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REVIEW

Loop diuretics in adult intensive care patients with fluid overload: A protocol for a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis

Sine Wichmann[1] | Marija Barbateskovic[2] | Jane Lindschou[2] | Christian Gluud[2] | Anders Perner[3] | Morten H. Bestle[1]

[1]Department of Anaesthesiology, Nordsjællands Hospital, University of Copenhagen, Hillerød, Denmark

[2]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[3]Department of Intensive Care, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Correspondence
Sine Wichmann, Nordsjællands Hospital, University of Copenhagen, Dyrehavevej 29, 3400 Hillerød, Denmark.
Email: sine.wichmann@regionh.dk

Background: In the intensive care unit, fluid overload is frequent and a risk factor for organ dysfunction and increased mortality. Primarily, lung and kidney functions may be impaired by fluid overload resulting in acute respiratory failure and acute kidney injury. No clinical guidelines exist for treatment of fluid overload in intensive care patients. Loop diuretics, most often furosemide, appear to be the most frequently used pharmacological intervention. The aim of this protocol is to describe the methods of a systematic review assessing the evidence of treatment with loop diuretics in adult intensive care patients with fluid overload.

Methods: We will conduct a systematic review with meta-analysis and report it according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statements, use the recommendations of the Cochrane Handbook and assess the quality of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. We will include randomised clinical trials identified through searches of major international databases and trial registers. Two authors will independently screen and select trials for inclusion, extract data and assess the methodological quality using the Cochrane risk of bias tool. Extracted data will be analysed using Review Manager and Trial Sequential Analysis. The protocol is registered at PROSPERO.

Discussion: We aim to provide reliable evidence on the use of loop diuretics in adult intensive care patients with fluid overload to guide clinicians, decision makers and trialists on clinical practice.

1 | BACKGROUND

Intensive care patients are often treated with substantial amounts of fluids and medicine leading to accumulation of fluid in the body. Excess fluid may result in oedema in tissues and organs which may affect their function. In this protocol we aim to describe the rationale and methods of a planned systematic review of randomised clinical trials assessing at the evidence of treating fluid overload with diuretics in adults admitted to the intensive care unit (ICU).

2 | DESCRIPTION OF THE CONDITION

Fluid overload can be defined as net positive fluid balance where fluid intake is larger than output. It is often presented as a percentage of the bodyweight. Fluid overload is common in ICU patients. It has become increasingly evident that fluid overload is a risk factor for organ dysfunction and increased mortality.[1-3] All organs get affected by fluid overload, but especially the lungs and kidneys are involved and frequently demands additional and prolonged treatment.

Excess fluid in the lungs may result in longer time on mechanical ventilation[4] and a restrictive fluid therapy is recommended for acute respiratory distress syndrome.[4-6] Fluid overload is also associated with development of acute kidney injury[7-10] which has an incidence of up to 57% in the ICU and is associated with increased mortality.[11] In one observational study of patients in ICU with acute kidney injury showed that 53% and 29% of the patients accumulated, respectively, 5% and 10% fluid overload after 5 days of admission.[12]

3 | DESCRIPTION OF THE INTERVENTION

Treatment of fluid overload can be done with fluid restriction, diuretics and dialysis. However, the optimal way to treat fluid overload is not established and it is unknown when and how fluid overload should be treated. Conservative fluid management and/or de-resuscitation with fluid removal may lead to reduced mortality.[13] In ICU patients, a reduction in fluid administration is often not enough to treat fluid overload and, in addition, the frequent development of acute kidney injury impairs the kidneys ability to excrete water. Diuretics is used in 49% of all ICU admissions and it is the predominant way to treat fluid overload.[14] Of these drugs, the loop diuretic furosemide is the predominant diuretic used in about 94%.[14] Other loop diuretics are torsemide, bumetanide, ethycrinic acid or azosemide, but they are sparsely used. Combinations of diuretics are uncommon in the ICU, and approximately 80% of the patients treated with diuretics receive only furosemide.[14]

Loop diuretics can be administered intravenous or orally. The diuretic effect is variable and adverse effects as electrolyte derangements are common. Other groups of diuretics such as thiazides/thiazide-type diuretics, mineralocorticoid receptor antagonists, carbonic anhydrase inhibitors and epithelial sodium channel blockers are also used in the ICU, but to a much lesser extent, and rarely as the only diuretic but often as adjunctive treatment.[14] Some diuretics are also used for other indications than fluid overload, eg hypernatraemia[15] and metabolic alkalosis.[16]

Acute respiratory distress syndrome is a condition with acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, pulmonary oedema and loss of ventilated lung tissue.[6] Treatment with mechanical ventilation and positive end expiratory pressure help the oxygenation, recruitment of not ventilated lung areas and minimising the lung oedema. Restrictive fluid therapy or diuretics is a part of the treatment of the lung oedema in acute respiratory distress syndrome,[5,6] but is relevant to consider in all kinds of respiratory failure with wet lungs.

4 | HOW THE INTERVENTION MIGHT WORK

Furosemide is a weak acid where > 95% is bound to plasma proteins (almost exclusively to albumin). Only a very small fraction of furosemide is filtered through the glomerulus but the protein-bound furosemide is actively secreted into the lumen in the proximal tubule via organic acid transporter pathways.[17,18] In the tubules furosemide inhibits the sodium-potassium-chloride transporter in the thick ascending limb of the loop of Henle resulting in decreased reabsorption of water, sodium and chloride.[19] The renal action of furosemide peaks within 5 minutes after intravenous bolus and 1 hour after oral administration. Elimination half-life varies from 0.5 to 2 hours in healthy subjects, but in advanced chronic renal failure the mean plasma half-life of furosemide can be prolonged up to 24 hours and in case of liver failure up to 4.3 hours.[20]

The other loop diuretics (torasemide, bumetanide, etacrynic acid and azosemide) all primarily work as furosemide in the thick ascending limb of Henle.[21]

5 | WHY IT IS IMPORTANT TO DO THIS REVIEW

Fluid overload is a common condition associated with serious adverse effects and represents a detrimental outcome in intensive care patients. Guidelines for treating fluid overload do not exist, and the condition is often treated with loop diuretics on the physician's discretion.

We have not identified any systematic reviews investigating treatment of fluid overload in general intensive care patients, but we have found systematic reviews investigating furosemide in patients with acute decompensated heart failure,[22] co-administration of furosemide and albumin in patients with hypoalbuminemia[23] and furosemide's impact on mortality and requirement for renal replacement therapy in acute kidney injury.[24] Those reviews included only few randomised clinical trials among ICU patients.

6 | OBJECTIVES

We aim to assess the benefits and harms of loop diuretics in adult ICU patients with fluid overload based on results of randomised clinical trials.

7 | METHODS

This protocol has been reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist (see Appendix 1).[25,26] We will follow the recommendations stated in The Cochrane Handbook of Interventions Reviews[27] and the eight-step assessment suggested by Jakobsen et al.[28]

The protocol is registered on the PROSPERO database.

8 | CRITERIA FOR CONSIDERING TRIALS FOR THIS REVIEW

8.1 | Types of trials

We will only include randomised clinical trials, irrespective of reported outcomes, publication date, publication language, publication type and

publication status. Unpublished trials will be included if methodological descriptions and trial data are provided from the trial investigators.

8.2 | Types of participants

We will include intensive care patients above 18 years of age. The patients must have fluid overload, as defined by the trialists. Definition of fluid overload varies among studies. In some studies, fluid overload is defined as a net positive fluid balance, whereas other trials present fluid accumulation in percentage adjusted for body weight (total intake (litres) – total output (litres)/baseline body weight).[7,8,12,29]

We will also include trials with adult ICU patients with acute kidney injury, acute decompensated heart failure or pulmonary oedema as these groups are considered to have fluid overload.

8.3 | Types of Interventions

Loop diuretics compared with placebo or no intervention.
Loop diuretics compared with other diuretics.
Loop diuretic compared with other pharmacological interventions.
Higher-dose loop diuretics compared with lower doses of loop diuretics.

We will accept any dose, formulation, timing and duration of intervention. In case the same loop diuretic is tested in two different doses, the highest dose will be considered the experimental group.

8.4 | Types of outcome measures

Primary outcomes.

1. All-cause mortality at longest follow-up.
2. Quality of life (any valid continuous quality of life scale will be accepted) at longest follow-up.
3. Proportion of participants with one or more serious adverse events at longest follow-up. We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation and resulted in persistent or significant disability or jeopardised the participant.[30] If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term "serious adverse event." If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data, if the event clearly fulfils the ICH-GCP definition for a serious adverse event.

Secondary outcomes.

1. Plasma concentration of creatinine at longest follow-up.
2. Proportion of participants without resolution of fluid overload, as defined by trialists, at longest follow-up.
3. Number of days in mechanical ventilation.
4. Length of stay in the ICU.
5. Proportion of participants with adverse events or reactions not considered serious at longest follow-up.

Explorative outcomes.

1. Single serious adverse events at longest follow-up.
2. Single adverse events not considered serious at longest follow-up.
3. Plasma concentration of sodium, potassium and chloride at longest follow-up.

9 | SEARCH METHODS FOR IDENTIFICATION OF STUDIES

9.1 | Electronic searches

Randomised clinical trials that fulfil the inclusion criteria will be identified through searching the literature with systematic search strategies designed to identify relevant trials without restrictions to language, publication year and journal.

The following databases will be searched from inception:

- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue)
- Medline (OvidSP)
- PubMed
- EMBASE (OvidSP)
- Science Citation Index (web of science)
- Biosis Previews (web of science)
- Latin American Caribbean Health Sciences Literature (LILACS)
- China National Knowledge Infrastructure (CNKI)
- Wanfang Data
- VIP Chinese Science Journals Database
- Sinomed

For details on full search strategies, see Appendix 2.

9.2 | Searching other resources

Reference lists of relevant papers, reviews, randomised trials and non-randomised studies and editorials will be screened manually for potentially includable trials. Furthermore, authors of identified studies, experts for each area and pharmaceutical companies (if relevant) will be contacted and asked for knowledge on additional trials. Unpublished trials will be included if data and methodology on the trial can be assessed. A search in Google Scholar will also be performed.

On-going and unpublished trials will be searched on the following trial registers:

- ClincalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)
- EU Clinical Trial Register
- Australian New Zealand Clinical Trials Registry (ANZCTR)

Furthermore, we will search for unpublished trials, clinical study reports on the websites of:

- US Food and Drug Administration (FDA)
- European Medicines Agency (EMA)

10 | DATA COLLECTION AND ANALYSIS

The following methods on data collection and data analysis will be used.

10.1 | Selection of studies

Two authors (SW and MB) will independently screen all titles and abstracts of the trials identified by the searches. All relevant and potentially relevant articles will be screened in full text. Any disagreement will be resolved through consensus of a third reviewer (MHB, JL, AP or CG).

10.2 | Data extraction and management

A predefined data extraction form, developed by the review team, will be used when the two authors independently extract data from the included trials. In case of disagreement concerning the extracted data, consensus will be reached through discussion or through consultation with a third reviewer (MHB, JL, AP or CG). Whenever necessary, corresponding authors will be contacted to clarify issues related to data reporting or if further trial details are needed. We will extract the following data:

1. Trial: country, date of publication, duration, design (multi- or single-centre trial)
2. Participants: number of participants, number of analysed and lost to follow-up/withdrawn, type of participants, gender, age (median/mean), inclusion and exclusion criteria.
3. Interventions: type of intervention, comparator and concomitant medications.
4. Outcomes: primary and secondary outcomes specified, and time points reported.
5. Other: trial funding and notable conflicts of interest of the trial authors.

11 | ASSESSMENT OF RISK OF BIAS IN INCLUDED TRIALS

SW and MB will independently assess the methodological quality of each included trial, defined by the design of the trial and reporting. Any disagreement will be discussed between the two authors. We will assess the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions[27] by using RoB2 tool.[31] Based on the risk of bias assessment, the included trials and each outcome result will be defined as overall low risk of bias if all bias domains are judged as low risk of bias.

12 | MEASURES OF TREATMENT EFFECT

For dichotomous outcomes risk ratio (RR) with confidence interval (CI) and Trial Sequential Analysis (TSA)-adjusted CI will be calculated. For continuous outcomes, both end scores and change scores will be included in the analyses. End scores will be used if both are reported. Mean difference (MD) and standardised mean difference (SMD) with CIs and TSA-adjusted CIs will be calculated for continuous outcomes.

13 | UNIT OF ANALYSIS ISSUES

Dealing with missing data.

We will contact trial investigators of the original papers for relevant missing data.

For both dichotomous and continuous outcomes, we will not be imputing missing data for any outcomes in the primary analysis and intention-to-treat data will not be used if the original report did not contain such data.

If standard deviations (SD) are not reported, the SDs will be calculated using data from the trial if possible.

In the sensitivity analysis, best-worst case scenario and worst-best case scenario for dichotomous and continuous outcomes, imputed data will be used, see 'Sensitivity analysis'.

14 | ASSESSMENT OF HETEROGENEITY

We will assess signs of heterogeneity by visual inspection of the forest plots. We will assess presence of statistical heterogeneity by Chi squared test with significance set at P 0 < .10 and by measuring the quantities of heterogeneity by I^2 static.[32] We will follow the recommendations for thresholds in The Cochrane Handbook for Systematic Reviews of Interventions[27]: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity.

We will explore potential clinical heterogeneity by conducting the pre-specified sub-group analyses, see 'Subgroup analysis and investigations of heterogeneity', which may explain the statistical heterogeneity.

15 | ASSESSMENT OF REPORTING BIASES

We will visually assess funnel plots for signs of asymmetry if 10 or more trials are included in an analysis.[27,28]

We will test asymmetry within dichotomous outcomes with the Harbord's test[33] and for continuous outcomes regression asymmetry test.[34]

16 | DATA SYNTHESIS

16.1 | Meta-analysis

We will conduct meta-analyses for outcomes with comparable effect measures if more than one trial is included. The statistical software Review Manager provided by The Cochrane Collaboration[35] and the TSA software[36] provided by the Copenhagen Trial Unit will be used. If clinical and statistical heterogeneity are large or unexpected, we will reconsider doing the meta-analysis. We will report the results narratively if a quantitative synthesis is not appropriate.

16.2 | Assessment of significance

We will assess our intervention effects with both random-effects model meta-analyses and fixed-effect model meta-analyses.[37,38] If the estimates from the two models are approximately equal, we will use the estimate with the widest CI. We will adjust our thresholds for statistical significance because of multiplicity problems due to multiple outcomes by dividing the pre-specified P-value threshold with the value halfway between 1 (no adjustment) and the number of primary or secondary outcome comparisons (Bonferroni adjustment).[28,39] We have defined three primary outcome and five secondary outcomes; thus, we will consider a P-value of 0.025 or less as significant for the primary outcomes and a P-value of 0.017 or less as significant for the secondary outcomes. We will report TSA-adjusted CIs which means that these CIs are adjusted for where the cumulative Z-curve of the TSA has reached in relation to the required information size. We will report 95% CIs as well. We will use the eight-step procedure to assess if the thresholds for significance are crossed.[28]

16.3 | Trial sequential analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data.[40-48] Therefore, TSA[36] can be applied to control this risk.[49] The required information size and the required number of trials[50] (the number of participants and trials needed in a meta-analysis to detect or reject an a priori pre-specified realistic intervention effect) can be calculated to minimise random errors.[51] The required information size is based on the event proportion in the control group, the assumption of a plausible relative risk reduction (RRR) or relative risk increase (RRI), and the heterogeneity variance[52] of the meta-analysis.[51] TSA enables testing for significance to be conducted each time a new trial is included in the meta-analysis. Based on the required information size and the required number of trials, 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.[43,44,46,48] We will analyse all primary and secondary outcomes with TSA. We will estimate the diversity-adjusted required information size[51] based on the proportion of patients with an outcome in the control group. In addition, we will use a family-wise error rate of 5%[28] leading to a statistical significance level of 2.5% for each of the primary outcomes, and 1.7% of the secondary outcomes a beta of 10% corresponding to a power of 90%, and the diversity (D^2) of the meta-analysis[51] suggested by the trials in the meta-analysis.[28] As anticipated intervention effects for dichotomous outcomes in the TSA, we will use realistic a priori RRR or RRI increases of 20%. For continuous outcomes, we will in the TSA use the observed SD, and a mean difference of the observed SD/2.

17 | SUBGROUP ANALYSIS AND INVESTIGATION OF HETEROGENEITY

We will try to determine if the benefits and harms of the treatment options are influenced by the following subgroup analyses:

- Trials at overall high risk of bias compared to trials at overall low or uncertain risk of bias.
- According to population:
  a. Type of ICU patients (medical compared to surgical as these likely have different responses and prognoses)
  b. Severity of fluid overload (up to 5% compared to 6% to 10% compared to over 10% as these groups may have different responses and prognoses)
  c. Diagnosis of acute kidney injury or decompensated heart failure or other diagnoses at randomisation as these groups may have different responses and prognoses

18 | SENSITIVITY ANALYSIS

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary dichotomous outcomes.

- 'Best-worst-case' scenario
- 'Worst-best-case' scenario

We will present results of both scenarios in our review. For a detailed explanation of analyses see Appendix 3.

Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.[28]

19 | SUMMARY OF FINDINGS TABLES

We will use the GRADE system[53] to assess the certainty of the body of evidence associated with the outcomes by constructing Summary of Findings (SoF) per comparison using the GRADEpro software.[54] We will present the following seven outcomes in the SoF: all-cause mortality, quality of life, proportion of patients with one or more serious adverse events, concentration of plasma creatinine, proportion of participants with no resolution of fluid overload, number of days in mechanical ventilation and length of stay in the ICU. For each outcome, first we will present summary of findings in randomised clinical trials with overall low risk of bias and secondarily, results in all trials. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates[34] and risk of publication bias. We will primarily base our conclusions on the analyses of trials with overall low risk of bias.

20 | DISCUSSION

This systematic review will present data from existing randomised clinical trials elucidating treatment modalities for fluid removal with diuretics in intensive care patients with fluid overload. Hopefully, the review will contribute with evidence for patient-important outcomes to diuretic treatment in intensive care patients with fluid overload.

This protocol has several strengths. It follows the PRISMA-P guideline and uses a methodology based on The Cochrane Handbook for Systematic Reviews of Interventions,[27] the eight-step assessment suggested by Jakobsen et al,[28] TSA[49] and GRADE assessment.[53] Hence, this protocol considers the risks of both random and systematic errors.

We are aware that by focusing only on randomised clinical trials we run the risk of focusing more on benefits than on harms. By not searching for observational studies, we will likely overlook observational studies reporting adverse events, especially late or rare adverse events. Therefore, if we demonstrate benefits of the loop diuretics, there will be a need to assess the occurrence of adverse events based on observational studies.

Our ambition with this systematic review is to provide reliable and powered evidence to better inform decision makers on clinical practice on the use of diuretics in intensive care patients with fluid overload.

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CONFLICT OF INTEREST

AP is the sponsor of a fluid restriction trial in patients with septic shock and receives grants from the Novo Nordisk Foundation. MHB is the sponsor of a fluid removal trial in ICU patients and has received a grant from the Novo Nordisk Foundation. SW, CG, MB and JL have no conflict of interest.

AUTHORS' CONTRIBUTIONS

SW drafted the manuscript and registered the protocol in PROSPERO. All authors contributed to the manuscript and read and approved the final manuscript.

ORCID

Sine Wichmann https://orcid.org/0000-0003-0360-8655
Marija Barbateskovic https://orcid.org/0000-0001-8566-3660
Anders Perner https://orcid.org/0000-0002-4668-0123

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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