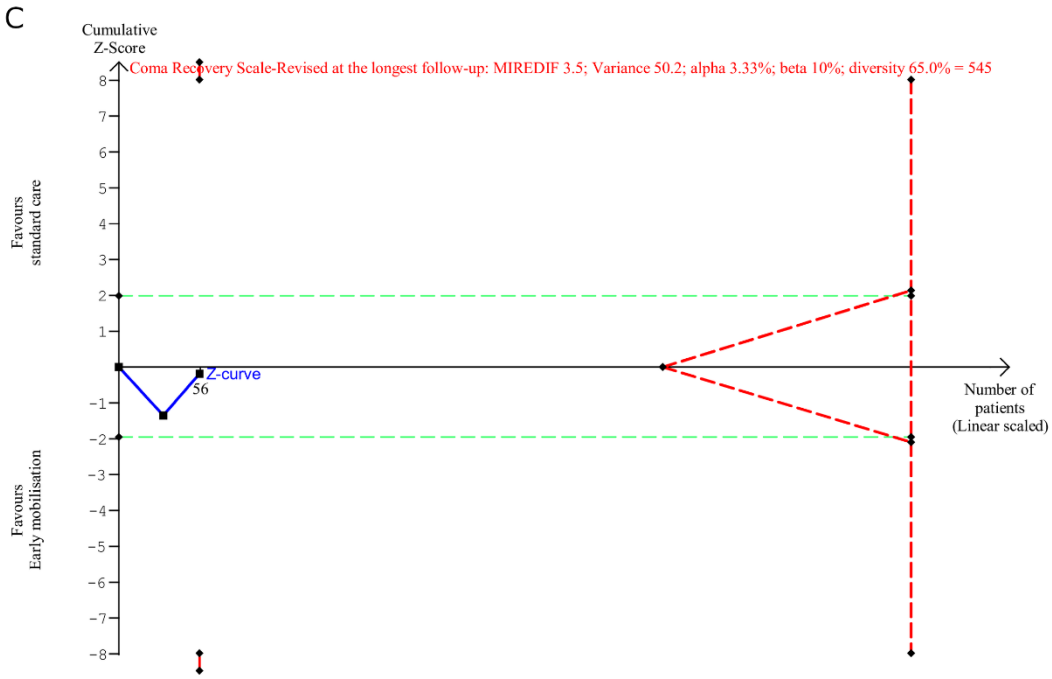


Figure 16 A and B. Forest-plot showing the results from the meta-analysis of the outcome Coma Recovery Scale-Revised at the longest follow-up with subgroup divided according to risk of bias (A) or diagnosis (B).

Figure 16 C. Trial Sequential Analysis of the cumulative meta-analysis assessing early mobilisation versus standard care on Coma Recovery Scale-Revised in patients with severe acquired brain injury is based on a minimal relevant difference (MIREDIF) of 3.5 and a variance of 50.2, calculated from the control group data, an alpha of 2.5%, a beta of 10%, and diversity of 65% and equals 582 patients. The cumulative Z-curve (blue) is far from breaking any boundaries for benefit, harm (upper and lower red lines), or futility (the two rightmost red lines).

Exploratory outcomes

Three trials reported data on other adverse events besides death [5,19,35]. The RR of patients experiencing the following serious adverse events in the early mobilisation group versus the standard care group were as follows:

For death, please see analysis in **fig 6 and fig 7**.

The RR of pneumonia in the early mobilisation group compared with the standard care group was 1.00 (95% CI 0.76 to 1.31), three trials, 346 patients [5,19,35].

The RR of stroke progression or recurrent stroke in the early mobilisation group compared with the standard care group was 0.93 (95% CI 0.59 to 1.48), two trials, 308 patients [5,19].

The RR of depression in the early mobilisation group compared with standard care was 1.27 (95% CI 0.89 to 1.82), two trials, 329 patients [5,35].

Acute myocardial infarction occurred in three patients in the early mobilisation group compared with no patients in the standard care group. The risk difference between early mobilisation group compared with the standard care group were 0.50 (95% CI 0.44 to 0.55), three trials, 346 patients [5,19,35].

The RR of having a blocked tracheal tube in the early mobilisation group compared with the standard care group was 1.37 (95% CI 0.58 to 3.28), one trial, 38 patients [35].

The RR of delirium in the early mobilisation group compared with the standard care group was 0.37 (95% CI 0.06 to 2.18), one trial, 38 patients [35].

The RR of sepsis in the early mobilisation group compared with the standard care group was 1.65 (95% CI 0.95 to 2.87), one trial, 38 patients [35].

Other serious infections occurred in one patient in the standard care group. The risk difference between early mobilisation group compared with the standard care group were -0.51 (95% CI -0.67 to -0.35), one trial, 38 patients [35].

Seizures occurred in two patients in the early mobilisation group. The risk difference between early mobilisation group compared with the standard care group was 0.53 (95% CI 0.36 to 0.69), one trial, 38 patients [35].

The RR of patients experiencing the following adverse events not considered serious in the early mobilisation group versus standard care group are as follows:

The RR of falls in the early mobilisation group versus the standard care group was 0.94 (95% CI 0.74 to 1.19), three trials, 346 patients [5,19,35].

The RR of urinary tract infection in the early mobilisation group versus the standard care group was 0.96 (95% CI 0.71 to 1.29), three trials, 346 patients [5,19,35].

The RR of developing a pressure ulcer in the early mobilisation group versus the standard care group was 1.23 (95% CI 0.89 to 1.70), three trials, 346 patients [5,19,35].

The RR of developing angina in the early mobilisation group versus the standard care group was 0.33 (95% CI 0.05 to 1.96), two trials, 329 patients [5,35].

The RR of vomiting in the early mobilisation group versus the standard care group was 0.70 (95% CI 0.27 to 1.83), one trial, 38 patients [35].

The RR of patients removing their nasogastric tube in the early mobilisation group versus the standard care group was 0.89 (95% CI 0.44 to 1.78), one trial, 38 patients [35].

The RR of acquiring other infections that were not considered serious as the above mentioned in the early mobilisation group versus the standard care group was 0.70 (95% CI 0.27 to 1.83), one trial, 38 patients [35].

The RR of a patient developing paroxysmal sympathetic hyperactivity in the early mobilisation group versus the standard care group was 1.00 (95% CI 0.42 to 2.39), one trial, 38 patients [35].

The RR of getting withdrawal symptoms in the early mobilisation group versus the standard care group was 1.90 (95% CI 1.12 to 3.24), one trial, 38 patients [35].

The RR of anaemia in the early mobilisation group versus the standard care group was 0.78 (95% CI 0.25 to 2.39), one trial, 38 patients [35].

The RR of diarrhoea in the early mobilisation group versus the standard care group was 0.78 (95% CI 0.25 to 2.39), one trial, 38 patients [35].

The RR of developing oral mycosis in the early mobilisation group versus the standard care group was 1.00 (95% CI 0.35 to 2.81), one trial, 38 patients [35].

The RR of acquiring a wound in the early mobilisation group versus the standard care group was 1.59 (95% CI 0.82 to 3.11), one trial, 38 patients [35].

The RR of hyponatremia in the early mobilisation group versus standard care group was 0.47 (95% CI 0.08 to 2.65), one trial, 38 patients [35].

The RR of hypokalaemia in the early mobilisation group versus the standard care group was 1.59 (95% CI 0.82 to 3.11), one trial, 38 patients [35].

The RR of developing tachycardia in the early mobilisation group versus the standard care group was 0.65 (95% CI 0.13 to 3.32), one trial, 38 patients [35].

Confusion occurred in three patients in the early mobilisation group. The risk difference between early mobilisation group compared with the standard care group was 0.54 (95% CI 0.38 to 0.71), one trial, 38 patients [35].

The RR of getting conjunctivitis in the early mobilisation group versus the standard care group was 1.37 (95% CI 0.58 to 3.28), one trial, 38 patients [35].

The RR of bleeding from a surgical wound in the early mobilisation group versus the standard care group was 0.65 (95% CI 0.13 to 3.32), one trial, 38 patients [35].

Some adverse events considered non-serious were rare and can be found in supplementary table 3 (**S3 Table**).

Adverse events in observational studies

We were able to retrieve data on serious adverse events and adverse events not considered serious from the observational case-control study by Karic et al. 2016 [69]. This study included 25 patients with severe subarachnoid haematoma (Hunt and Hess grade IV or V) [70]. Serious adverse events occurred in 11/14 patients in the early mobilisation group compared to 10/11 patients in the standard care group. Adverse events not considered serious were reported in 13/14 of patients in the early mobilisation group compared to 10/11 in the standard care group. These events were not described further.

Summary of Findings

Please see **Table 2**.

Table 2. Summary of findings for early mobilisation versus delayed mobilisation.

Early mobilisation compared with standard care (delayed mobilization) for patients with severe acquired brain injury

Patient or population: patients with severe acquired brain injury including traumatic brain injury, stroke, anoxic brain injury

Setting: stroke unit or critical care unit

Intervention: early mobilisation

Comparison: standard care (delayed mobilisation)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with early mobilisation				
Death or poor functional outcome at the end of the intervention	565 per 1.000	**673 per 1.000** (526 to 865)	**RR 1.19** (0.93 to 1.53)	91 (3 RCTs)	⨁⨁◯◯ LOW [a, b]	Large difference in the populations between trials, although we did not observe subgroup differences regrading intervention effects. Small number of patients in trials. Extreme beneficial effects to harmful effects are found in the TSA-adjusted CI.
Death or poor functional outcome at the maximal follow-up	603 per 1.000	**621 per 1.000** (537 to 730)	**RR 1.03** (0.89 to 1.21)	381 (4 RCTs)	⨁⨁◯◯ LOW [a, b]	Large difference in the populations between trials, although we did not observe subgroup differences regrading intervention effects. Beneficial effects to harmful effects are found in the TSA-adjusted CI.
Quality of Life at the maximal follow-up assessed with: AQoL (4D)	The mean quality of Life was **0** AQoL points	MD **0 AQoL points** (0.05 lower to 0.05 higher)	-	208 (2 RCTs)	⨁⨁◯◯ LOW [a, b]	Patients included in this analysis are from trials only including patients with severe stroke. Beneficial effects to harmful effects are found in the TSA-adjusted CI.
Patients with at least one serious adverse event at the end of the intervention	358 per 1.000	**394 per 1.000** (308 to 497)	**RR 1.10** (0.86 to 1.39)	385 (4 RCTs)	⨁⨁◯◯ LOW [a, b]	Large difference in the populations between trials, although we did not observe subgroup differences regrading intervention effects. Beneficial effects to harmful effects are found in the TSA-adjusted CI.
Patients with at least one serious adverse event at the maximal follow-up	483 per 1.000	**522 per 1.000** (421 to 653)	**RR 1.08** (0.87 to 1.35)	308 (2 RCTs)	⨁⨁◯◯ LOW [a, b]	Patients included in this analysis are from trials only including patients with severe stroke. Beneficial effects to harmful effects are found in the TSA-adjusted CI.
Coma Recovery Scale-Revised (CRS-R) at end of the intervention	The mean coma Recovery Scale-Revised (CRS-R) at end of the intervention was **-0.00** CRS-R points	MD **0 CRS-R points** (8.23 lower to 8.23 higher)	-	60 (2 RCTs)	⨁◯◯◯ VERY LOW [b, c, d]	The two trials have high risk of bias. There is inconsistency between the two trials estimates. Extreme beneficial effects to harmful effects are found in the TSA-adjusted CI.

Early mobilisation compared with standard care (delayed mobilization) for patients with severe acquired brain injury

Patient or population: patients with severe acquired brain injury including traumatic brain injury, stroke, anoxic brain injury

Setting: stroke unit or critical care unit

Intervention: early mobilisation

Comparison: standard care (delayed mobilisation)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	**Risk with early mobilisation**				
Coma Recovery Scale-Revised (CRS-R) at the maximal follow-up (Random)	The mean coma Recovery Scale-Revised (CRS-R) at the maximal follow-up (Random) was **0.62** CRS-R points	MD **0.62 CRS-R points higher** (4.82 lower to 6.06 higher)	-	56 (2 RCTs)	⨁◯◯◯ VERY LOW [b, c, d]	The two trials have high risk of bias. There is inconsistency between the two trials estimates. Extreme beneficial effects to harmful effects are found in the TSA-adjusted CI.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Downgraded for indirectness; b. Downgraded for imprecision; c. Downgraded for high risk of bias; d. Downgraded for inconsistency

Discussion

Summary of main results

We identified four trials assessing early mobilisation compared with standard care. In general, the sample size was far from large enough to make firm conclusions on the benefits or harms of early mobilisation. Thus, no difference between early mobilisation or standard care was found on death or poor functional outcome either at the end of intervention or at maximal follow-up. In patients with a severe stroke, there seems to be enough evidence to conclude that early mobilisation does not change the quality of life. However, given the moderate certainty of the evidence and the fact that this conclusion was based on a subgroup analysis, this result should be confirmed by future trials. Serious adverse events were almost evenly divided between intervention groups but given that only 18% to 24% of the required information size was reached more trials are needed. However, we noted increased risk of acute myocardial infarction and confusion in the experimental group.

Early intervention was started far sooner in the two trials including patients with severe stroke [5,19] than in the two trials including patients with severe traumatic brain injury [35,68]. The type of mobilisation used also differed, as the two latter trials used a tilt table whereas the former used manual mobilisation to the edge of bed/chair or standing position if possible. However, these differences did not seem to affect the estimated intervention effects as we found no heterogeneity and no difference in subgroup analyses.

The subgroup analysis between patients with stroke and non-stroke acquired brain injury showed no difference in the estimates of the primary outcomes.

The other outcomes investigated in this trial did not reach the boundaries for futility but required larger information sizes (between 393 and 4,342). Thus, this review strongly indicates a need for more research on patients with severe acquired brain injury to answer questions on the effects of early mobilisation.

Overall completeness and applicability of evidence

Our search was comprehensive and employed an inclusive approach. Besides searching medical databases, we also searched clinical trial registries and grey literature (Google Scholar etc.). We contacted 17 primary investigators of other trials with experience in the field of early mobilisation and brain injury. The six non-responders could potentially have trials that fitted our inclusion criteria.

There is a clear growing interest in early mobilisation in other patients than the stroke population, although the latter constituted the majority in this review. Besides “wrong study design” (observational or quasi-randomised), “not doing early mobilisation” but rather other early interventions and “wrong patient population” were the main reasons for excluding studies. Thus, one very large trial [16] using elevation of the head of the bed to 30 degrees did not fulfil our inclusion criteria.

In general, information about the effect of mobilising in patients with severe acquired brain injury is limited. Even when we combine patients with different types of brain injury (which could be considered going too far), the amount of data is still sparse within every single pathology.

Quality of the evidence

All four trials used random sequence generation and one trial showed risk of attrition bias [35]. Two trials attempted to blind patients and staff [5,19] by not revealing details of the treatment protocols and providing the treatment behind curtains so the risk of bias was reduced. The staff and the patients in two trials were not blinded to the protocol or treatment allocation [35,68]. One could argue that the patients had low enough Glasgow Coma Score to be considered indirectly blinded. Blinded outcome assessors were used in different degree in all four trials. The AVERT trials [5,19] blinded assessors for all outcomes, the trial by Frazzitta et al. blinded for all outcomes except for all adverse events [68] while the last trial [35] only blinded for two outcomes (Coma Recovery Scale-Revised and adverse events). Risk of selective outcome reporting was not possible to assess in one trial [68] since the trial was retrospectively reported to clinicaltrials.gov. There were some differences in baseline characteristics in the two small trials [35,68] in that those in the early mobilisation group were older in one study and younger in the other .

The homogeneity of the interventions applied in the included studies could be questioned. There was a large variety of the definition of early mobilisation ranging from hours to weeks after injury.

Nevertheless, some common ground can be found. Thus, all trials attempted to administer mobilisation at an earlier time than was standard for the respective patient groups. This should be considered when interpreting the findings in the context of clinical practice.

Potential biases in the review process (strengths and limitations)

The strength of this review is that we published the protocol on PROSPERO (CRD42018088790) before searching. We conducted thorough searches on relevant databases, trial registries, searched for unpublished data and a wide search strategy was applied for the intervention "early mobilisation" as the term is poorly defined. We also used a rigorous selection procedure by only including randomised clinical trials where at least 10 patients matched our inclusion criteria. All included studies were assessed using Cochrane's Risk of Bias Tool and the quality was assessed using the GRADE methodology. Furthermore, we utilised the TSA to control for random errors.

Chinese- and Russian-language trials were translated into English before the full text was assessed for relevance. Some discrepancies could occur during the translation process, which may have affected the decision of exclusion. Also, the interventions and patient populations were somewhat loosely described in Chinese-language trials, probably due to cultural differences.

Due to our selection of designs in this review our chances of discovering harms were limited, especially long-term and exceedingly rare harms resulting from the interventions. Therefore, we decided to present the characteristics of serious adverse events and adverse events not

considered serious and to include observational studies for the investigation of harms. Because we applied a “randomised clinical trial”-filter in our search, only one relevant study was identified.

The results of this review are highly driven by the data from the AVERT III trial and, therefore, mostly reflects the effect of the intervention on patients with severe stroke. The younger population of patients with traumatic brain injury could react differently to this intervention, although they are a very heterogeneous group. More trials are needed to draw firm conclusions, for younger patients and traumatic brain injury.

The four included trials used different outcome scales for our primary outcome exploring physical function. Therefore, we dichotomized these outcomes as a poor or good outcome and this incurs a risk of losing information. The analysis of the results can then be greatly affected by the distribution of the outcome and the specific cut-off between “poor” or “good”. Furthermore, the statistical power of the analysis is lower when dichotomising a continuous scale [71,72]. We dichotomised the mRS with 5 and 6 as a poor outcome and 1 to 4 as a good outcome. This could be considered somewhat uncommon. But given that we are including patients with severe brain injury it could also be considered successful to move patients to a better outcome than 5 or 6. Alternatively, we could have used the standardised mean difference to analyse different outcome measures used to assess physical function, but we believe this method can be hard to interpret for clinical relevance.

We were only able to complete the subgroup analysis exploring the low risk of bias versus the high risk of bias and one of the planned clinical subgroup analyses (stroke versus other brain injuries). The included trials did not differ enough in duration, intensity, frequency, timing or type of mobilisation to make these analyses relevant.

The small sample size in this review was reflected in the TSA required information size for the different selected outcomes. Future trials are needed to gain sufficient knowledge about the benefits and harms of the treatment, but will most likely increase the heterogeneity and the required information size would increase accordingly [73].

Because of the low number of included trials in this review, it was not rational to make a funnel plot for analysing publication bias. The published randomised controlled trials were few, and future studies should emphasize blinding participants, personnel, and outcome assessments to avoid downgrading the certainty of evidence.

Agreements and disagreements with other studies or reviews

No other review has undertaken the challenge of investigating the effect of early mobilisation in patients with severe acquired brain injury. A Cochrane review on patients with stroke and early mobilisation found no benefits of early mobilisation on the number of people who survived or made a good recovery [74], but patients with severe stroke are underreported in these trials, even though 14% of the patients in the single largest study [5] had a severe stroke. Interestingly, these results are very similar to the results in the present review on the outcome of death or poor

function at three months [74]. It could, therefore, be hypothesised that patients with severe stroke (NIHSS>16) experience the same harms from an early mobilisation as do other patients with stroke. Likewise, a recently published analysis from the AVERT III trial showed that quality of life is not improved from early mobilisation, which aligns with our results [75].

Another recently published review found benefits on functional recovery of early rehabilitation interventions in patients with traumatic brain injury starting at the trauma centre and more intensive neurorehabilitation afterwards [76]. The included studies were small (largest n=86) and included a quasi-randomised trial, which could lead to a risk of type I or II errors. Trials investigating complicated rehabilitation programs such as “systematic reality orientation program” or “multisensory stimulation” can be difficult to replicate in a rigid clinical trial and therefore also difficult to transform into a clinical patient setting.

This review differs from other reviews because patients with severe acquired brain injury were specifically selected for analysis. In the search for more homogenous patient populations, the patients with severe brain injury have often been excluded from other randomised controlled trials of early mobilisation in critically ill patients.

Authors' conclusions

Implications for practice

We found no evidence of a difference between the early mobilisation of patients with severe acquired brain injury compared with standard care in important outcomes such as death and poor functional outcome, or serious adverse events. Our analyses also do not indicate a major impact on the quality of life as measured with AQoL(4D), although smaller effects and effects on other measures of life quality cannot be excluded. Our systematic review strongly highlights the insufficient evidence in patients with severe brain injury, and no firm conclusions on the potential benefit or harm from early mobilisation can be drawn from these data.

Implications for research

More research is needed within the area of early mobilisation and severe brain injury, especially in the subgroups of participants, namely patients with traumatic brain injury, stroke, and hypoxic brain injury. Outcomes such as the effect on death alone or functional outcome alone and quality of life in other patients with a brain injury than stroke, as well as harms (serious adverse events) should be further investigated. Future trials should monitor patients for potential adverse events like AMI and confusion.

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Contributions of authors

CGR, CG, JL, JM and KM conceived the original idea for this review. CGR and VW developed the search strategy with the assistance of a Copenhagen Trial Unit specialist. CGR and VW screened titles and abstracts and full-text articles. Risk of bias assessment and data extraction were conducted by CGR, VW, and JL. Statistical analysis was conducted by CGR under supervision from CG. CGR, CG, JM, and KM interpreted the analysis. CGR drafted the manuscript, which was critically revised by all authors. All authors read and approved the final version of the manuscript.

Data availability

All relevant data in this review are included in the paper. Data were obtained through database searches as described in the method section. Specific data from each trial was retrieved through contact to the specific institute or primary investigator.

Declarations of interest

The authors declare no conflict of interest

Differences between protocol and review

Only one of the two trials including patients with traumatic brain injury reported post-traumatic amnesia. Therefore, we added the Glasgow Coma Score to determine whether a brain injury was severe or not. This was added to the "types of participant" section.

Not all subgroup analyses were performed due to the small number of included studies and homogeneity of the studies. Therefore, subgroup analysis besides the analysis between high and low risk of bias and the analysis between stroke and other acquired brain injuries were redundant.

We added an exploratory analysis of individual serious and non-serious adverse events.

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S1

MEDLINE Ovid SP (1946 to May 2018) (4116 hits)

1. exp Brain Diseases/

2. exp Craniocerebral Trauma/

3. (brain and (disease* or disorder* or injur* or lacerati* or accident* or hemorrhage*)).ti,ab.

4. (craniocerebral and (trauma* or injur*)).ti,ab.

5. (cerebrovascular and (disease* or disorder* or occlusion* or insufficienc* or accident* or apoplex* or stroke*)).ti,ab

6. (intracranial and (disease* or disorder* or aneurism* or hemorrhage*)).ti,ab.

7. (head and (trauma* or injur*)).ti,ab.

8. ((posterior fossa or subarachnoid) and hemorrhage*).ti,ab.

9. (encephalo* or apoplex* or cerebral stroke*).ti,ab.

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. exp early ambulation/ or exp exercise therapy/ or exp neurological rehabilitation/

12. exp Posture/

13. ((early and (ambulation* or mobili* or rehab*)) or accelerated ambulation*).ti,ab.

14. (exercis* and (therap* or rehab* or remedial)).ti,ab.

15. ((neurologic* and rehab*) or neurorehab*).ti,ab.

16. (continuous passive and (motion or movement) and therap*).ti,ab.

17. ((position* and (seated or standing or sitting)) or posture* or head*up).ti,ab.

18. 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 10 and 18

20. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

21. 19 and 20

22. limit 21 to humans

S2. Characteristics of excluded studies and trials

Study	Reason for exclusion
Abdulwahab 1996 [1]	Wrong study design, no adverse events reported
Abouzari 2007 [2]	Wrong intervention, one group in supine and the other only to 40 degrees elevation
Abruzzi 2017 [3]	Wrong patient population, not severe brain injury
Adeolu 2012 [4]	Wrong patient population, not severe subdural haematoma
Agbeko 2012 [5]	Wrong study design, observational study on 10 children
Allison 2007 [6]	Wrong comparator, both groups mobilised head-up
Ancona 2019 [7]	Wrong intervention, does not emphasize early mobilisation
Andelic 2012 [8]	Wrong study design (quasi-randomised), no adverse events reported
Anderson 2017 [9–15]	Wrong intervention, did not mobilise above 30 degrees
Asberg 1989 [16]	Wrong study design (quasi-randomised), no adverse events reported
AVERT-DOSE [17]	Ongoing trial. Wrong patient population, not severe brain injury
Awad 2016 [18]	Wrong study design, review
Bai 2012 [19]	Wrong intervention, does not emphasize early mobilisation
Bernhardt 2008[20]	Wrong study design, comparison between stroke units in Trondheim, Norway and Melbourne, Australia
Bernhardt 2011 [21]	Wrong study design, response to letter
Bernhardt 2017a [22]	Wrong study design, response to letter
Bernhardt 2017b [23]	Wrong study design, review
Bernhardt 2017c [24]	Wrong study design, review
Borg 2011 [25]	Wrong study design, not patient data
Brummel 2012 [26]	Wrong study design, study protocol
Brummel 2014 [27]	Wrong patient population, not severe brain injury
Chang 2017 [28]	Wrong intervention, not emphasizing early mobilisation
Chen 2008 [29]	Wrong study design, describes the clinicians experience of participating in a multicentre trial
Collier 2007 [30]	Wrong study design, no adverse events reported
Collier 2010a [31]	Wrong study design, not patient data
Collier 2010b [32]	Wrong study design, not patient data
Collier 2010c [33]	Wrong study design, not patient data
Craig 2010 [34]	Wrong study design, systematic review, not unique data
Cuthbertson 2017 [35]	Wrong study design, editorial
English 2016 [36]	Wrong patient population, not severe stroke
Fink 2018 [37]	Wrong intervention, not emphasizing early mobilisation
Garrote 2016 [38]	Wrong study design, review
Kumaran 2013 [39]	Wrong patient population, not severe stroke
Kutlubaev 2015 [40]	Wrong study design, review
Langhorne 2010 [41]	Wrong patient population, not severe stroke
Langhorne 2011 [42]	Wrong study design, letter
Lavados 2014 [43]	Wrong study design, systematic review
Liang 2005 [44]	Wrong study design, not randomised, no adverse events reported
Liu 2014 [45]	Wrong patient population, not severe stroke
Logan 2017 [46]	Wrong comparator, control group received soft mobilisation to sitting position
Luk'ianov 2010 [47]	Wrong comparator, both groups mobilised head-up
Martinsson 2003 [48]	Wrong comparator, both groups mobilised head-up
Mayor 2017 [49]	Wrong study design, review
Melchers 1999 [50]	Wrong intervention, no early mobilisation as part of the stimulation process

Meng 2005 [51]	Wrong comparator, both groups mobilised head-up
Morreale 2016 [52]	Wrong comparator, does not emphasize early mobilisation
Na 2018 [53]	Wrong intervention, not emphasizing early mobilisation
Olkowski 2013 [54]	Wrong study design, observational
Pang 2003 [55]	Wrong intervention, not emphasizing early mobilisation
Poletto 2016 [56]	Wrong patient population, not severe stroke
Qi 2012 [57]	Wrong intervention, not specified
Rocca 2016 [58]	Wrong intervention, does not emphasize earlier mobilisation
Rybalko 2009 [59]	Wrong comparator, standard care group where mobilised
Sarfati 2017 [60]	Wrong patient population, not severe brain injury
Schmidt 2016 [61]	Wrong study design, review
Seeto 2013 [62]	Wrong study design, observational
Seo 2006 [63]	Wrong patient population, not severe stroke
SEVEL 2016 [64]	Wrong patient population, not severe stroke
Sundseth 2012 [65]	Wrong patient population, not severe stroke
Thompson 2013 [66]	Wrong study design, observational
Tong 2017 [67]	Wrong patient population, not severe stroke
Trevena-Peters 2017 [68]	Wrong intervention, not emphasizing early mobilisation
Van Vuuren 2016 [69]	Wrong study design, observational
Venturelli 2015 [70]	Wrong study design, international survey among physicians
Wang 2004 [71]	Wrong intervention, not emphasizing early mobilisation
Wang 2005 [72]	Wrong intervention, both groups could potentially do exercises. The control group was asked to exercise
Wang 2014 [73]	Wrong patient population, not severe stroke
Wang 2017 [74]	Wrong study design, review
Witcher 2015 [75]	Wrong study design, observational
Yelnik 2017 [76]	Wrong comparator, control group received soft mobilisation to sitting position
Zeng 2007 [77]	Wrong patient population, not severe stroke
Zhang 2005 [78]	Wrong patient population
Zhao 2003 [79]	Wrong intervention, no description of the intervention
Zhong 2006 [80]	Wrong comparator, both groups mobilised head-up
Zhu 2004 [81]	Wrong comparator, standard care group where mobilised

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S3. Number of patients with at least one adverse event not considered serious and only represented in two or fewer patients

Adverse events not considered serious	Early mobilisation	Standard care	Total	Relative risk or risk difference – (95% CI)
Blocked tracheal tube	0	2	2	RD -0.53 (-0.69 to -0.36
Ventriculitis	0	2	2	
Removal of venous or arterial catheter	0	2	2	
Restless	0	2	2	
Rash	0	2	2	
Hypertension	2	0	2	RD 0.53 (0.36 to 0.53)
Hyperkalaemia	2	0	2	
Hypercapnia	1	1	2	RR 1.00 (0.24 to 4.15)
Hypernatraemia	1	1	2	
Tongue biting	1	1	2	
Respiratory secretion (atelectasis)	1	0	1	RD 0.51 (0.35 to 0.67)
Bleeding urethra	1	0	1	
Removal of tracheotomy	1	0	1	
Alkalosis	1	0	1	
Hypermagnesaemia	1	0	1	
Hyperglycaemia	1	0	1	
Acute tubulointerstitial nephropathy	1	0	1	
Thrombocytosis	1	0	1	
Dental fracture	1	0	1	
Loose external ventricular drain screw	1	0	1	
Dysfunctional arterial catheter	1	0	1	
Distended anal sphincter	1	0	1	
Pancreatitis	1	0	1	
Nose bleeding	1	0	1	
Haematoma lower extremity	1	0	1	
Joint swelling	1	0	1	
Desaturation	0	1	1	RD -0.51 (-0.67 to -0.35)
Hypotension	0	1	1	
Agitated	0	1	1	
Removal of wound dressing	0	1	1	
Calf pain	0	1	1	
Subcutaneous emphysema	0	1	1	
Heart murmur	0	1	1	
Displacement of fracture	0	1	1	
Epidermolysis arm	0	1	1	
Fever without origin	0	1	1	
Increased saliva	0	1	1	
Obstipation	0	1	1	

Sleep apnea	0	1	1	
Gastrointestinal bleeding	0	1	1	

S4. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P 4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	P 6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P 6-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P 9-10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P 10-11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P 11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P 11-12

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P 12-15
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P 14
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P 12-13, p 15
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P 12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P 13-16
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1, 16-19
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, p 18
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1, Figure 2, p 19-20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 4-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P 20-24
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P 20-28
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P 28-29
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P 30-33

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P 34-35
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P 35

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Paper V

Reliability of the transcranial Doppler ultrasound-derived mean flow index for assessing dynamic cerebral autoregulation in healthy volunteers

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Abstract

The transcranial Doppler ultrasound-derived mean flow index (Mxa) is widely used for assessing dynamic cerebral autoregulation (dCA) in different clinical populations. This study aimed at estimating the relative and absolute reliability of Mxa in healthy participants in the supine position and during head-up tilt (HUT). Fourteen healthy participants were examined on two separate occasions during which, mean middle cerebral artery blood flow velocity (MCAv), non-invasive blood pressure, and heart rate were continuously recorded in the supine position and during HUT. Mxa was calculated as the correlation coefficient between mean arterial blood pressure and MCAv using either 3-, 5-, or 10-second averages collected over a 300 second period. Intraclass correlation coefficient ($ICC_{1.1}$) was calculated to assess relative reliability, while the standard error of measurement (SEM), and limits of agreement (LOA) were used to assess absolute reliability. Mxa-based 3-second averages yielded a similar relative and absolute reliability in both positions. When Mxa was calculated from 5-second averages, the most reliable values were obtained during HUT. The poorest reliability was achieved using 10-second averages, regardless of posture. The Mxa shows fair reliability with acceptable LOA in healthy volunteers when based on 3-second averages, both in the supine position and during HUT.

Keywords

Head-up tilt test; ICC; standard error of the measurement; limits of agreement; autoregulatory index; healthy

Introduction

Several methods are used to quantify the ability of the cerebrovasculature to buffer the impact of acute fluctuations in mean arterial pressure (MAP) on cerebral blood flow [1], so-called dynamic cerebral autoregulation (dCA). However, there is currently no widely accepted gold standard for assessing dCA, and as recently demonstrated by Sanders et al., the reproducibility of the different methods differ markedly [2].

The so-called mean flow index (Mxa) is notably used for continuous monitoring of dCA in various clinical populations [3–6]. It reflects the correlation between transcranial Doppler-derived middle cerebral artery blood flow velocity (MCAv) and mean arterial blood pressure (MAP) over a given time and with a specified sampling frequency [7,8].

According to a recent study, Mxa obtained during standing may be superior to that obtained in the seated position [9]. It may thus be valuable to supplement supine or seated Mxa with assessments obtained during orthostatic stress, which can safely be applied in a standardized fashion by head-up tilt (HUT) testing [10]. Indeed, recent findings in patients with traumatic brain injury suggest that Mxa assessment may specifically unveil impaired dCA during HUT, but not in the supine position [10]. As of now, the reliability of Mxa for assessing dCA during HUT has not been examined, neither in healthy nor in clinical populations.

In the present study, we sought to elucidate the relative and absolute reliability of Mxa in a group of healthy participants in the supine position and during HUT; we furthermore compared Mxa estimates based on 3-, 5- and 10-second averages of MAP and MCAv in each postition. We hypothesised that Mxa is a reliable index of dCA in both postures and

that the reproducibility of Mxa based on 3-second averages would be superior to Mxa based on 5- or 10-second averages.

Material and Methods

Participants

The study was designed as an intra-observer reliability study. Fourteen healthy participants (5 males, age: 28 ± 9 (mean ± SD) years, height: 175 ± 7 cm, weight: 72 ± 12 kg, BMI: 23 ± 4 $kg \cdot m^{-2}$) with no prior history of neurologic disease, diabetes, or psychiatric illness were included. The study was approved by the Research Ethics Committees of the Capital Region of Denmark (H-16042103). All procedures complied with the Helsinki Declaration, and all participants provided written informed consent before participating in the study.

Measurements

All data were digitized and synchronized through an AD-converter Powerlab 8/35 with a sample rate of 1000 Hz (ADInstruments Inc., Oxford, UK) and recorded using LabChart (LabChart ver. 8.10.05, ADInstruments Inc., Oxford, UK).

Continuous blood pressure was measured non-invasively by photoplethysmography (Nano System, ADInstruments Inc., Oxford, UK). The finger cuff was kept at heart level during the experiment, and MAP was calculated as the cyclic mean, which was extracted from LabChart. The electrocardiogram was obtained continuously from a single precordial lead to derive instantaneous heart rate (HR) using a bio-amplifier (ADInstruments Inc., Oxford, UK).

MCAv was obtained by insonating the middle cerebral artery through the right temporal ultrasound window using TCD (Multidop X; DWL, Sipplingen, Germany) with a 2 MHz

probe. Changes in MCAv were considered to reflect changes in global cerebral blood by assuming a constant diameter of the middle cerebral artery [5,11].

Procedure

The tests were conducted in a room with a constant temperature (22° C). Each participant took part in two sessions with an interval of approximately four weeks (23 ± 3 days) and at the same time of day (between 12:00 and 16:00). During each session, the participant was strapped to the tilt table and the equipment was attached. The participants placed the hand with the blood pressure cuff at heart level and kept it there during the experiment. After 30 minutes of rest in the supine position, the measurements were started. After calibration of the continuous blood pressure (approximately two minutes), a five-minute baseline period was recorded, and the participant was then tilted head-up to 30 degrees tilt for one minute, 50 degrees for one minute, and 70 degrees HUT for five minutes. Before starting the measurements, the participants were instructed to not speak unless experiencing discomfort, i.e. symptoms of pre-syncope such as light-headedness, dizziness, sweating etc. Such events were recorded.

Data analysis

Data analysis was performed using MATLAB 2017b (Mathworks, Natick, USA). Prior to this, all data were visually inspected according to current guidelines and artefacts arising from the transcranial Doppler signal or the blood pressure signal were removed or interpolated [12].

The 300-second baseline period and the 300-second maximum tilt period were divided into 3-second, 5-second and 10-second blocks. The baseline and the maximum tilt period were then separately divided into epochs as follows: Twenty 3-second blocks were

assembled into one epoch to yield five epochs of 60 seconds per period; thirty 5-second blocks were assembled into one epoch to yield two epochs of 150 seconds per period; and thirty 10-second blocks were assembled into one 300-second epoch per period [7,8,13]. Within each epoch, MAP values were correlated against the corresponding MCAv from each block, producing the Mxa. When there was more than one epoch and consequently, more than one Mxa value per period (i.e., for the 3-second and 5-second blocks), the mean of these values was calculated, yielding one Mxa value at baseline and one at HUT (**Fig. 1**).

Statistics

All data were analysed using SAS ver. 7.11 (SAS Institute Inc., Cary, NC, USA.) except for the intra-class correlation coefficient which was analysed using Stata ver. 11.1 (StataCorp, College Station, Texas, USA).

Data are presented as mean ± SD unless otherwise stated. Haemodynamic variable (HR, MAP and MCAv) averages were calculated from the 300-second baseline and 300-second HUT period. Differences between these variables were examined using paired t-test.

The sample size was based on data from the study by Liu et al (2015), who studied patients with traumatic brain injury and reported an Mxa based upon MAP and MCAv of 0.18 with a standard deviation of ± 0.24 [7]. Assuming a similar standard deviation in healthy volunteers, 14 subjects would be necessary to detect a test-retest difference in Mxa of 0.3 at an alpha level of 0.05 and a beta level of 0.20 (corresponding to a power of 80%), using the sample size equation suggested by Hopkins [14] with a 0.3 test-retest difference.

Relative reliability was assessed by a one-way mixed effects model (intraclass correlation coefficient [$ICC_{1.1}$]) with corresponding 95% confidence intervals for investigating

consistency taking into account the difference between tests when using a single rater (CGR) [15]. The $ICC_{1.1}$ was interpreted as suggested by Cicchetti [16], so that an $ICC_{1.1}$ below 0.40 indicated poor, between 0.40 and 0.59 fair, between 0.60 and 0.75 good, and above 0.75 excellent reliability.

Systematic variations between test sessions were tested using paired t-test and visualised through Bland-Altman plots. The latter was used for evaluation of heteroscedasticity and detection of outliers.

Absolute reliability was calculated as the standard error of measurement (SEM) using a one-way random effects model as well as the SEM_{95} (SEM x 1.96) to express the variation with 95% certainty for individual participants [17]. Limits of agreement (LOA) were calculated from the Bland-Altman plot under the assumption that the mean value was zero.

In order to compare the agreement between repetitive measurements for the different averages (3, 5, and 10 seconds), we used a generalized linear model for the squared day-to-day differences, using a gamma distribution with log-link. The estimation was performed using generalized estimating equations to take account of the correlation between the three differences for each individual, and the quoted p-values are for score tests.

Results

None of the volunteers showed clinical signs of cerebral hypoperfusion (syncope etc.) during the experiments. The right temporal window allowed for insonation of the ipsilateral middle cerebral artery in all volunteers.

Both MAP and HR increased during HUT, while MCAv decreased; changes in these variables were similar between the two study days (**Table 1**). Mxa values did not differ between the supine position and HUT on any of the study days (**Table 2**). The scatter plot between test sessions indicated a larger variance when going from 3-seconds towards 10-seconds analysis (**Fig. 2A-B**). Bland-Altmann plots showed no signs of heteroscedasticity and outliers were only present when using 10-second blocks (**Fig. 3A-B**).

Table 1. Haemodynamic variables

	Test session	**Supine**	**HUT**
MAP (mmHg)	1	65 ± 8	77 ± 7*
	2	67 ± 11	78 ± 12*
HR (bpm)	1	63 ± 9	82 ± 13*
	2	62 ± 10	83 ± 12*
MCAv (cm/s)	1	75 ± 10	68 ± 9*
	2	75 ± 11	66 ± 9*

All data are presented as mean ± SD. * $P<0.05$ compared to supine position, using paired t-test; MAP: mean arterial pressure; HR: heart rate; MCAv: Middle cerebral artery mean flow velocity; HUT: head-up tilt to 70 degrees.

Table 2. Mean flow index (Mxa) calculated from different block sizes

Test session	1	2
Mxa supine		
3-second analysis	-0.07 ± 0.13	-0.11 ± 0.13
5-second analysis	0.01 ± 0.19	-0.03 ± 0.16
10-second analysis	0.11 ± 0.19	0.04 ± 0.26
Mxa HUT		
3-second blocks	-0.16 ± 0.18	-0.20 ± 0.16
5-second blocks	-0.08 ± 0.21	-0.11 ± 0.19
10-second blocks	-0.03 ± 0.32	-0.12 ± 0.37

All data are presented as mean ±SD. HUT: head-up tilt to 70 degrees.

The relative and absolute reliability estimates are summarised in **Table 3**. Overall, $ICC_{1.1}$ tended to be higher with shorter averages, both in the supine position and during HUT. For Mxa calculated from 3-second blocks, $ICC_{1.1}$ was similar in the supine position and during HUT, indicating fair relative reliability in both positions. When calculated from 5-second blocks, $ICC_{1.1}$ indicated that the relative reliability was poor in the supine position and fair during HUT, while it was poor both in the supine position and during HUT when using 10-second blocks. In terms of absolute reliability, SEM and LOA were lowest when based on 3-second blocks and tended to increase with longer time blocks, regardless of position. There was no significant difference in the squared day-to-day

differences between analysis methods (3-, 5-, and 10-seconds) in supine or during HUT (P=0.096 and P=0.086, respectively).

Table 3. Relative and intra-observer reliability of the mean flow index (Mxa) in healthy volunteers.

	$ICC_{1.1}$ (LL_{95}; UL_{95})	SEM	SEM_{95}	LOA
Mxa supine				
3-second blocks	0.53 (0.04; 0.82)	0.09	0.18	0.25
5-second blocks	0.22 (-0.32; 0.66)	0.15	0.30	0.43
10-second blocks	0.21 (-0.33; 0.65)	0.20	0.39	0.57
Mxa HUT				
3-second blocks	0.46 (-0.05; 0.79)	0.12	0.24	0.35
5-second blocks	0.57 (0.10; 0.84)	0.13	0.26	0.37
10-second blocks	0.15 (-0.38; 0.61)	0.32	0.63	0.90

HUT: head-up tilt to 70 degrees; ICC: Intra-class correlation coefficient; LL_{95} and UL_{95}: Lower and upper limit of the 95% confidence interval, respectively; SEM: Standard error of measurement using a one-way random effects model; SEM_{95}: SEM with 95% confidence interval; LOA: Limits of agreement under the assumption that the mean is zero (corresponding to the 95% limits in a Bland-Altman plot).

Discussion

Our findings indicate that the reliability of Mxa for assessing dCA in healthy volunteers depends critically on the method used for analysing the data. In a group of healthy volunteers, we thus found that the most reliable Mxa estimates were achieved when basing them on 3-second rather than 5- or 10-second averages of continuously recorded MCAv- and MAP-values.

While the relative reliability of Mxa estimates has rarely been assessed in previous studies, our $ICC_{1.1}$ values do agree with findings from two recent studies. Hence, one study reported ICC values for Mxa, calculated from 3-second blocks, of 0.42 and 0.46 in the right and left hemisphere respectively, in 19 healthy individuals positioned in the 45 degrees seated position [18]. Another study indicated that $ICC_{1.1}$ for Mxa was higher during active standing than in the supine position, i.e. with good to excellent vs. poor relative reliability, respectively [9]. Unfortunately, the block length for calculating Mxa was not specified, but these findings are consistent with the better relative reliability during HUT when Mxa was based on 5-second averages in the present study.

Absolute reliability estimates of Mxa based on 3-second averages using SEM, the smallest change that can reliably be detected on the group level, was ≤ 0.12. Using LOA derived by the same method, the smallest change that can reliably be detected on the individual level, was ≤ 0.35. Our findings thus indicate that Mxa is not suited for assessing subtle physiological changes in dCA on the individual level, at least not in healthy subjects.

The difference in reliability estimates found in this study may be influenced partly by the mathematics and partly by the physiology. When using shorter blocks and more epochs

to correlate the Mxa a regression towards the mean may occur. On the other hand, shorter blocks will hold more information and the baroreflex and spontaneous breathing may be more prominent in the Mxa at this sampling frequency [19].

Whether or not an orthostatic stressor may be useful for increasing the signal-to-noise ratio in the context of dCA assessments has been the subject of some debate [20,21]. While the application of orthostatic stress by e.g. HUT, active standing, or lower body negative pressure may be relevant to detect subtle changes in dCA by other methods, our findings indicate that this is not necessarily the case for Mxa when sufficiently short (≤ 3-second) MCAv-MAP averages are used for the analysis. However, when using 5-second averages, HUT does appear to improve both relative and absolute reliability, while 10-second averages yield unreliable Mxa values regardless of posture. It remains to be determined whether this is also the case in various clinical populations, as well as when the Mxa assessments are based on other basal arteries of the brain than the middle cerebral artery as in the present study.

A major limitation of this study is the low number of participants. Assuming similar LOA values, the inclusion of a larger sample could lead to a larger variation and thereby increase the ICC [22]. Moreover, we assumed a stable $PaCO_2$ value in both supine and during HUT, and furthermore that the diameter of the middle cerebral artery remained constant during the assessments, factors that should be critically reassessed in future studies. In any event, and given that monitoring of end-tidal CO_2 is currently recommended when assessing dCA by transfer function analysis [12], it would be reasonable to implement this in the context of Mxa in future studies. However, the most important limitation relates to the Mxa estimate itself, as it is based on MAP and not cerebral perfusion pressure, which yields the closely related index Mx. Mxa correlates

well with Mx (r = 0.78) in patients with traumatic brain injury [23], but they are not identical, and their exact relationship in healthy volunteers is unknown. Thus, even subtle changes in intracranial pressure may have decreased $ICC_{1.1}$ and increased SEM and LOA in the present study.

In conclusion, the reliability of Mxa is fair and acceptable, both when obtained in the supine position and during HUT when 3-second MCAv-MAP blocks are used for the analysis in healthy volunteers. Hence, orthostatic stress is not necessary for obtaining reliable estimates, but may be necessary if 5-second averages are used. It remains to be determined whether this is also the case in different clinical populations in which dCA may be impaired.

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Competing Interest

The authors declare no competing interests.

Author contributions

CGR, KM and JM conceived and designed the study. CGR and MHO performed the experiments and CGR and LTS analysed the data. CGR, MHO, LTS, RMGB, KM and JM interpreted the results. CGR and MHO prepared the figures and CGR drafted the manuscript. MHO, RMGB, LTS KM and JM revised the manuscript critically. All authors read and approved the final version of the manuscript.

Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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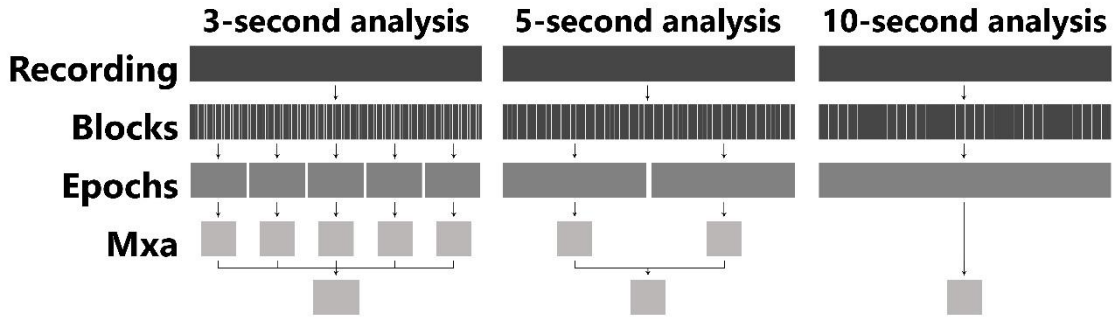
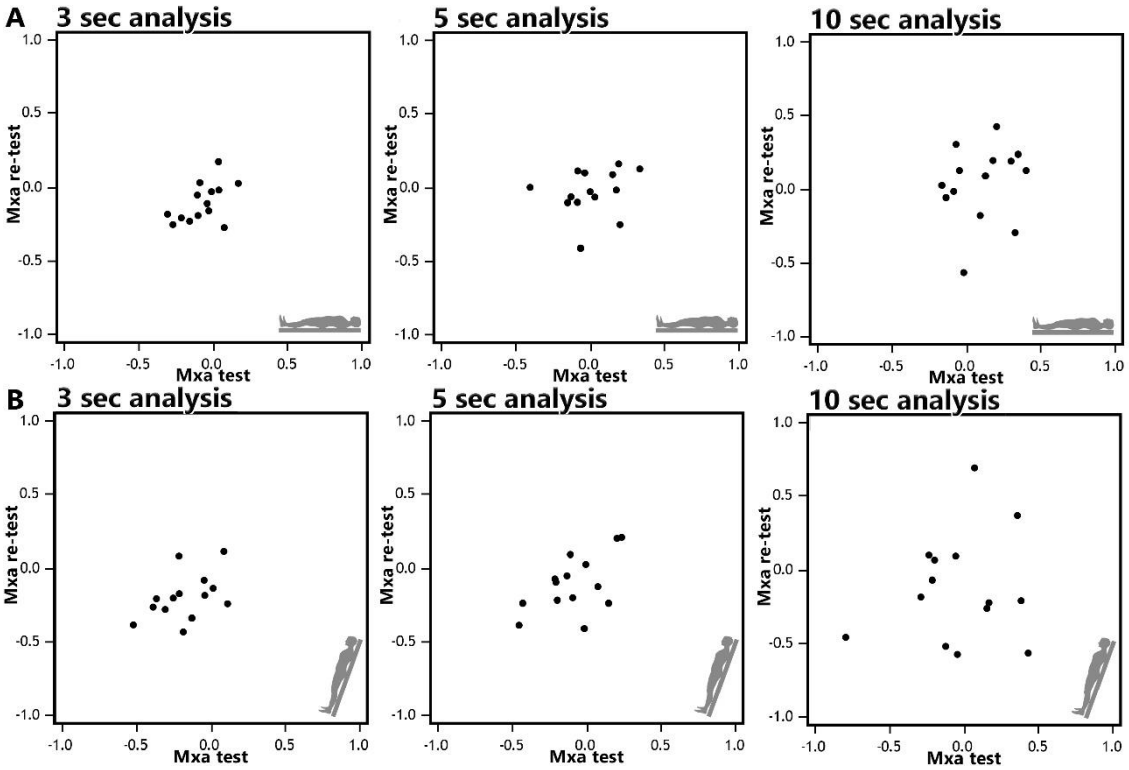
Fig. 1. Graphical representation of data analysis for Mxa using 3, 5 and 10-second blocks.



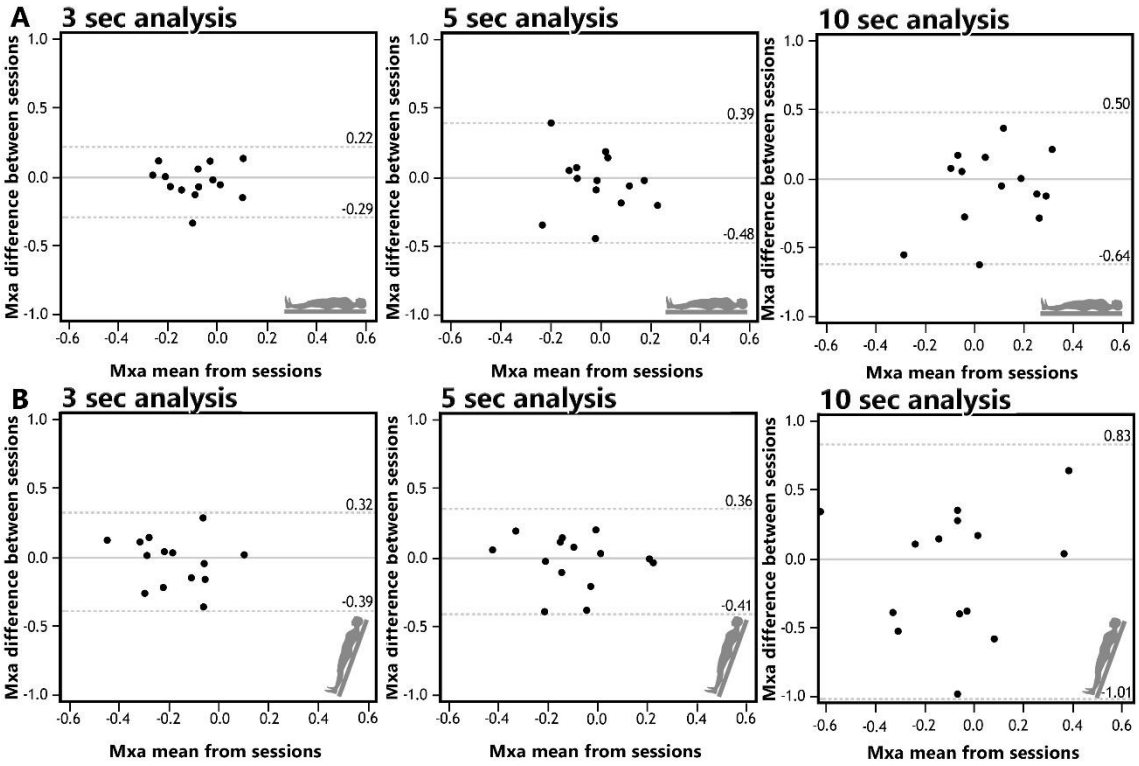
Recording length in this study was 300 seconds. Mxa: Mean-flow-index calculated using MAP and MCAv

Fig. 2. Scatter plot for the test and re-test of Mxa in supine and during HUT.



Mxa: Mean-flow-index calculated using MAP and MCAv

Fig. 3. Bland-Altman plots illustrating the mean and the difference between the first and second test session in supine and during HUT.



Mxa: Mean-flow-index calculated using MAP and MCAv.

Paper VI

Dynamic cerebral autoregulation during early orthostatic exercise in patients with severe traumatic brain injury: results from a randomized clinical feasibility trial

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The authors have no conflicts of interest to declare.

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Abstract

Objective: The clinical effect of early orthostatic exercise is unknown in patients with severe traumatic brain injury, but may strengthen either the systemic or cerebral hemodynamic response to head-up tilt and thereby minimize orthostatic intolerance. We examined the effect on dynamic cerebral autoregulation (dCA) and the occurrence of orthostatic intolerance after four weeks of regular orthostatic exercise by head-up tilt using a tilt table with integrated stepping.

Settings and Participants: Thirty-four patients with severe traumatic brain injury admitted to a neurocritical care unit.

Design: Randomized controlled trial.

Main measures: Middle cerebral artery blood flow velocity (MCAv), and dCA evaluated by the non-invasive mean flow index (nMxa).

Results: The transition from the supine position to head-up tilt triggered a 10% to 16% decrease in MCAv and increased nMxa in both groups at all time points ($P < 0.05$), with no differences between groups. There was no difference in the number of episodes with orthostatic intolerance, and no association between changes in $PaCO_2$-adjusted nMxa and the occurrence of orthostatic reactions (P=0.35).

Conclusions: Early orthostatic exercise does not affect dynamic cerebral autoregulation and does not protect against orthostatic intolerance in patients with severe traumatic brain injury.

Trial registration: ClinicalTrials.gov identifier: NCT02924649. Registered on 3rd October 2016

Keywords: early mobilization; head-up tilt test; dynamic cerebral autoregulation; traumatic brain injury; orthostatic intolerance;

Introduction

Recent studies report that early mobilization may have beneficial effects on functional outcomes in critically ill patients; [1], although the effects are less well studied in patients with traumatic brain injury (TBI) [2,3]. Many patients with TBI, particularly those with severe injuries, require prolonged deep sedation to treat intracranial pressure increases and metabolic stress [4]. Such immobilization may lead to orthostatic intolerance [5] due to haemodynamic decompensation and changes in autonomic regulation [6], which may subsequently manifest itself during mobilization to the upright position [7,8]. Conversely, regular mobilization on a tilt table, here designated 'orthostatic exercise', has previously been reported to restore orthostatic tolerance in patients with neurally mediated syncope, which may both involve beneficial effects on systemic vascular tone, fluid retention, and dynamic cerebral autoregulation (dCA) [9]. It remains to be determined whether this is also the case in patients with severe TBI.

The present study was part of a randomized trial that investigated the feasibility of early orthostatic exercise in patients with severe traumatic brain injury. We hypothesized that early orthostatic exercise, compared to standard care, would strengthen dCA and reduce the occurrence of orthostatic intolerance.

Methods

The randomized feasibility study (Riberholt CG et al., submitted) was conducted following the latest version of the Helsinki Declaration [10] and the ICMJE Recommendations for the Protection of Research Participants (www.icmje.org). The study protocol was approved by the Scientific-Ethics Committee of the Capital Region in Denmark (H-16041794) and registered at ClinicalTrials.gov (NCT02924649) [11].

Participants

Thirty-eight patients were included within 12.8 (SD ±5.2) days (time of first autoregulation assessment) after admission with severe TBI (**Supplementary Table 1**). The inclusion criteria were Glasgow Coma Score (GCS) < 11, suspected persisting disorder of consciousness (unresponsive wakefulness syndrome or minimally consciousness state), and a stable intracranial pressure (< 20 mmHg) during the past 24 hours. The exclusion criteria were fractures of the lower extremities that prohibited weight-bearing, spinal cord injury, or lack of informed consent from the next of kin. Patients were randomly assigned to either early orthostatic exercise or standard care for the following four weeks.

Randomization and masking

Patients were randomly assigned (1:1) to either early orthostatic exercise (intervention group) or standard care (control), using a web-based computer-generated block-randomization procedure. Block sizes were randomly assigned as either 4, 6, or 8 patients in each block. We stratified the randomization according to either low or high GCS (3-6 and 7-10, respectively). Due to the nature of the intervention (tilt-table), it was not possible to mask the intervention to the clinical staff or the patient.

Orthostatic intolerance

As described in the trial protocol [11], orthostatic intolerance was defined as "relative" when systolic blood pressure dropped more than 30 mmHg systolic or 15 mmHg diastolic or heart rate increased with more than 30 bpm from supine measures during head-up tilt, and as "absolute" in case of a

reduction of blood pressure to 80 mmHg systolic or 50 mmHg diastolic or an increase in heart rate to 180 bpm.

Intervention and standard care

The early orthostatic exercise consisted of daily (weekdays) head-up tilt on an ERIGO® tilt-table (Hocoma, Switzerland) to 70 degrees tilt for 20 minutes. In case of a critical reduction in either blood pressure, cerebral perfusion pressure, or an increase in intracranial pressure or heart rate as described above, the patient was moved to 0 degrees until stable and then returned to standing [11]. These short breaks were not considered part of the 20-minute session. Patients who regained the ability to stand up during the four-week intervention period had the intervention period terminated, but remained in the study.

The treatment in the standard care group was decided by the treating physician, nurses, and therapists. Mobilization could be a part of the standard care but to a much smaller scale, and the focus of standard care was primarily on respiratory function and re-positioning to avoid pressure ulcers.

Measurements

At baseline and 2- and 4-week follow-up, a 5-minute head-up tilt was performed in both groups using the same tilt table as described above. During tests, continuous non-invasive arterial blood pressure was measured using a photoplethysmograph on the middle index finger at heart level (ADInstruments, Oxford, UK), while heart rate was measured from three-lead ECG. Transcranial Doppler ultrasound was used to measure unilateral linear middle cerebral artery blood flow velocity (MCAv) by the continuous measurement of backscattered Doppler signals using a 2-MHz pulsed transcranial Doppler (TCD) ultrasound system (Multi-Dop® T digital, Compumedics Germany

GmbH, Singen, Germany). Following a standardized search technique [12], the Doppler probe was secured over the transtemporal window with an adjustable metal LAM rack (Compumedics Germany GmbH, Singen, Germany) and an insonation depth for MCAv of 45–60 mm. Arterial blood samples were obtained from the radial artery contralaterally to the plethysmography, both in the supine position and at the end of the head-up tilt, and were immediately analyzed on a nearby arterial blood gas analyzer (ABL800, Radiometer, Copenhagen, Denmark).

Data analysis

Data in the supine position and during head-up tilt was visually inspected using Labchart reader (ADInstruments, Oxford, UK). Two data files, containing periods of artefacts in the continuous blood pressure and Doppler signals were generated alongside the visual inspection and were analyzed using an R-script (R version 3.6.1, R Core Team, Vienna, Austria**)**. Quality control of the data was done through the R-script and presented in S**upplementary Table 2**. The following indices were calculated: the non-invasive mean flow index (nMxa), the cerebrovascular resistance index (CVR), and the Gosling's Pulsatility index (GPI).

Statistical analyses

As stated in the trial protocol [11], the statistical analysis plan for the present study was prepared before the data analysis (available at https://www.hvidovrehospital.dk/afdelinger-og-klinikker/traumatisk-hjerneskade/om-klinikken/Sider/forskningsenheden-rubric.aspx). However, due to an unexpected amount of missing data, we were unable to comply entirely with the original plan.

Briefly, the nMxa was used as a continuous variable for analyzing the patient's dCA. Firstly, we compared the nMxa after four weeks for between-group differences using a mixed-effects model. Secondly, the mixed-effects model was used to investigate differences over time and between groups for the nMxa and each of the other hemodynamic variables. Thirdly, a mixed-effects model was used to investigate the association between the nMxa and orthostatic intolerance, as we applied the latter to the model. Finally, the association between the dichotomized nMxa (where nMxa > 0.3 was considered to signify impaired autoregulation) [13] and the orthostatic intolerance was calculated using Fischer's exact test.

All statistical analyses and graphical presentations were done using SAS/STAT software and SAS/GRAPH version 3.71 (SAS Institute Inc., Cary, NC, USA).

Results

Of 38 patients included in the feasibility study (19 in each group), 34 patients (17 in each group) underwent a head-up tilt test at baseline. Thus, two patients had poor insonation window, one measurement was of poor quality, and we experienced equipment malfunction in one patient. For analysis between groups, 16 patients had the head-up tilt performed at four weeks (9 in early orthostatic exercise, 7 in the standard care). Four patients died during the study period and could, therefore, not be re-tested at four-weeks (**Figure 1**).

Insert Figure 1 here

During head-up tilt, MAP and HR both increased at all time points in both groups (**Table 1**). Although MAP was lower during head-up tilt at baseline in the early orthostatic exercise group compared to the control group, the MAP and HR responses did not differ between groups at 2- and 4-week follow-up. MCAv also decreased during head-up tilt in both groups at all time points, with a concomitant increase in CVR; no differences were observed between groups. Arterial blood gas values also did not differ between groups (**Supplementary Table 3**).

Insert Table 1 here

The nMxa increased from supine to head-up tilt ($P < 0.05$) at all time points with no difference between groups; except for the two-week time point where the nMxa decreased from supine to head-up tilt in the standard care group ($P < 0.05$) (**Table 2)**. The increase in nMxa was not associated with orthostatic intolerance when adjusting for $PaCO_2$ as the mixed-effects model estimated a decrease in nMxa of -0.048 when orthostatic intolerance was present and no association between orthostatic intolerance and impaired dCA (nMxa > 0.3) (Fisher's exact test P=1.00) (**Table 1 and 2**).

Insert Table 2 here

Discussion

In the current study, we found no evidence to suggest that early orthostatic exercise compared to standard care affected dCA over four weeks in patients with severe TBI, neither in the supine nor in the head-up tilt position. A quarter of all patients experienced orthostatic intolerance, but this was not associated with impaired dCA.

Our results suggest that early orthostatic exercise is safe in patients with severe TBI, at least in those with stable intracranial pressure. The patients did experience a drop in MCAv during head-up tilt, at the same magnitude as that observed in healthy males (12 % in the present study vs 9 % in healthy volunteers at 60 degrees tilt) [14]. Head-up tilt was associated with a slightly less effective dCA, as indicated by an increase in nMxa, which is consistent with the changes observed in healthy volunteers in transfer function analysis-based studies of negative lower body pressure [15]. The development of orthostatic intolerance was unrelated to changes in $PaCO_2$-adjusted dCA, and in none of the patients was the transition from the supine position to head-up tilt associated with a change in nMxa from maintained (nMxa $\leq$ 0.3) to impaired (nMxa > 0.3) dCA. Hence, our findings do not support the contention that orthostatic intolerance in these patients is related to changes in dCA.

We were limited in our ability to extract data, partly due to missing recordings but also due to poor quality data in some patients. It is not uncommon for studies using transcranial Doppler ultrasound only to use good quality data, though this does render the interpretation of data susceptible to bias. These considerations should be taken into account when interpreting the data.

The missing data at the follow-up are a clear limitation to this study. Patients were lost for several reasons, notably by being transferred out of the hospital when they no longer needed specialized neurosurgical treatment. Apart from the declining sample size, which increases the risk of a type II

error, the lack of an effect of early orthostatic exercise on dCA may reflect that the remaining patients represent a subgroup of patients with a poorer prognosis than the patient group as a whole. Furthermore, patients with short duration of measurements are more likely to have a poor quality of data which often occurs in patients with orthostatic intolerance.

In conclusion, early orthostatic exercise does not appear to affect the systemic or cerebral haemodynamic response to head-up tilt in patients with severe TBI; although dCA was impaired by head-up tilt, this was unchanged after early orthostatic exercise compared to standard care. Thus, our findings do not support the hypothesis that early orthostatic exercise protects patients with severe TBI from experiencing orthostatic intolerance.

Author contributions

CGR, JM, and KM designed the study. CGR collected the data, and CGR and MHO analyzed the data. All authors were involved in the interpretation of the results. CGR drafted the manuscript, and all authors revised it critically. All the authors approved the manuscript.

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Table 1. Hemodynamic variables in supine position and during head-up tilt

Test session	Baseline		2 weeks		4 weeks	
	EOE	SC	EOE	SC	EOE	SC
MAP (mmHg)						
Supine	[a] 79 ±12†	[a] 94 ±21	[d] 85 ±17	[d] 83 ±11	[d] 81 ±14	[e] 81 ±15
HUT	[b] 88 ±19	[c] 99 ±25	[e] 98 ±18	[e] 99 ±19	[d] 91±10	[e] 91 ±14
Δ (%) 95% CI	11% [-2, 23]	5% [-3, 13]	16% [-2, 34]	21% [0, 41]	18% [4, 32]	14% [6, 22]
HR (bpm)						
Supine	[a] 92 ±23	[a] 95 ±17	[d] 102 ±16‡	[d] 84 ±10	[d] 91±14	[e] 84 ±10
HUT	[b] 101 ±24	[c] 109 ±22	[e] 119 ±25	[e] 113 ±15	[d] 97 ±13	[e] 105 ±11
Δ (%) 95% CI	11% [0, 23]	14% [8, 20]	20% [9, 31]	34% [23, 46]	11% [-1, 23]	27% [15, 39]
MCAv (cm/sec)						
Supine	[a] 73 ±29	[a] 70 ±28	[d] 63 ±18	[d] 59 ±17	[d] 61 ±17	[e] 52 ±14
HUT	[b] 68 ±27	[c] 67 ±22	[e] 57 ±14	[e] 58 ±13	[d] 51 ±15‖	[e] 45 ±10‖
Δ (%) 95% CI	-11% [-14, -6]	-10% [-16, -3]	-16% [-27, -6]	-10% [-20, 1]	-13% [-20, -6]	-11 [-20, -3]
CVR (mmHg/cm/sec)						
Supine	[a] 1.23 ±0.47	[a] 1.71 ±1.08	[d] 1.49 ±0.59	[d] 1.55 ±0.57	[d] 1.54 ±0.59	[e] 1.69 ±0.64

HUT	[b] 1.44 ±0.47	[c] 1.70 ±0.84	[e] 1.80 ±0.52	[e] 1.79 ±0.53	[d] 2.06 ±0.65	[e] 2.16 ±0.84
Δ (%) 95% CI	24% [11, 37]	18% [4, 31]	40% [23, 56]	36% [4, 68]	36% [25, 48]	30% [7, 53]
GPI						
Supine	[a] 0.87 ±0.20	[a] 0.93 ±0.38	[d] 0.86 ±0.22	[d] 0.87 ±0.10	[d] 0.86 ±0.21†	[e] 0.94 ±0.22†
HUT	[b] 1.02 ±0.23	[c] 0.95 ±0.29	[e] 0.82 ±0.25	[e] 0.80 ±0.12	[d] 0.90 ±0.25‡	[e] 0.91 ±0.22‡
Δ (%) 95% CI	17% [10, 24]	13% [5, 21]	5% [-13, 23]	-7% [-14, 0]	5% [-2, 12]	-8% [-27, 11]
Orthostatic intolerance						
Number of patients (%)	5 (29)	3 (18)	1 (14)	2 (29)	1 (11)	0 (0)

All values in table are mean ±standard deviation unless otherwise stated; EOE: Early orthostatic exercise; SC: Standard care; MAP: Mean arterial pressure; 95% CI: 95% confidence interval; HUT: Head-up tilt; HR: Heart rate; MCAv: Middle cerebral artery flow velocity; CVR: Cerebrovascular resistance; GPI: Gosling's pulsatility index; OI: Orthostatic intolerance; Δ-values are calculated as (HUT-supine)/supine; a: n=17; b: n=16; c: n=12; d: n=9; e: n=7; †Significant difference at baseline (mixed-effects model) $P < 0.05$; ‡Significant difference at two weeks (mixed-effects model) $P < 0.05$; ‖Both groups are significant lower at 4-weeks (mixed-effects model) $P < 0.05$; All analyses were adjusted for stratification and interaction between group and the time of measurement. No significant difference in patients experiencing OR at baseline (Fischer's exact test P=0.688);

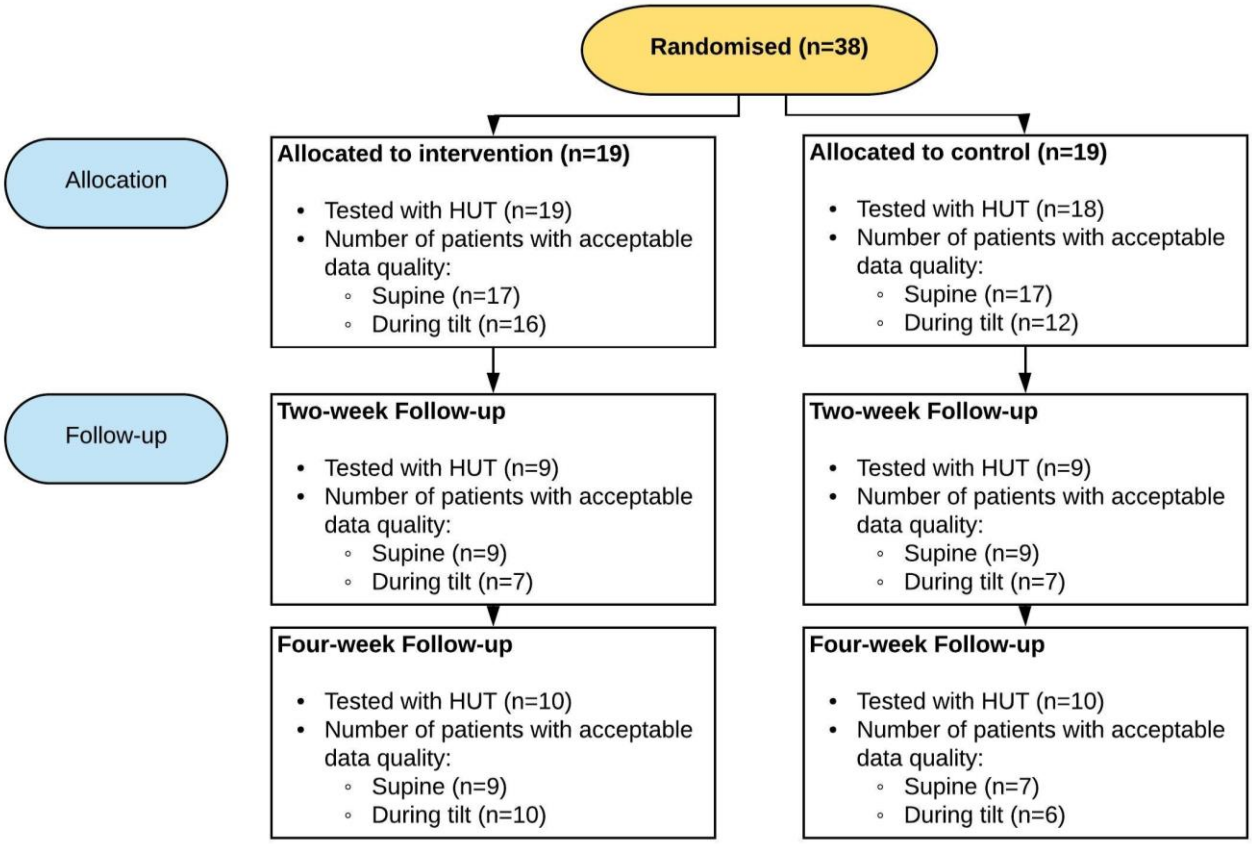
Table 2

. Dynamic cerebral autoregulation.

Test session	**Baseline**		**2-weeks**		**4-weeks**	
	EOE	**SC**	**EOE**	**SC**	**EOE**	**SC**
Supine	N=17	N=17	N=9	N=9	N=9	N=7
nMxa	0.15 ±0.32	0.21 ±0.24	0.11 ±0.30	0.47 ±0.18	0.21 ±0.20	0.22 ±0.16
Patients with nMxa > 0.3 (%)	5 (29)	7 (41)	2 (22)	7 (78)	3 (33)	3 (43)
HUT	N=16	N=12	N=7	N=7	N=10	N=6
nMxa	0.30 ±0.23*	0.37 ±0.16*	0.39 ±0.12*	0.17 ±0.15†	0.32 ±0.12*	0.34 ±0.22*
Patients with nMxa > 0.3 (%)	8 (50)	9 (75)	6 (85)	2 (29)	6 (60)	4 (67)

Legend: SC: Standard care; EOE: Early orthostatic exercise; *The nMxa was significantly higher during HUT than supine in both groups $P < 0.05$, when adjusting for the difference in $PaCO_2$; † $P < 0.05$, compared to EOE during HUT at the same time; All analyses were adjusted for stratification variable, $PaCO_2$ level and interaction between the group and the time of measurement.

Figure 1. Flow chart



Legend: HUT: Head-up tilt;

Supplementary material

Supplementary Table 1. Baseline characteristics in the two intervention groups and the group of excluded patients

	Patients re-tested at four weeks (n=16)	**Patients not re-tested at four weeks (n=22)**
Age (years) – mean (±SD)	44 ±21	45 ±18
Female – n (%)	3 (19%)	8 (36%)
Brain injury (initial CT-scan) – n (%)		
tSAH	10 (63%)	17 (77%)
aSDH	12 (75%)	19 (86%)
cSDH	1 (6%)	2 (9%)
EDH	2 (13%)	4 (18%)
IVH	9 (56%)	4 (18%)†
Contusion	10 (63%)	13 (59%)
Mechanism of injury – n (%)		
Traffic	7 (44%)	9 (41%)
Fall	6 (38%)	8 (36%)
Blunt force	3 (19%)	2 (9%)
Suicide attempt	-	2 (9%)
Unknown	-	1 (5%)
Secondary injury – n (%)		
1 fracture of extremities or trunk	6 (38%)	2 (9%)

>1 fracture of extremities or trunk	4 (25%)	6 (27%)
No fractures	6 (38%)	14 (64%)
Comorbidities – n (%)		
Type II diabetes	-	1 (5%)
Pulmonary heart disease	-	1 (5%)
Hypertension	-	1 (5%)
Schizophrenia	-	2 (9%)
Chronic obstructive lung disease	-	2 (9%)
Atrial fibrilation	-	2 (9%)
None	16 (100%)	17 (77%)
Neurosurgical procedures performed – n (%)		
Evacuation of haematoma	6 (38%)	9 (41%)
Craniotomy	6 (38%)	12 (55%)
Craniectomy	5 (31%)	5 (23%)
EVD	11 (69%)	16 (73%)
VP shunt	3 (19%)	1 (5%)
First measured GCS – median (IQR)	6 (3 to 9)	5 (3 to 9)
GCS at inclusion - n (%)		
Low GCS (3-6)	8 (50%)	12 (55%)
High GCS (7-10)	8 (50%)	10 (45%)
Sedated at randomization – n (%)	5 (31%)	7 (32%)
RASS– median (IQR)	-3 (-4 to -3)	-4 (-5 to -3)
Days from injury to randomization – median (IQR)	12 (11 to 16)	12 (10 to 15)

Days to first mobilisation - median (IQR)	14 (11 to 18)	13 (11 to 15)
Days at the NCCU – median (IQR)	29 (23 to 38)	25 (17 to 34)
Days at the RU – median (IQR)	76 (57 to 101)	63 (31 to 87)
End of PTA (days) – median (IQR)	74 (45 to 104)	74 (53 to 84)

SD: Standard deviation; n: number; tSAH: traumatic subarachnoid hematoma; aSDH: acute subdural hematoma; cSDH: chronic subdural hematoma; EDH: epidural hematoma; IVH: intraventricular hematoma; TBI: traumatic brain injury; EVD: external ventricular drainage; VP shunt: ventriculoperitoneal shunt; GCS: Glasgow Coma Score; IQR: Interquartile range; RASS: Richmond Agitation Sedation Scale; NCCU: Neurocritical care unit; RU: Rehabilitation unit; PTA: Posttraumatic amnesia; † Fischer's exact test P=0.0199;

Supplementary Table 2. Quality control of transcranial doppler and non-invasive blood pressure.

Visual inspection of measurements of arterial blood pressure (ABP) and middle cerebral artery flow velocity (MCAv) for artefacts and periods with artefacts in just one of the variables resulted in deletion in both. If at least 50% of valid raw data were present then blocks of 3 seconds ABP and MCAv were created. For every 60 seconds, i.e. 20 blocks, a Pearson's correlation coefficient between ABP and MCAv were calculated, generating an epoch. Again, at least 50% of blocks must remain, otherwise the epoch will be deleted. Thus, ideally five epochs and five correlation coefficients are created for both supine and standing position. nMxa is then calculated as the average of all five epochs for the given position. Patients with poor insonation window or poor-quality transcranial Doppler ultrasound signal were excluded from the analysis.

	EOE		**SC**	
Baseline	Supine	HUT	Supine	HUT
Number of patients*	17	16	17	12
Time analyzed (sec) [IQR]	311 [301, 360]	320 [271, 352]	310 [304, 339]	335 [309, 357]
Epochs (n) [IQR]	5 [5, 6]	5 [5, 6]	5 [5, 5]	5 [5, 6]
Missing measures (%) [IQR]	12 [7, 23]	13 [8, 17]	18 [12, 32]	14 [9, 24]
Missing blocks in epochs (%) [IQR]	7 [4, 17]	8 [4, 12]	9 [7, 24]	6 [4, 19]
2 weeks				
Number of patients*	9	7	9	7
Time analyzed (sec) [IQR]	317 [304, 336]	336 [290, 445]	333 [300, 384]	299 [276, 386]
Epochs (n) [IQR]	5 [5, 6]	5 [3, 6]	5 [5, 6]	5 [3, 6]

Missing measures (%) [IQR]	12 [10, 16]	23 [14, 41]	17 [11, 43]	26 [12, 47]
Missing blocks in epochs (%) [IQR]	8 [5, 10]	17 [9, 36]	9 [5, 32]	22 [7, 37]
4 weeks				
Number of patients*	9	10	7	6
Time analyzed (sec) [IQR]	360 [340, 397]	317 [266, 476]	321 [297, 384]	322 [308, 436]
Epochs (n) [IQR]	6 [5, 7]	5 [4, 7]	5 [5, 6]	5 [5, 7]
Missing measures (%) [IQR]	9 [7, 10]	17 [10, 27]	16 [9, 22]	13 [12, 14]
Missing blocks in epochs (%) [IQR]	6 [4, 7]	11 [8, 17]	12 [4, 17]	9 [5, 10]

SC: Standard care; EOE: Early orthostatic exercise; *refers to the number of patients who had acceptable measurements performed.

Supplementary Table 3. Blood gas values

Test session	Baseline		2 weeks		4 weeks	
	EOE	SC	EOE	SC	EOE	SC
PaO_2 (kPa)						
Supine	[a] 11.8 ±2.5	[b] 13.6 ±4.5	[e] 13.1 ±5.5	[f] 11.7 ±2.1	[f] 9.2 ±2.5	[h] 14.0 ±4.2
HUT	[b] 11.2 ±2.1	[d] 11.7 ±3.4	[f] 10.2 ±2.7	[h] 12.1 ±0.1	[f] 9.8 ±3.1	[i] 16.7
Δ (%) [95% CI]	[c] 1 [-17 to 19]	[d] -9 [-2 to 2]	[f] 3 [-73 to 80]	[h] -10 [-57 to 39]	[g] 9 [-30 to 48]	[i] -1
SaO_2 (%)						
Supine	[a] 0.96 ±0.02	[b] 0.96 0 ±0.07	[e] 0.96 ±0.05	[f] 0.97 ±0.02	[f] 0.91 ±0.10	[h] 0.99 ±0.02
HUT	[b] 0.96 ±0.02	[d] 0.95 ±0.08	[f] 0.95 ±0.05	[h] 0.98 ±0.00	[f] 0.92 ±0.11	[i] 1.0
Δ (%) [95% CI]	[c] 0 [-2 to 2]	[d] -1 [-2 to 1]	[f] 1 [-16 to 17]	[h] 0 [-3 to 3]	[g] 1 [-2 to 4]	[i] 0
CaO_2 (mM)						
Supine	[a] 5.9 ±1.0	[b] 6.2 ±0.9	[e] 6.5 ±1.2	[f] 7.6 ±2.4	[f] 5.9 ±1.5	[h] 8.3 ±1.7
HUT	[b] 6.0 ±0.9	[d] 6.0 ±0.8	[f] 6.0 ±0.3	[h] 6.7 ±0.9	[f] 6.0 ±1.5	[i] 7.3

Δ (%) [95% CI]	[c] 1 [-2 to 4]	[d] 1 [-1 to 2]	[f] 2 [-15 to 17]	[h] -15 [-252 to 221]	[g] 2 [-2 to 7]	[i] 4
pH						
Supine	[a] 7.45 ±0.04	[b] 7.45 ±0.03	[e] 7.47 ±0.04	[f] 7.46 ±0.01	[f] 7.46 ±0.05	[h] 7.46 ±0.01
HUT	[b] 7.46 ±0.04	[d] 7.44 ±0.04	[f] 7.45 ±0.01	[h] 7.47 ±0.00	[f] 7.49 ±0.06	[i] 7.41
Δ (%) [95% CI]	[c] 0.1 [-0.1 to 0.3]	[d] 0.0 [-0.2 to 0.3]	[f] 0.1 [-0.3 to 0.5]	[h] 0.1 [-0.1 to 0.4]	[g] 0.3 [-0.3 to 0.9]	[i] -0.6
$PaCO_2$ (kPa)						
Supine	[a] 5.2 ±0.8	[b] 5.1 ±0.6	[e] 5.2 ±0.9	[f] 5.4 ±0.5	[f] 5.8 ±0.9	[h] 5.0 ±0.8
HUT	[b] 5.1 ±0.6	[d] 5.2 ±0.7	[f] 5.4 ±0.9	[h] 5.1 ±0.8	[f] 5.5 ±1.0	[i] 6.3
Δ (%) [95% CI]	[c] -3% [-6 to 0]	[d] -1% [-6 to 3]	[f] -4% [-13 to 6]	[h] -2% [-25 to 20]	[g] -6% [-24 to 11]	[i] 12%
$StHCO_3^-$ (mM)						
Supine	[a] 27.0 ±1.7	[b] 26.4 ±1.8	[e] 27.8 ±2.7	[f] 28.4 ±1.9	[f] 30.4 ±5.4	[h] 26.9 ±2.9
HUT	[b] 26.9 ±1.8	[d] 26.5 ±2.0	[f] 27.7 ±2.7	[h] 27.6 ±3.2	[f] 31.1 ±5.0	[i] 28.4
Δ (%) [95% CI]	[c] -1 [-2 to 0]	[d] 0 [-2 to 2]	[f] -1 [-5 to 3]	[h] 0 [-13 to 14]	[g] -1 [-3 to 2]	[i] -2
Base excess (mM)						

Supine	[a] 2.9 ±2.1	[b] 2.2 ±2.2	[e] 3.8 ±3.2	[f] 4.75 ±2.5	[f] 6.9 ±6.1	[h] 2.8 ±3.7
HUT	[b] 2.7 ±2.1	[d] 2.4 ±2.4	[f] 3.7 ±3.2	[h] 3.6 ±4.2	[f] 7.8 ±5.8	[i] 4.9
Δ (%) [95% CI]	[c] -10 [-27 to 8]	[d] 29 [-25 to 83]	[f] -4 [-73 to 65]	[h] -18 [-302 to 267]	[g] -6 [-27 to 15]	[i] -9

PaO_2: Partial arterial oxygen pressure; SaO_2: arterial oxygen saturation; CaO_2: arterial content of oxygen; $PaCO_2$: Partial arterial pressure of carbon dioxide; $StHCO_3^-$: standardized bicarbonate concentration; Base excess: the excess amount of base in the blood; HUT: Head-up tilt; Δ-values are calculated as (HUT - supine)/supine; EOE: Early orthostatic exercise; SC: Standard care; a: n=16; b: n=15; c: n=14; d: n=11; e: n=7; f: n=4; g: n=3; h: n=2; i: n=1;

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PHD-THESIS
DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Christian Gunge Riberholt
E-mail	christian.riberholt@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	Early mobilisation

2. The declaration applies to the following article	
Title of article	Early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury – Protocol for a randomised clinical feasibility trial
Article status	
Published ☒ Date: 8th of November 2018	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Trials, 2018, 19, 612, https://doi.org/10.1186/s13063-018-3004-x

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	F
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student's specific contribution to the article. Conceived and designed the study with input from experts in the field, collected information on previous studies on the research topic, drafted and finalised the manuscript after input from co-authors. This is a trial manuscript, i.e., it describes the plan for conducting a randomised trial. No new data were collected, but the existing literature was searched for previous studies, which is acknowledged under 4. No analysis of these data was performed.	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertation[II]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[III]

	Date	Name	Title	Signature
1.	23/04-2020	Jane Lindschou	MSc	
2.	Apr 23, 2020	Christian Gluud	Dr. Med. Sci	C Gluud
3.	04/05-20	Jesper Mehlsen	MD	
4.	05 May, 2020	Kirsten Møller	Professor	
5.				
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 05 May, 2020
Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 15.05.2020.
PhD student:

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.
[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):
"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."
[iii] If more signatures are needed please add an extra sheet.

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1. Declaration by	
Name of PhD student	Christian Gunge Riberholt
E-mail	christian.riberholt@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	Early mobilisation

2. The declaration applies to the following article	
Title of article	Early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury – A statistical analysis plan
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 01.06.2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	F
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student´s specific contribution to the article.[i]
Conceived and designed the study, collected data, analysed data with assistance from experts in the field, and drafted and finalised the manuscript after input from co-authors.
This is a manuscript reporting a statistical analysis plan, so no data analysis was conducted.

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	May 19, 2020	Christian Gluud	M.D. Dr. Med. Sci.	C Gluud (May 19, 2020 13:14 GMT+2)
2.	May 20, 2020	Janus Chrisitan Jakobsen	MD	Janus Jakobsen (May 20, 2020 17:40 GMT+2)
3.	May 21, 2020	Christian Ovesen	MD, PhD	
4.	04/6/20	Jesper Mehlsen	MD	
5.	02 June, 2020	Kirsten Møller	MD, PhD, DMSc	
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 03 June, 2020
Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 18/5-2020
PhD student: Christian

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[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):
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1. Declaration by	
Name of PhD student	Christian Gunge Riberholt
E-mail	christian.riberholt@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	Early mobilisation

2. The declaration applies to the following article	
Title of article	Early orthostatic exercise by head-up tilt with stepping versus standard care after severe traumatic brain injury. A randomized clinical feasibility trial
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 15.05.2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	B
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student´s specific contribution to the article.[i]
Conceived and designed the study, collected data, analysed data in collaboration with two independent statisticians, and drafted and finalised the manuscript after input from co-authors.

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	15/5-20	Markus Harboe Olsen	MD	
2.	19/5/20	Christian Baastrup Søndergaard	MD	
3.	May 19, 2020	Christian Gluud	M.D. Dr. Med. Sci.	C Gluud (May 19, 2020 13:14 GMT+2)
4.	May 21, 2020	Christian Ovesen	MD, PhD	
5.	May 20, 2020	Janus Christian Jakobsen	MD	Janus Jakobsen (May 20, 2020 17:40 GMT+2)
6.	02/06-20	Jesper Mehlsen	MD	
7.	02 June, 2020	Kirsten Møller	MD, PhD, DMSc	
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6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 03 June, 2020
Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 15.05.2020
PhD student:

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[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):
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[iii] If more signatures are needed please add an extra sheet.

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1. Declaration by	
Name of PhD student	Christian Gunge Riberholt
E-mail	christian.riberholt@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	Early mobilisation

2. The declaration applies to the following article	
Title of article	Early head-up mobilisation versus standard care for patients with severe acquired brain injury: a systematic review of randomised clinical trials with meta-analyses and Trial Sequential Analyses
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 07.05.2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD student's contribution to the article A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	B
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.' Conceived and designed the study, used methods for a systematic review that are best standard and which have previously been developed by Copenhagen Trial Unit, collected data in collaboration, analysed data, and drafted and finalised the manuscript after input from co-authors.	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	23.04.2020	Vibeke Wagner		
2.	23/4-20	Jane Lindschou	MSc	
3.	Apr 23, 2020	Christian Gluud	Dr. Med. Sci	
4.	04/5-20	Jesper Mehlsen	MD	
5.	05 May, 2020	Kirsten Møller	Professor	
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9.				
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6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 05 May, 2020
Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 15.05.2020
PhD student: Christian

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[iii] If more signatures are needed please add an extra sheet.

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1. Declaration by	
Name of PhD student	Christian Gunge Riberholt
E-mail	christian.riberholt@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	Early mobilisation

2. The declaration applies to the following article	
Title of article	Reliability of the transcranial Doppler ultrasound-derived mean flow index for assessing dynamic cerebral autoregulation in healthy volunteers
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 16th of January 2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	B
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student´s specific contribution to the article.[i]
Conceived and designed the study, collected and analysed data in collaboration, drafted and finalised the manuscript after input from co-authors.

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	15/05-20	Markus Harboe Olsen	M.D.	
2.	18/5-20	Lene Theil Skovgaard	Cand. Stat.	Lene Theil Skovgaard
3.	18.05.2020	Ronan M.G. Berg	Dr.	
4.	02 June, 2020	Kirsten Møller	MD, PhD, DMSc	
5.	02.06.2020	Jesper Mehlsen	MD	
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10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 03 June, 2020
Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 15-05-2020
PhD student:

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

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1. Declaration by	
Name of PhD student	Christian Gunge Riberholt
E-mail	christian.riberholt@regionh.dk
Name of principal supervisor	Kirsten Møller
Title of the PhD thesis	Early mobilisation

2. The declaration applies to the following article	
Title of article	Dynamic cerebral autoregulation during early orthostatic exercise in patients with severe traumatic brain injury: results from a randomized clinical feasibility trial
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 28.05.2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	B
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student´s specific contribution to the article.[i]
Conceived the study in collaboration, designed the study, collected and analysed data, and drafted and finalised the manuscript after input from co-authors.

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	15/5-20	Markus Harboe Olsen	MD	
2.	18.05.2020	Ronan M. G. Berg	Dr.	
3.	02/06/20	Jesper Mehlsen	MD	
4.	02 June, 2020	Kirsten Møller	MD, PhD, DMSc	
5.				
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 03 June, 2020
Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 15.05.2020
PhD student:

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