Intraoperative clonidine for prevention of postoperative agitation in children anaesthetised with sevoflurane (PREVENT AGITATION): a randomised, placebo-controlled, double-blind trial

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Summary

Background Postoperative agitation is a frequent and stressful condition for a child, their family, and their health-care providers, and prevention would be of benefit. We aimed to assess the effects of intravenous clonidine administered intraoperatively on the incidence of postoperative agitation, pain, and adverse events.

Methods We did this randomised, placebo-controlled, double-blind trial (PREVENT AGITATION) at one tertiary-level hospital and two urban-district hospitals in Denmark. Children aged 1–5 years, with an American Society of Anesthesiologists physical classification score of 1–2, who were scheduled for anaesthesia with sevoflurane and fentanyl were randomly assigned (1:1) in blocks of ten by computer-generated centralised randomisation, stratified by age (<2 years or ≥2 years) and site, to receive either intravenous clonidine 3 μg/kg or an equal quantity of isotonic saline in identical vials, administered around 20 min before the completion of surgery. Data were collected from the postoperative care unit (24 h) and at follow-up (30 days). Our primary outcome was the proportion of patients with one or more episodes of postoperative agitation, measured every 15 min in the postoperative care unit (POCU) with the four-point Watcha scale (ie, Watcha >2). We analysed by intention to treat. The trial is registered with ClinicalTrials.gov (number NCT02361476).

Findings Between January and December, 2015, of the 379 eligible children, we randomly assigned 191 to receive clonidine treatment and 188 to receive placebo; 75 were girls (20%). Nine were excluded from the primary outcome analysis because of missing data points. 46 (25%) of 187 clonidine participants compared with 86 (47%) of 183 placebo participants had one or more episodes of postoperative agitation (Watcha score >2; relative risk 0·56, 95% CI 0·43–0·73; p<0·0001). 30 (20%) of 150 boys in the clonidine group were agitated compared with 69 (47%) of 147 boys in the placebo group (0·43, 0·30–0·61; p<0·0001). The observed effect was not significant in girls. Incidence of adverse events was similar in the clonidine and placebo groups.

Interpretation On the basis of our results, clonidine might be used to safely prevent postoperative agitation in boys anaesthetised with sevoflurane.

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Introduction

Postoperative agitation refers to a condition of psychomotor agitation, excessive motor activity, and perceptual disturbances in the early postanaesthetic period as a result of pain, discomfort, and anxiety and it most commonly occurs in children younger than 6 years.[1,2] Postoperative agitation in children anaesthetised with sevoflurane is a common problem, with an incidence of at least 25%, ranging from 10% to 80% in the published work.[2–4]

Sevoflurane is frequently used in paediatric anaesthesia for several reasons including both induction and maintenance of anaesthesia because it renders the need for intravenous access redundant and provides quick adjustments of anaesthetic depth. However, the use of sevoflurane is associated with a higher incidence of postoperative agitation in children.[5]

Various pharmacological interventions have previously been investigated for prevention of postoperative agitation.[2] Clonidine has been suggested as a potential prophylactic intervention against sevoflurane-induced postoperative agitation.[6] It is an α-2-receptor agonist with sedative, anxiolytic, and pain-relieving properties, which in the perioperative setting is most commonly used as premedication to achieve anxiolysis and sedation. The known side-effects are mainly bradycardia and hypotension, often presenting at higher bolus doses or during continued administration and rarely reported in paediatric trials with lower bolus doses.[7–10] Clonidine is used off-label for several indications in children, including treatment of shivering and pain, prevention of postoperative agitation, and for withdrawal symptoms following long-term sedation.[6,11–13]

We aimed to investigate whether an intravenous clonidine bolus of 3 μg/kg administered around 20 min before the expected completion of surgery in children anaesthetised with sevoflurane could reduce the

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See **Online** for appendix

Evidence before this study
Our assumption before this trial was that clonidine, an α-2-receptor agonist, could potentially reduce the incidence of postoperative agitation despite the scarce data to support its use for prevention of agitation. To assess the evidence in favour of the use of clonidine, we searched for studies published until May 2014, with no language restrictions, in PubMed, MEDLINE, Cochrane Central Register of Controlled trials, ClinicalTrials.gov, and EU Clinical Trials Register using the following search terms: "sevoflurane", "paediatric", and "postoperative agitation" or "clonidine".

The incidence of postoperative agitation was reported with great variation (10–80%) in the published work. We found ten paediatric randomised clinical trials with conflicting results, potentially because of small sample sizes (40–169 children), different routes of administration (oral, intravenous, or epidural), different doses (0·75–5 µg/kg), and the use of different scales for assessment of postoperative agitation.

Clonidine has haemodynamic effects (ie, reduction of blood pressure and heart rate). However, clonidine is considered a drug with few reported adverse effects or safety issues in children and the haemodynamic effects are often not considered to be of clinical importance when used for off-label treatment of postoperative agitation, pain, or withdrawal symptoms. To our knowledge, no previously published paediatric trial has assessed the safety concerns of clonidine at long-term follow-up.

Added value of this study
In the PREVENT AGITATION trial, clonidine significantly reduced the proportion of boys with postoperative agitation when anaesthetised with sevoflurane. A bolus of 3 µg/kg administered intravenously, approximately 20 min before the end of surgery, indicated an acceptable safety profile in healthy children (American Society of Anesthesiologists classification 1–2) admitted for elective surgery. Furthermore, clonidine reduced postoperative opioid consumption, prolonged the time to first analgesic administration, and decreased postoperative nausea and vomiting; although, recovery times were prolonged. The anticipated decrease of heart rate and blood pressure after drug administration were found in the clonidine treatment group, but no haemodynamic adverse events were reported and no interventions for bradycardia or hypotension were required. Furthermore, no difference in reported adverse events were found at 24-h and 30-day follow-up.

Implications of all the available evidence
Taking all the existing evidence into account, clonidine prevents postoperative agitation in healthy boys for non-cardiac surgery anaesthetised with sevoflurane. Future trials are needed to confirm this effect in girls. Data for critically ill children with concomitant medications or cardiac disease are still needed.

proportion of patients with one or more episodes of postoperative agitation. We also investigated postoperative pain relief (morphine equivalents and time to first analgesic administration postoperatively), adverse events, postoperative nausea and vomiting, shivering, and time to discharge.

Methods

Study design and participants

We did this investigator-initiated, randomised, placebo-controlled, double-blind trial (PREVENT AGITATION) at a tertiary hospital with around 4000 children admitted for elective surgery per year (Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark) and at two urban district hospitals (Vejle Hospital, Vejle, and Zealand University Hospital, Køge, Denmark) with an annual census of 700 and 600 children, respectively.

We included children aged 1–5 years who were scheduled for surgery under general anaesthesia with sevoflurane and fentanyl. We excluded children if they were American Society of Anesthesiologists (ASA) classification of 3 or higher, had been premedicated with clonidine, were born premature (before gestational week 37 and younger than 60 weeks old), were intubated before induction of anaesthesia or not planned for extubation

after anaesthesia, had critical illness with haemodynamic instability, active bleeding, cancer, cardiac diseases including arrhythmias, malignant hyperthermia, intellectual disability, or neurological illness with agitation-like symptoms, weighed more than 50 kg, were allergic to clonidine, or were receiving methylphenidate.

The trial complied with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) tripartite guidelines for good clinical practice (GCP): the Helsinki Declaration, the SPIRIT guidelines, and the CONSORT statement. Written informed parental consent was obtained for all patients. The trial was monitored by independent monitors from the GCP units of the participating hospitals. The clinical trial protocol and the detailed statistical analyses plan were published before the completion of the trial.[10] This trial was approved by the National Committee on Biomedical Research Ethics (H-2-2014-072), the Danish Medicines Agency (EudraCT 2014-001466-10), and the Danish Data Protection Agency (30-1348), and is registered with ClinicalTrials.gov (number NCT02361476).

Randomisation and masking

Before surgery, centralised randomisation was done on a website hosted by the Copenhagen Trial Unit,

Rigshospitalet, with adequate computer random number generation to establish the allocation sequence. We randomly assigned participants (1:1) with blocks of ten, stratified for sites and age (<2 years or ≥2 years) with the aim to limit baseline imbalance for these variables. Once a randomisation number was received, we selected the corresponding vial containing the study medication (clonidine or placebo).

The clonidine and placebo vials were identical, containing similar clear liquid, and were packed and labelled with randomisation numbers (The Hospital Pharmacy, The Capital Region of Denmark, Copenhagen, Denmark). All patients received the same protocol-based care. We masked the trial to all participants, investigators, other health-care providers, and statisticians. Additionally, we extended the masking to the authors of the abstract for this Article who initially drafted two versions in which intervention and placebo were defined as one and two, and vice versa. We unmasked the trial once both abstracts were approved by all authors and the Article was then written in full length.

Procedures

Anaesthesia was induced either with inhalation of sevoflurane and 100% oxygen or with intravenous propofol. Anaesthesia was maintained solely with sevoflurane and fentanyl according to clinical assessment with no dose limitation. Paracetamol was administered after induction according to weight and age, unless contraindicated, or administered before arrival at the operating theatre. Premedication, non-steroid anti-inflammatory drugs, and local, peripheral, and central nerve blocks were permitted, but without addition of α-2 agonists. In previous trials[14–18] with clonidine, the intravenous bolus dose range was reported between 1 μg/kg and 3 μg/kg, indicating a dose-response effect with no safety concerns. On the basis of an anticipated dose-response effect and clonidine's perceived pharmacokinetic and pharmacodynamic profile, 3 μg/kg of intravenous clonidine was chosen as the intervention.[19] Around 20 min before the end of surgery, the children either received 3 μg/kg of intravenous clonidine (Catapresan 150 μg/mL in 1 mL vials; Boehringer Ingelheim, Ingelheim am Rhein, Germany) or equal quantity of intravenous isotonic saline (sodium chloride 9 mg/mL in 1 mL vials; Skanderborg Pharmacy, Skanderborg, Denmark). Our choice of 20 min before completion of surgery for administration of study drug was from a pragmatic point of view, since it is often difficult to precisely foresee the time by which the surgery is finalised and to achieve a high plasma concentration of clonidine upon arrival at the recovery room. We recorded vital parameters, including blood pressure, oxygen saturation, and heart rate, during surgery (including baseline values before administration of the drug) and in the postoperative care unit (POCU). Postoperative treatment was in accordance with a standardised flowchart (figure 1).
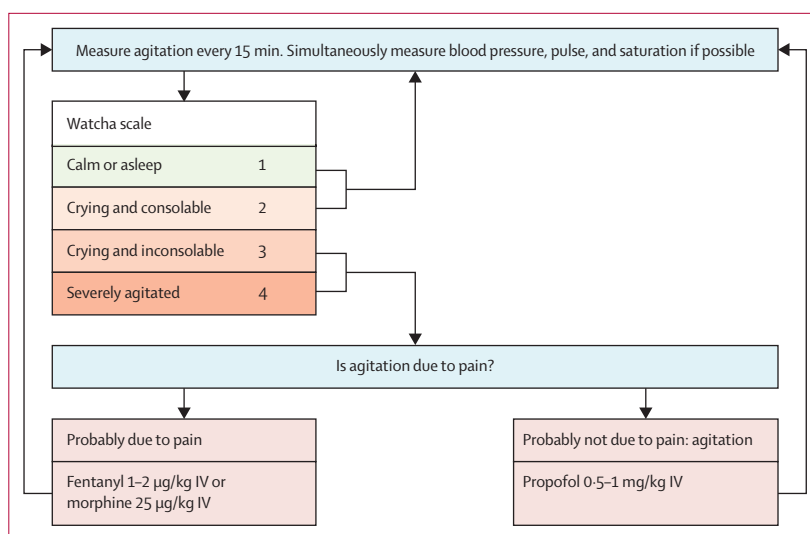
Figure 1: Agitation and treatment flowchart for the postoperative care unit, until discharge
Agitation was measured as score on the Watcha scale. IV=intravenous.

All assessors (nurses in POCU) and local investigators received standardised training by the study taskforce members before trial initiation. Additionally, all sites underwent continuous monitoring and feedback during the trial period to reduce the risk of reporter bias and variability between hospitals.

Outcomes

Our primary outcome was proportion of patients with one or more episodes of postoperative agitation measured every 15 min in the POCU using the four-point Watcha scale (ranging from 1, calm or asleep; to 4, severely agitated; figure 1). A Watcha score of more than 2 was considered as postoperative agitation. We chose the Watcha score instead of other tools such as the Paediatric Anaesthesia Emergence Delirium scale because agitation is its main strength, it has been previously validated in a paediatric postoperative setting, and is already implemented at the largest participating site.[20] As a consequence, we believed that we could provide a high quality and uniform training for all of our masked assessors across the various participating sites by using a tool that was easy to implement.[20,21]

We registered a baseline value before induction of anaesthesia. For each participant, we used the Watcha score values for our analysis only if all of the values were registered. If one or more of the Watcha scores were missing, the participant's agitation status was defined as missing. We also measured pain with the Face, Legs, Activity, Cry, Consolability (FLACC) scale.

Our secondary outcomes were opioid requirements in the POCU, time to first administration of opioid in the POCU, and adverse events. Our exploratory outcomes were postoperative nausea and vomiting (PONV) measured by a four-point PONV-scale (ranging from 0,
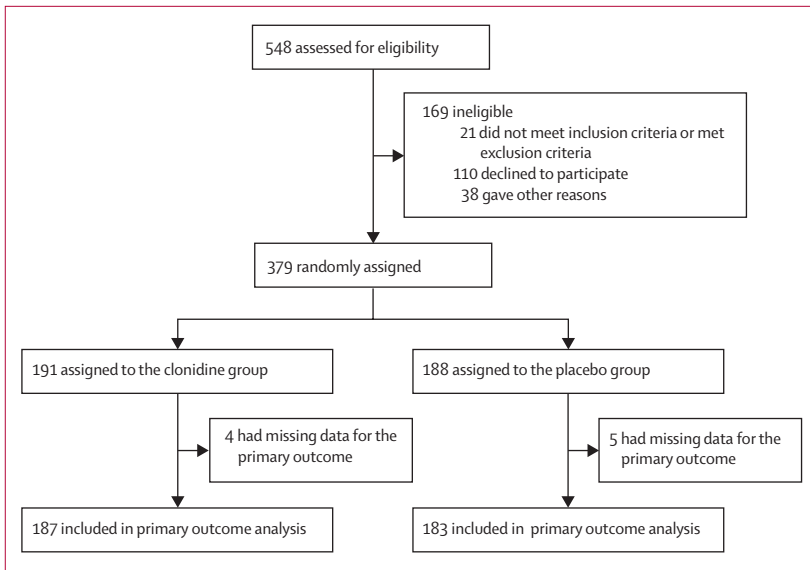
Figure 2: Trial profile

	Clonidine group (n=191)		Placebo group (n=188)	
	Boys (n=154)	Girls (n=37)	Boys (n=150)	Girls (n=38)
Age				
<2 years	40	6	34	9
≥2 years	114	31	116	29
Site				
Rigshospitalet	115	12	115	10
Køge Hospital	10	3	4	7
Vejle Hospital	29	22	31	21
Premedicated	26	9	24	11
Induction with propofol	58	8	60	5
Local anaesthetics*	137	29	134	30
Agitated before anaesthesia†	29	5	32	3
Duration of surgery, min	27·7 (18·3)	36·0 (30·9)	30·2 (25·1)	33·1 (25·3)
Type of surgery‡				
Hernia repair	18	9	26	8
Male genital	93	0	83	0
Laparoscopy	1	0	3	0
Urology	3	2	3	2
Ear	3	2	4	3
Nose	1	0	0	1
Eye	1	4	3	3
Throat				
Tonsillectomy	21	12	22	14
Non-tonsillectomy	11	6	5	7
Superficial	2	2	1	0

Data are n or mean (SD). *Use of local anaesthetics (local infiltration and blocks). †Defined as Watcha score more than 2. ‡Grouped by specialty.

Table 1: Baseline characteristics

(including blood pressure, oxygen saturation, and heart rate) until discharge from the POCU.

A structured follow-up interview with the parents was done the day after surgery (at the bedside for patients admitted to hospital or by a phone call for discharged patients) to assess agitation, PONV, dizziness, contact with hospital or emergency department or other health-care providers, and other adverse events. Additionally, we did a 30-day follow-up using the Danish National Patient Register for detection of long-term serious adverse events requiring hospital admission.[22] No revision of the choice or priority of outcomes was done in the trial period.[10]

Statistical methods

For the sample size calculation, we used a proportion of postoperative agitation of 25% reported in previously published studies and systematic reviews.[6,10] We calculated a sample size of 380 children (190 per group), to provide an 80% power targeting a relative risk reduction of 41%, with a maximal 5% risk of type I error. Initially we planned to include 304 patients. However, the proportion of postoperative agitation has varied considerably in previous studies and so we decided to do a status evaluation after 200 inclusions, without unmasking the allocation groups. We assessed the proportion of patients with agitation and concluded that we potentially could have anticipated too large an intervention effect (relative risk reduction of 50%) and proportion of postoperative agitation. We received permissions from the legal authorities to increase sample size from 304 to 380 by addressing a relative risk reduction of 41% instead of 50%, and a total of 379 patients were included. No other changes to the protocol were made during the trial period.

We analysed the results based on the intention-to-treat population. Our primary analysis of postoperative agitation was adjusted for the stratification variables: site and age (<2 years or ≥2 years). However, when analysing count data with the van Elteren test,[23] the analysis was only adjusted for site. We did one secondary analysis adjusted for the stratification variables and additional design variables: use of local anaesthetics; propofol administration; duration of surgery (min from start to intervention); premedicated; and preanaesthesia agitation score. We assessed one primary outcome and planned to consider results on secondary outcomes as hypothesis generating. A p value of 0·05 was considered as the threshold for statistical significance.[24] We analysed dichotomous outcomes with generalised linear models using a log link function to obtain relative risk (RR), continuous outcomes using linear regression, and count data using the van Elteren test.[23] Using eight tests of interaction, we planned to adjust the level of significance for multiplicity to 0·0063. Multiple imputation was planned if more than 5% of all relevant data were missing.

no nausea or vomiting; to 3, severe nausea or repeatedly vomiting), shivering, and time to discharge from the POCU. We recorded all outcomes postoperatively

	Clonidine group			Placebo group			p values (clonidine vs placebo)		
	Boys (n=154)	Girls (n=37)	All (n=191)	Boys (n=150)	Girls (n=38)	All (n=188)	Boys	Girls	All
Duration of surgery (min)	22 (4–135)	28 (4–157)	23 (4–157)	25 (3–181)	25 (10–122)	25 (3–181)	0·28	0·54	0·54
Use of opioids during surgery (morphine equivalents)	3·66 (1·39)	3·49 (1·31)	3·63 (1·38)	4·04 (1·44)	3·90 (1·88)	4·01 (1·54)	0·021	0·28	0·011
Pain observations*	..	..	..	..	..	..	<0·0001	0·92	<0·0001
Pain	52	22	74	100	17	117	..	..	..
No pain	1529	315	1844	1225	235	1460	..	..	..
Maximum FLACC pain score for each patient in the POCU†									
Mean pain score	1·34 (2·59)	2·51 (2·53)	1·57 (2·62)	2·58 (3·18)	1·95 (2·69)	2·45 (3·10)	0·00031	0·21	0·0057
Median pain score	0 (0–10; 0–1)	1 (0–7; 0–5)	0 (0–10; 0–3)	0 (0–10; 0–5)	0 (0–10; 0–4)	0 (0–10; 0–5)	..	..	..

Data are median (range), mean (SD), n, or median (range; IQR). FLACC=Face, Legs, Activity, Cry, Consolability. POCU=postoperative care unit. *Pain is FLACC score more than 3 (not sufficient pain relief) and no pain is FLACC score of 3 or less (sufficient pain relief). †FLACC score from 0 to 10 (severity increases with increasing score).

Table 2: Duration of surgery, use of opioids, and pain score
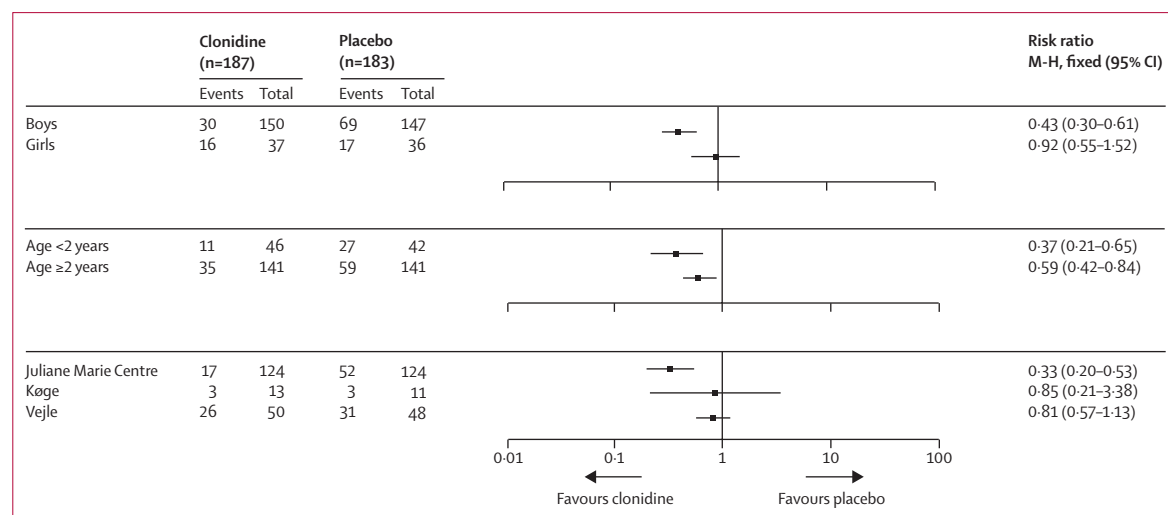
Role of the funding source

Funded by the participating departments and by two unrestricted scientific grants from the Danish Society of Anaesthesia and Intensive Care. Funders/sponsors had no role in the design of the study, collection of data, analysis of data, interpretation of data or writing the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between January and December, 2015 (not including the 30-day follow-up period), we randomly assigned 379 participants and excluded nine from the primary outcome analyses because of missing data points; none were lost to follow-up (figure 2). The baseline characteristics of the two groups were similar with boys over-represented in both groups because most surgeries in our sample were male genital surgeries (table 1).

46 (25%) of 187 clonidine participants compared with 86 (47%) of 183 placebo participants had one or more episodes of postoperative agitation (Watcha score >2; appendix). Results of generalised linear models showed that clonidine reduced the number of patients with postoperative agitation compared with placebo (RR 0·56, 95% CI 0·43–0·73; p<0·0001; appendix). The clonidine group received less opioids during surgery than the placebo group (table 2).

We found no interaction for our subgroup analyses for design variables: premedication (p=0·51), propofol induction (p=0·82), the use of local anaesthetics (p=0·58), agitation before anaesthesia (agitation score >2 or <2; p=0·21), duration of surgery (p=0·63), and sex (p=0·044). We found no interaction for the stratification variables age (<2 years or ≥2 years; p=0·069) and site (Køge Hospital odds ratio [OR] 0·67, Vejle Hospital 0·58, and Rigshospitalet 0·21; appendix).

	Clonidine (n=187)		Placebo (n=183)		Risk ratio M-H, fixed (95% CI)
	Events	Total	Events	Total	
Boys	30	150	69	147	0·43 (0·30–0·61)
Girls	16	37	17	36	0·92 (0·55–1·52)
Age <2 years	11	46	27	42	0·37 (0·21–0·65)
Age ≥2 years	35	141	59	141	0·59 (0·42–0·84)
Juliane Marie Centre	17	124	52	124	0·33 (0·20–0·53)
Køge	3	13	3	11	0·85 (0·21–3·38)
Vejle	26	50	31	48	0·81 (0·57–1·13)

Figure 3: Forest plots of agitation events
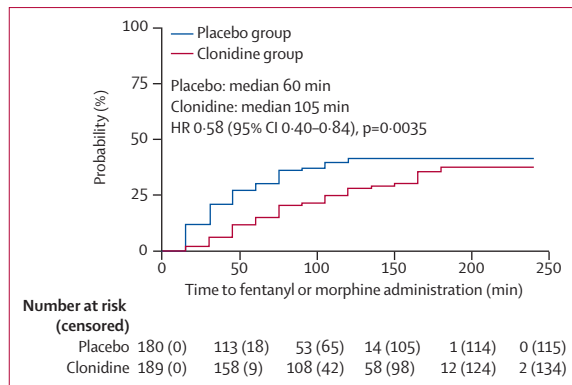Measured as Watcha scores more than 2. M-H=Mantel-Haenszel.

Figure 4: Kaplan-Meier plot for time to first opioid admistration in the postoperative care unit after administration of clonidine or placebo

When we used a Bonferroni-adjusted threshold for statistical significance, the test of interaction between sex and the effect on agitation (p=0·044) did not reach statistical significance (p=0·0063) when adjusted for multiplicity. However, only 73 girls were analysed for the primary outcome. 16 (43%) of 37 girls in the clonidine group were agitated compared with 17 (47%) of 36 girls in the placebo group (RR 0·92, 95% CI 0·55–1·52; p=0·73) and 30 (20%) of 150 boys in the clonidine group were agitated compared with 69 (47%) of 147 boys in the placebo group (0·43, 0·30–0·61; p<0·0001; figure 3).

For the secondary outcomes, the clonidine group received a mean of 0·46 units (SD 0·94) of morphine equivalents (mg) and the placebo group received a mean of 0·70 units (1·11) of morphine equivalents (mg; Van Elteren test p=0·040) after surgery. 56 (29%) of 191 participants in the clonidine received opioid drugs compared with 73 (39%) of 188 participants in the placebo group. The median time after administration of clonidine or placebo to administration of opioids or censoring was 105 min in the clonidine group compared with 60 min in the placebo group (figure 4). Cox regression analysis showed a significant difference between the groups when analysing time to first analgesic administration (HR 0·58, 95% CI 0·40–0·84; p=0·0035; figure 4). We recorded nine adverse events before discharge from the POCU, of which four were categorised as serious (two in the clonidine group and two in the placebo group; table 3). The adverse events were hospital admission, prolonged hospital stay, conversion from ambulatory surgery, opioid-related side-effects, and surgery or airway management issues.

Reductions in both blood pressure and heart rate were detected in the clonidine group after administration of the drug and up to admission into POCU (table 4). Treatment of hypotension and bradycardia was up to the attending physician's assessment in accordance with local guidelines. However, no patient was considered eligible for a haemodynamic intervention (table 4). The appendix provides detailed information on pain scores

	Clonidine group (n=191)	Placebo group (n=188)
Patients with adverse events*		
Opioid-related side-effects	0	3
Laryngeal spasm	0	1
Prolonged anaesthesia	0	1
Total	0	5
Patients with serious adverse events (events leading to admission)		
Re-bleeding	0	1
Late arrival in the postoperative care unit	0	1
Pale and not drinking and eating	1	0
PONV	1	0
Total	2	2
Events at 24-h follow-up		
Agitation	2	2
PONV	30	44
Dizziness	18	20
Syncope	0	0
Admission (fever, swelling, or PONV)	0	3
Patients at 30-day follow-up (reasons for contact)		
Ambulatory visit	21 (1)	20
Infection	9 (1)	6 (1)
Surgical	3 (2)	2 (1)
Injury	3	1
Other	9	6
Total (total admissions)	45 (4)	35 (2)

Data are n or n (total admissions). PONV=postoperative nausea and vomiting. *15 adverse event reports of PONV were disregarded because PONV was an exploratory outcome in this trial; these events have been reported separately.

Table 3: Adverse events, serious adverse events, and reasons for contact during follow-up

during stay in POCU and use of opioids during surgery.

Regarding the exploratory outcomes, clonidine treatment decreased new events of PONV in the POCU with 25 participants having PONV versus 43 participants in the placebo group (RR 0·58, 95% CI 0·38–0·89; p=0·012; appendix). The incidence of shivering did not differ between the groups (two in the clonidine group *vs* seven in the placebo; p=0·17; appendix). The time from intervention to discharge from the POCU was prolonged in the clonidine group compared with the placebo group (135 min *vs* 105 min; p<0·0001; appendix).

The groups did not differ at the initial 24-h follow-up interview and two patients in each group were described as agitated (measured with the Watcha scale). PONV was reported by 30 patients in the clonidine group versus 44 in the placebo group. The number of patients with one or more episodes of dizziness were 18 (clonidine group) versus 20 (placebo group); however, no case of syncope was reported. Three patients in the placebo group were admitted to hospital with either fever or swelling at the area of surgery (two patients) or PONV (one patient; table 3). The groups also did not

	Clonidine group (n=191)	Placebo group (n=188)	p values
Systolic blood pressure (mm Hg)			
Baseline	88 (10)	87 (11)	..
5 min	82 (10)	87 (10)	<0·0001
10 min	82 (10)	88 (11)	<0·0001
15 min	83 (10)	89 (11)	<0·0001
POCU arrival	89 (14)	96 (15)	<0·0001
Diastolic blood pressure (mm Hg)			
Baseline	40 (8)	40 (8)	..
5 min	37 (6)	40 (8)	0·00066
10 min	38 (7)	40 (7)	0·022
15 min	38 (8)	40 (9)	0·017
POCU arrival	44 (13)	50 (14)	0·00023
Pulse rate (beats per min)			
Baseline	109 (19)	111 (18)	..
5 min	103 (16)	110 (17)	<0·0001
10 min	101 (14)	109 (17)	<0·0001
15 min	99 (14)	106 (16)	<0·0001
POCU arrival	92 (14)	103 (15)	<0·0001

Data are mean (SD). Baseline is before administration of study drug. Timepoints are measurements after study drug administration. POCU=postoperative care unit.

Table 4: Blood pressure and pulse rate

differ at the final 30-day database follow-up (p=0·24; table 3) and all patients remained alive. 77 patients had been in contact with a hospital after initial discharge (three patients twice) and six patients (four in the clonidine group versus two in the placebo group) had been readmitted (three with surgical complications, two with infections, and one because of other considerations after an outpatient visit; table 3).

Discussion

The findings of this trial support the beneficial effect of intravenous clonidine bolus of 3 μg/kg administered around 20 min before the expected completion of surgery for prevention of postoperative agitation in healthy boys anaesthetised with sevoflurane.

There was a possible interaction between sex and effect on agitation, but only a fifth of the participants analysed were girls, the observed effect might have been restricted entirely to the boys who participated. This difference might be because of random error, but an interaction between sex and a greater clonidine effect on agitation in boys cannot be ruled out. However, our trial remains inconclusive regarding the effect of clonidine treatment on agitation in girls. Nevertheless, it is important to point out that we do not advocate against the use of clonidine in girls, but with the population that we were able to recruit we are unable to make a recommendation about efficacy in girls. The sex imbalance of the sample reflects the case-mix distribution across the participating sites based on the surgical procedures provided and not as a result of selection bias or other confounders.

Our results are in line with the overall assumption that α-2 agonists can prevent postoperative agitation as previously reported in various trials. In a systematic review,[6] perioperative administration of α-2 agonists without premedication reduced the number of children with one or more episodes of postoperative agitation (OR 0·28, 95% CI 0·19–0·40; p<0·001). However, only two paediatric trials[14,15] with clonidine were included in this review and only one[15] showed a statistically significant reduction in postoperative agitation. Additionally, the optimal clonidine dose in the perioperative setting for children has little consensus.[7,10,25]

The conflicting results in previous paediatric trials might be explained by small sample sizes (40–169 children), different routes of administration (oral, intravenous, or epidural), different doses (0·75–5 μg/kg), and the use of different scales for assessment of postoperative agitation. Additionally, these trials had a high risk of bias.[10,14–19,26–29] In two trials (60 patients and 61 patients, respectively),[30,31] epidural clonidine administration (2–3 μg/kg) also reduced postoperative agitation.

The proportion of patients with one or more episodes of postoperative agitation is reported with great variation in previous trials, with a mean value of around 25% (10–80%). The frequency of patients with one or more episodes of postoperative agitation in our placebo group was 47%. This result is in line with a meta-analysis[32] reporting an incidence of 56%. Thus, one can argue that the clinical challenge of postoperative agitation is underestimated in previously published trials, and as such the desire to try to prevent postoperative agitation should be even greater. This argument is further underlined by the findings of a survey[33] among paediatric anaesthesiologists in Germany, where postoperative agitation was perceived as a relevant clinical problem by 87% of physicians. However, the challenge was often underestimated, rarely documented using a scale, but one which German physicians tried to prevent with either total intravenous anaesthesia (56%) or with pre-emptive use of clonidine (30%).[33] A review[34] and a guideline[35] from the European Society of Anaesthesiology (ESA) further emphasise the need for screening and prevention of postoperative agitation in children.

Administration of clonidine can be accompanied by a decrease in heart rate and blood pressure. However, we included healthy children (ASA 1–2) often scheduled for elective surgery, and none of the included patients needed interventions for hypotension or bradycardia during anaesthesia or in the POCU. Depending on the duration of surgery the study drug could have been administered immediately after induction of anaesthesia or at the end of anaesthesia (according to study protocol 20 min before completion of anaesthesia). Nevertheless, we detected no episodes of haemodynamic instability.

We carried out postoperative follow-up at 24 h and 30 days with no difference in reported adverse events or any indications of safety concerns. The prolonged recovery time for the clonidine group is in line with the findings of a systematic review[6] of 12 trials with clonidine and dexmedetomidine. Clonidine administration seems rational and feasible despite the increased POCU stay, not only because of the low cost of the drug, but also because an agitated child is at risk of self-injury and thus will require more attention, care, and medical interventions from the staff.[2] Clonidine was listed on the European Medicines Agency's revised priority list for studies on off-patent paediatric medical products (August, 2013), in need of investigation regarding pain, efficiency, and safety.[36] To our knowledge, this is the largest paediatric randomised controlled trial investigating clonidine for prevention of postoperative agitation.[14–19,26–29] Previous trials[17] included sample sizes of up to 169 children. Generalisability and the external validity of our findings are enhanced by inclusion of children with different surgical procedures, including tonsillectomy, hernia repair, and cryptorchidism surgery, and recruitment from three hospitals. Our findings are also in line with recommendations from the recently published ESA guideline[35] for prevention of postoperative agitation.

A child with postoperative agitation is typically irritable, uncooperative, and inconsolable, and distinguishing postoperative agitation from postoperative pain or a tantrum is often challenging in clinical practice even for experienced clinicians.[21,37] We assessed postoperative agitation and pain every 15 min with the Watcha scale and the FLACC scale until discharge from POCU.[38] All patients with one or more episodes of Watcha score of more than 2 were considered to have postoperative agitation, irrespective of the FLACC score. However, for some patients pain can be the cause for agitation, which might explain why fentanyl also has been shown to reduce postoperative agitation.[32] Other adjunctive drugs, such as dexmedetomidine and propofol bolus, at the end of sevoflurane-based anaesthesia have also been reported to be beneficial for prevention and treatment of postoperative agitation.[2,39,40] The large variation in the reported incidence of postoperative agitation in the published work might depend on the diagnostic criteria, type and length of surgical procedure, and the use of inhalation aesthetic drugs.[41] Nevertheless, as previously explained, our findings do not differ much from the reported data.

Our choice of Watcha score limits our ability to distinguish delirium from agitation. In the scientific literature, the term postoperative or emergence agitation is often interchangeably used with emergence delirium to describe an inconsolable, irritable, and uncooperative child.[2] However, postoperative delirium and postoperative agitation differ not only in definition but also in clinical presentation and outcome because delirium is an acute state of confusion with cognitive impairment (ie, perceptual disturbances and hallucinations) and is often more difficult to diagnose and treat in children.[2]

Our exclusion of children with intellectual disability or any other form of neurodevelopmental disability is a limitation that reduces the external validity and generalisability of our findings. However, children with neurological disabilities often have disturbed behavioural patterns compared with children without such disabilities. Thus, we believed that our masked assessors would have difficulties distinguishing these behavioural disturbances from postoperative agitation. Furthermore, in children with neurodevelopmental disabilities, the tools used for assessment of pain are different (ie, revised-FLACC scale).

Time to discharge from POCU, shivering, and PONV were considered explorative outcomes in this trial. The assessment of PONV was limited by allowing all tonsillectomy patients to be treated with dexamethasone for prevention of oedema according to routine clinical care.

This confirmatory clinical trial was designed and carried out with the emphasis on minimising the risk of bias, while we addressed the benefits and potential harms of clonidine for prevention of postoperative agitation in children anaesthetised with sevoflurane. Our aim was to do a trial with an overall low risk of bias within the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other types of bias in accordance with the Cochrane Collaborations tool for assessing risk of bias. Equally, we complied with the Helsinki Declaration and the CONSORT and SPIRIT guidelines and our trial was approved and monitored in accordance with the ICH-GCP statement. However, we still had missing data for nine patients on the primary outcome, the magnitude of which was considered low, because the missing data were balanced between groups and therefore unrelated to the true outcome. Because of missing data and the varying length of time between intervention and discharge from the POCU, we were unable to do the planned mixed-model analysis for postoperative agitation, as described in our statistical analysis plan and our published protocol.[10] We detected a few cases in which the patients were treated with fentanyl, without an agitation score to justify such practices. As a direct consequence, the case report form was revised at the initial stage of the trial with an increased attention on such practices and subsequent information to staff. This revision could have prevented a potential underestimation of episodes of postoperative agitation and supported the higher proportion of patients with one or more episodes of postoperative agitation in our trial than reported in some previous trials.

In summary, this randomised trial shows that clonidine significantly reduces the proportion of boys with postoperative agitation when anaesthetised with sevoflurane. Furthermore, clonidine reduced the postoperative opioid

consumption, prolonged the time to first analgesic administration, and decreased PONV, although recovery times were increased. Clonidine had an acceptable safety profile in healthy children admitted for mostly elective surgery and appears to be cost-effective, but data for critically ill children with concomitant medication are needed.

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