

Effect of clonidine to prevent agitation in children after sevoflurane anaesthesia: a randomised placebo controlled multicentre trial

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ABSTRACT

INTRODUCTION: Post-operative agitation (PA) is a common problem (20-70%) in children anaesthetised with sevoflurane. Clonidine is widely used off-label in children for several indications, including PA; but the current level of evidence is limited. Our aim is to investigate the impact of prophylactic intravenous (IV) clonidine administered at the end of surgery on the incidence and degree of PA. Furthermore, the pharmacokinetic profile of IV clonidine in children is not well established and our aim is to obtain pharmacokinetic data relating hereto.

METHODS: This is a multicentre, randomised and blinded clinical trial in which we will be enrolling 380 children aged 1-5 years who are planned for anaesthesia with sevoflurane and fentanyl. Inclusion is based on computer-generated randomisation (1:1) and stratified by age and site. The study drug is administered IV approximately 20 min. before the expected completion of surgery (intervention: clonidine 3 µg per kg; placebo: equal quantity of saline).

CONCLUSION: The primary outcome is PA measured on the Watcha scale. The secondary outcomes include post-operative pain relief and adverse effects, including a 30-day follow-up. In total, 40 children will be allocated to drug assay sampling, enabling a compartmental pharmacokinetic analysis.

FUNDING: Funded by the participating departments and by two unrestricted scientific grants from the Danish Society of Anaesthesia and Intensive.

TRIAL REGISTRATION: This study was approved by the Danish Health and Medicines Authority (EudraCT number 2014-001466-10), the Ethics Committee of the Capital Region of Denmark (H-2-2014-072) and registered with Clinicaltrials.gov (NCT02361476).

The use of sevoflurane, a volatile anaesthetic, in paediatric anaesthesia is frequent since it is unnecessary to establish an intravenous (IV) access prior to initiation of anaesthesia. This is a clear benefit for children as a needle procedure can be painful and traumatising. Various pharmacological interventions have been investigated for the intervention against post-operative agitation (PA) in children anaesthetised with sevoflurane, including

clonidine. Clonidine is used off-label for a number of indications in children, including treatment of shivering, pain management and prevention of withdrawal symptoms following too long-term sedation, and PA.

In 2002, the use of clonidine, an alpha-2 receptor agonist, was proposed as a potential prophylactic intervention against sevoflurane-induced PA in children [1]. Several trials have since been published, examining the role of different strategies for clonidine administration and dosing in the perioperative setting (**Table 1**).

Presently, paediatric trials have found few safety issues, no serious adverse effects or significant decrease in blood pressure or heart rate (**Table 1** and **Table 2**). However, current knowledge about pharmacokinetics of clonidine and the relationship between plasma concentrations, safety and effect on PA and pain in children remains limited [2-4].

In a recent systematic review, alpha-2 agonists administered during anaesthesia without premedication were found to reduce the incidence of PA (odds ratio = 0.28; 95% confidence interval: 0.19-0.40, $p < 0.001$) [5]. However, only two trials with clonidine were included. One included 75 children, a third of whom received 1.5 µg/kg IV clonidine after induction, and this did not significantly reduce the incidence of PA [6]. The other included 120 children received either clonidine 2 µg/kg or placebo after induction, and the incidence of PA in these children decreased significantly from 41% to 22% [7].

The previously published trials have suffered from various methodological shortcomings such as small sample sizes, high risk of bias, low doses and various routes of administration (**Table 1** and **Table 2**) [8]. Furthermore, previous trials have suggested that clonidine in lower dosages of 1 µg/kg may reduce the incidence of PA by as much as 50%. This reduction is presumed to be dose-dependent; and as a consequence there is an urgent need for studies examining the impact of higher doses. Despite the known analgesic properties of clonidine, an optimal dose in a perioperative setting remains to be established as suggested in a recently published Cochrane review [9]. Equally important, the role of clonidine for other relevant outcomes such as shivering and post-

PROTOCOL ARTICLE

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operative nausea and vomiting (PONV) remains to be established. These outcomes are not only patient-relevant but may have important cost-benefit advantages such as reduced time to discharge from the recovery ward and reduced length of stay in hospital.

The purpose of this trial is to investigate whether IV clonidine 3 µg/kg, administered approximately 20 min. before the expected completion of surgery, will

reduce the incidence of PA and pain in children anaesthetised with sevoflurane. Safety issues and serious adverse events are evaluated for a follow-up period of 30 days. Additionally, in a representative group of the children, pharmacokinetic (PK) data will be obtained for characterisation of the PK profile and correlation of plasma concentrations of clonidine to the clinical response.

TABLE 1

Overview of paediatric clonidine-trials for prevention of post-operative agitation.

Reference	Number and design	Intervention	Results	Safety	Risk of bias
Ghai et al, 2010	n = 120 RCT Premedication: midazolam 0.5 mg/kg PO	IV: placebo (n = 40), clonidine 1 µg/kg (n = 39), 2 µg/kg (n = 41)	Agitation: 27,5%, 5,1%, 0%	No significant impact on blood pressure or pulse rate	Unclear
Tesoro et al, 2005	n = 169 RCT, blinded Premedication: midazolam 0.5 mg/kg PO and nerve block or local infiltration	IV, just before start of surgery: clonidine 2 µg/kg (n = 91), placebo (n = 78)	Incidence of agitation was reduced by 57% (p = 0.029) Incidence of severe agitation was reduced by 67% (p = 0.064)	No respiratory adverse effects Pulse rate: 116 ± 32, 112 ± 28 per min. MAP: 92 ± 18, 87 ± 21 mmHg	High
Tazeroualti et al, 2007	n = 60 RCT, blinded Paracetamol and penile block	PO, 30 min. prior to anaesthesia: midazolam 0.5 mg/kg (n = 20); clonidine 2 µg/kg (n = 20), 4 µg/kg (n = 20)	Agitation in the 1st post-operative h: 60%, 40%, 25% (p = 0.025)	No difference between groups regarding haemo- dynamic parameters	High
Ghosh et al, 2011	n = 90 RCT, blinded	Clonidine added to epidural: 1 µg/kg, 0.75 µg/kg, 0 µg/kg	Agitation: 6,6%, (p < 0.05), 26.6%, 40%	No effect on haemodynamic or respiratory systems	High
Bock et al, 2002	n = 80 RCT, blinded Premedication: midazolam 0.4 mg/kg PO	Clonidine added to epidural: 1 µg/kg (n = 18), 3 µg/kg (n = 18), 0 µg/kg (n = 18), 3 µg/kg IV (n = 18)	Agitation: 20%, 0%, 39%, 5%	No relevant respiratory or haemodynamic adverse events, despite a significant lower blood pressure in the 3 µg/kg group	Unclear
Kulka et al, 2001	n = 40 RCT, blinded Penile block Premedication: midazolam 0.5 mg/kg PO	IV, after induction: clonidine 2 µg/kg, placebo	<i>Number of patients</i> With agitation: 2 vs 16 (p < 0.001) Severe agitation: 0 vs 6 (p < 0.05)	No intraoperative difference between groups regarding haemodynamics Despite a significant lower blood pressure post-operatively in the clonidine group, no episodes of bradycardia or hypotension was recorded	High
Almenrader et al, 2007	n = 64 RCT, open Ibuprofen Paracetamol	Premedication PO: midazolam 0.5 mg/kg (n = 30), clonidine 4 µg/kg (n = 30)	Agitation: 7% , 0% (p = 0.13)	-	High
Bergendahl et al, 2004	n = 100 RCT, blinded Paracetamol	Premedication rectal: midazolam 0.3 mg/kg (n = 52), clonidine 5 µg/kg (n = 48)	Lower pain score (p = 0.011) Higher sedation score (p ≤ 0.001) Lower confusion (p = 0.001)	-	High

IV = intravenously; MAP = mean arterial pressure; PO = orally; RCT = randomised clinical trial.

TABLE 2

Previous trials with intravenous clonidine administered after induction of anaesthesia to prevent post-operative agitation, without premedication and local anaesthesia.

Reference	Number and design	Intervention	Results	Safety	Risk of bias
Lankinen et al, 2006 [6]	n = 75 RCT, blinded	Tropisetron 0.1 mg/kg (n = 25) Clonidine 1.5 µg/kg (n = 24) Placebo (n = 26)	Agitation: tropisetron 32%, clonidine 54%, placebo 62%	No adverse events	Unclear
Malviya et al, 2006 [7]	n = 120 RCT, blinded	Clonidine 2 µg/kg (n = 59) Placebo (n = 61)	Moderate-severe agitation: placebo 41%, clonidine 22% (p < 0.03)	No adverse events	High

RCT = randomised clinical trial.

METHODS

We have adhered to the CONSORT statement and SPIRIT guideline, and the 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). The trial was registered with clinicaltrials.gov (NCT02361476). We will adhere to the harmonised tripartite guidelines for good clinical practice (ICH GCP), including the Helsinki Declaration, and our trial will be monitored by independent monitors from the GCP unit at Rigshospitalet.

Prior to protocol writing, we systematically searched PubMed, EMBASE and the Cochrane Library for relevant references in order to define the ideal dose and study design using keywords such as: PA, sevoflurane, children, preclinical studies and clonidine. We applied no language or time restrictions.

The PREVENT AGITATION trial is designed as a randomised, placebo-controlled, blinded, multicentre superiority trial with two parallel groups. The trial will be conducted at Rigshospitalet: Department of Anaesthesiology, The Juliane Marie Centre, a tertiary hospital with approximately 4,000 children admitted for elective surgery a year; and the Departments of Anaesthesiology at Vejle Hospital and Zealand University Hospital, Køge. These are urban district hospitals with an annual census of 700 and 600 children, respectively. Participant inclusion and exclusion criteria are given in **Table 3**.

Centralised randomisation is performed on a website produced by the Copenhagen Trial Unit, Rigshospitalet, using adequate computer random number generation to establish the allocation sequence. Randomisation will be performed as block randomisation with a 1:1 allocation stratified for site and age (< 2 or ≥ 2 years) aiming to limit baseline imbalance for these variables. Participants, investigators, other healthcare providers, statisticians and authors of the trial report will be blinded to the assignment. Trial medications are delivered by The Hospital Pharmacy of the Capital Denmark Region in identical containers, relabelled with printed randomisation numbers.

Intervention group: 3 µg/kg of IV clonidine (Catapresan, Boehringer Ingelheim, 150 µg/ml, 1 ml vials).

Control group: equal quantity of IV saline (sodium chloride, Skanderborg Pharmacy, 9 mg/ml, 1 ml vials).

The trial results will remain blinded to the authors during preparation of the manuscript. Thus, two manuscripts will be prepared in which conclusions are based either on the assumption that the first group is the intervention group, while the other group is the control group and vice versa [10]. Once the manuscripts are approved by the Steering Committee, the results will be unveiled and the correct manuscript will be published.

Primary outcome

The primary outcome is the incidence of agitation measured by the Watcha Scale, which is validated in children in a post-operative setting. Scores 3-4 will be considered agitated [11-13].

Secondary outcomes

- Opioid requirements in the recovery room.
- Time to first administration of opioid in the recovery room.
- Pain score, assessment with the “face, leg, activity, cry, consolability” scale (only part B).
- Adverse events.

Exploratory outcomes

- Time to discharge from the recovery room.
- Incidence of shivering.
- Incidence of PONV.

Part A

Information is provided to all parents of children fulfilling the inclusion criteria prior to arrival at one of the three participating hospitals. Written informed consent is obtained from both parents. Data will be collected on paper case record forms (CRF). Any protocol violation will be recorded in the CRF. All relevant information will be recorded in the patient chart and CRF, including assessment of eligibility for inclusion, randomisation number, age, weight, type of surgery, administration of any type of analgesics or sedatives prior to arrival at the op-



TABLE 3

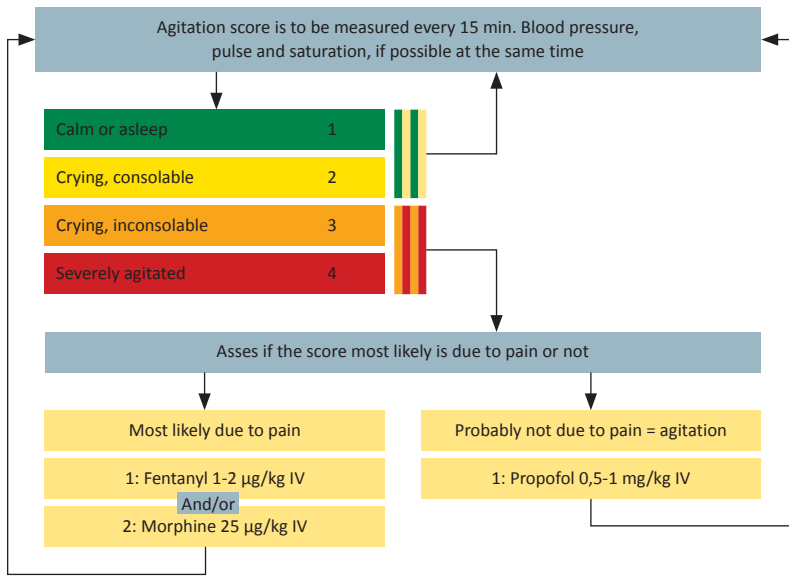
Inclusion and exclusion criteria.

<i>We will include children</i>
1-6 yrs of age
Scheduled for surgery with sevoflurane anaesthesia
<i>We will exclude children with any of the following</i>
ASA classification > 2
Premedication with clonidine
Ex-premature: born before week 37 + 0 and < 60 weeks old
Intubated before anaesthesia and/or no plans for extubation after anaesthesia
Critical illness with haemodynamic instability
Active bleeding
Cancer
Cardiac diseases including arrhythmias
Malignant hyperthermia
Mental retardation
Neurological illness with agitation-like symptoms
Weight > 50 kg
Allergy to clonidine
Patients treated with methylphenidate

ASA = American Society of Anesthesiologists.


FIGURE 1

Flow chart for assessment and treatment of agitation and pain in the recovery room. Intervention if Watcha-score is 3 or 4. If pain is the most probable cause (e.g. because of failing local anaesthesia), the patient is treated for pain. If pain is not the most probable cause or the clinician is in doubt, the patient is treated for agitation.



erating theatre, and when possible measurement of blood pressure, heart rate and oxygen saturation prior to the induction of anaesthesia, together with baseline agitation score.

Anaesthesia will be induced either via a mask with sevoflurane and 100% oxygen or IV propofol. Airway management and volume resuscitation will be according to local and national guidelines. No other opioids or hypnotics than fentanyl, sevoflurane and propofol (for induction only) are allowed during surgery. When muscular relaxation is needed, primarily rocuronium bromide or suxametonium is to be used. The anaesthesia is maintained solely with sevoflurane and fentanyl as analgesic with no limitation on dosage (clinical assessment of need). Paracetamol will be administered after induction according to weight and age if no contradiction and if it was not already administered prior to arrival in the operating theatre. Local, peripheral and central nerve blocks are permitted, but without adding e.g. clonidine. All administered drugs and dosages and their time of administration will be recorded throughout the trial period. Blood pressure, pulse and oxygen saturation are to be registered every 5 min. after induction of anaesthesia and every 15 min. in the recovery room.

In consultation with the surgeon and approximately 20 min. prior to awakening, the trial drug will be administered IV. This is based on the rationale of achieving maximum possible benefit of clonidine approximately 15 min. after administration. After awakening, we will regis-

ter the agitation score every 15 min. until discharge. In the post-operative recovery unit, only fentanyl and morphine are allowed to alleviate pain, and propofol is allowed to treat agitation according to a flow chart (Figure 1).

After discharge, patients will be followed up at 24 hours for any adverse events and at 30 days to register serious adverse events.

Part B – pharmacokinetics

In part B of the study, all patients are treated as described in Part A. Additionally, blood samples will be collected for pharmacokinetic analysis after administration of the study drug. Due to the possible differences in the distribution and elimination of clonidine in children younger than two years, we will carry out separate analyses for children older than two years and for children between one and two years. Blood samples are taken through a peripheral intravenous catheter at baseline (before study drug administration) and at 5, 10, 15, 30, 60 min. post dose and additionally for every hour until discharge from the recovery room. For each blood sample, 2 ml of heparinised blood is collected for analysis of the plasma clonidine concentration. The maximum number of blood samples drawn from each patient is nine. Blood samples are centrifuged immediately after collection, and the plasma samples are stored at -80°C pending analysis.

Statistics

Using a 25% PA incidence from previously published studies and systematic reviews [14], a total of 380 children (190 per group) were calculated with the software "Power and Sample Size" to provide a 80% power targeting a relative risk reduction (RRR) of 41%, with a maximal 5% risk of type 1 error.

The proposed incidence of PA closely resembles the findings of an internal audit (conducted with the blinding conserved) at the three study sites after trial commencement. We consider the proposed RRR as a realistic target and clearly more realistic than 50%, which is often perceived in the literature as a realistic beneficial effect. As a consequence, our sample size was increased from 304 to 380 by addressing a RRR of 41% instead of 50%.

We will assess and report all outcomes as "intention-to-treat" analysis including all randomised children meeting the inclusion criteria and not fulfilling the exclusion criteria with a standing consent to participate.

The primary analyses will be differences in outcomes adjusted for stratification variables. The secondary analyses will be analyses adjusted for baseline variables using multiple logistic regression in accordance with ICH-GCP recommendations on statistical principles

for clinical trials (E9). Complete case analysis will be carried out if the overall level of missing data is less than 5%. However, if exceeding the limit of 5% missing data and if Littles' test is statistically significant, multiple imputation will be used and considered the primary result of the trial to reduce bias from complete case analysis [15-17]. We will present "worst-case" and "best-case" scenarios. $p < 0.05$ will be considered statistically significant.

For each group, all children will be analysed for the primary outcome. For each primary and secondary outcome, the results and estimated effect sizes with 95% confidence interval will be provided. For binary outcomes, we will provide both absolute and relative effect sizes. Time-to-event outcomes (time to fentanyl administration and discharge) will be presented as survival curves using Kaplan Meier estimators, and differences between groups will be analysed using Cox regression analysis adjusted for stratification and baseline variables. We will provide detailed data for all other exploratory analyses (secondary and exploratory outcomes).

Subgroup analyses will be used (site, age, sex, the use of propofol or not, length of the operation, the use of premedication, preoperative Watcha score and the use of local, peripheral and central nerve blocks) [18, 19].

We will exclude patients with major protocol violations defined as failure to receive the total drug dose or failure to complete follow-up in a supplemental per-protocol analysis. We will carry out statistical analyses before revealing the code of allocation.

Trial registration: Approved by the Danish Health and Medicines Authority (EudraCT number 2014-001466-10), the Ethics Committee of the Capital Region of Denmark (H-2-2014-072) and registered with Clinicaltrials.gov (NCT02361476).

DISCUSSION

The results of a newly published trial in a vulnerable group of adults have prompted a more detailed assessment of paediatric data regarding harm and indication for use [20]. We do, however, not expect any problems or harm in this trial. First of all because of the different pharmacodynamics and pharmacokinetics in children. Secondly, because this trial has fundamental differences in patient population, dose, timing and duration of the intervention. And, finally, because, hypotension and bradycardia which are well-known side effects in adults have not been reported at similar rates in children in any of the published systematic reviews of trials.

PA due to volatile anaesthetic agents is more frequently observed in small children than in older children and adults. This remains a great challenge for healthcare

providers and causes great discomfort for children and their parents. Since volatile anaesthetic agents are used extensively in children, PA constitutes a great problem which we hope to alleviate and significantly reduce by carrying out this multicentre, randomised clinical trial with low risk of bias in accordance with the CONSORT statement and the SPIRIT initiative.

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