Received: 26 September 2022 | Revised: 15 June 2023 | Accepted: 24 July 2023

DOI: 10.1111/pan.14740

Pediatric Anesthesia WILEY

RESEARCH REPORT

Postoperative recovery in preschool-aged children: A secondary analysis of a randomized controlled trial comparing premedication with midazolam, clonidine, and dexmedetomidine

Åsa Bromfalk[1] | Magnus Hultin[1] | Tomi Myrberg[2] | Åsa Engström[3] | Jakob Walldén[4]

[1]Department of Surgical and Perioperative Sciences, Anesthesiology and Intensive Care Medicine, Umeå University, Umeå, Sweden

[2]Department of Surgical and Perioperative Sciences, Anesthesiology and Intensive Care Medicine (Sunderbyn), Umeå University, Umeå, Sweden

[3]Division of Nursing and Medical Technology, Department of Health, Education and Technology, Lulea University of Technology, Luleå, Sweden

[4]Department of Surgical and Perioperative Sciences, Anesthesiology and Intensive Care Medicine (Sundsvall), Umeå University, Umeå, Sweden

Correspondence
Åsa Bromfalk, Department of Surgical and Perioperative Sciences, Anesthesiology and Intensive Care Medicine, Umeå University, 901 87 Umeå, Sweden.
Email: asa.bromfalk@umu.se

Funding information
Medicinska fakulteten, Umeå Universitet; Region Norrbotten, Grant/Award Number: RN-785981, NLL-486841 and NLL-485451; Region Västerbotten, Grant/Award Number: RV-865681 and RV-940554

Section Editor: Thomas Engelhardt

Abstract

Background: Preoperative anxiety in pediatric patients can worsen postoperative outcomes and delay discharge. Drugs aimed at reducing preoperative anxiety and facilitating postoperative recovery are available; however, their effects on postoperative recovery from propofol-remifentanil anesthesia have not been studied in preschool-aged children. Thus, we aimed to investigate the effects of three sedative premedications on postoperative recovery from total intravenous anesthesia in children aged 2–6 years.

Methods: In this prespecified secondary analysis of a double-blinded randomized trial, 90 children scheduled for ear, nose, and throat surgery were randomized (1:1:1) to receive sedative premedication: oral midazolam 0.5 mg/kg, oral clonidine 4 μg/kg, or intranasal dexmedetomidine 2 μg/kg. Using validated instruments, outcome measures including time for readiness to discharge from the postoperative care unit, postoperative sedation, emergence delirium, anxiety, pain, and nausea/vomiting were measured.

Results: After excluding eight children due to drug refusal or deviation from the protocol, 82 children were included in this study. No differences were found between the groups in terms of median time [interquartile range] to readiness for discharge (midazolam, 90 min [48]; clonidine, 80 min [46]; dexmedetomidine 100.5 min [42]). Compared to the midazolam group, logistic regression with a mixed model and repeated measures approach found no differences in sedation, less emergence delirium, and less pain in the dexmedetomidine group, and less anxiety in both clonidine and dexmedetomidine groups.

Conclusions: No statistical difference was observed in the postoperative recovery times between the premedication regimens. Compared with midazolam, dexmedetomidine was favorable in reducing both emergence delirium and pain in the postoperative care unit, and both clonidine and dexmedetomidine reduced anxiety in the postoperative care unit. Our results indicated that premedication with α_2-agonists

had a better recovery profile than short-acting benzodiazepines; although the overall recovery time in the postoperative care unit was not affected.

KEYWORDS
child, clonidine, dexmedetomidine, midazolam, postoperative period, premedication

1 | INTRODUCTION

In the early postoperative period after anesthesia, preschool-aged children are at risk of developing and experiencing adverse outcomes such as emergence delirium (ED), anxiety, pain, and/or nausea/vomiting, which might result in prolonged emergence and delayed recovery and discharge.[1] Preoperative anxiety activates a stress response that increases the risk of these events. Thus, in preschool-aged children proper premedication to reduce preoperative anxiety is crucial.[2]

Midazolam, a short-acting benzodiazepine, has traditionally been used in pediatric anesthesia to reduce perioperative anxiety.[3] Side effects of midazolam are increased risk of ED and amnesia.[4] However, the effect of midazolam on the risk for postoperative delirium remains unclear. Furthermore, some reports suggest that midazolam may even prevent such events.[5] Clonidine and dexmedetomidine—α_2-agonists—are widely used as alternatives to midazolam for premedicating children.[4] The α_2-agonists are reported to reduce episodes of ED and postoperative pain when compared to midazolam.[4] Further, clonidine seems superior at preventing postoperative nausea and vomiting (PONV) compared to midazolam.[6] The use of total intravenous anesthesia with propofol-remifentanil is associated with a shorter recovery, less ED, and less PONV when compared to volatile anesthesia.[7] However, knowledge and consensus regarding the optimal premedication regimen to be used along with propofol-remifentanil to reduce adverse postoperative outcomes in preschool-aged children is limited and unclear.

The aim of this study was to compare postoperative recovery in preschool-aged children randomized into three different premedication groups: midazolam, clonidine, or dexmedetomidine. We aimed to assess the recovery time from total intravenous anesthesia after ear, nose, and throat (ENT) surgery, using the criteria for discharge as outcomes. Consequent evaluations of sedation levels, occurrence of postoperative episodes of ED, anxiety, pain, and PONV until reaching the discharge criteria were performed using validated observation tools. We hypothesized that clonidine and dexmedetomidine are associated with a shorter recovery time and lower risk of ED, anxiety, postoperative pain, and PONV in the post anesthesia care unit (PACU) when compared with midazolam.

What is already known?

Preoperative anxiety and stress in children are associated with postoperative anxiety, emergence delirium, pain, and nausea/vomiting. Premedication regimens may influence postoperative outcomes, but there is no consensus regarding the optimal premedication regimen.

What this article adds?

This study showed that premedication with midazolam was associated with increased emergence delirium, anxiety, and pain than premedication with clonidine or dexmedetomidine alone. There were no differences in recovery time between the regimens.

2 | METHODS

2.1 | Study design

This study was a preplanned secondary analysis of a double-blinded clinical trial evaluating premedications in preschool-aged children undergoing anesthesia for ENT surgery at Sunderby Hospital, Luleå, Sweden, from February 2017 to May 2019. Aspects of preoperative anxiety and perioperative cardiac response in the trial cohort were previously published.[8,9] The study protocol followed Good Clinical Practice and was approved by the Regional Ethic Review Board in Umeå (Dnr 2016-46-31M, March 30, 2016, chair: A Iacobæus) and the Swedish Medical Products Agency (Dnr 5.1-2016-17854, May 13, 2016). Written informed consent was obtained from parents on the day of the procedure. All children were accompanied by a parent throughout the preoperative and postoperative periods, and one parent was allowed to attend during anesthesia induction.

The trial protocol was registered in the European Union Drug Regulation Authorities' Clinical Trials Database (EudraCT 2015-003676-70) and adhered to the CONSORT guidelines for reporting the study.

2.2 | Participants

Inclusion criteria were children of both sexes aged 2–6 years without severe comorbidities (American Society of Anesthesiologists Physical Status (ASA-PS) I–II), weight of ≤30 kg, scheduled for elective tonsillotomies, tonsillectomies, adenotomies or adenectomies, propofol-remifentanil anesthesia, and written informed consent from their parents. The exclusion criteria were ASA-PS > II, severe comorbidities, use of psychotropic medications, and history of recent surgery (within a year).

2.3 | Interventions

The children were randomized to one of the three interventions groups and received premedication with per oral midazolam 0.5 mg/kg (MID-group) (APL Stockholm, 1 mg/mL), per oral clonidine 4 μg/kg (CLO-group) (APL Stockholm, 20 μg/mL), or intranasal dexmedetomidine 2 μg/kg (DEX-group) (Dexdor®, Orion Pharma, 100 μg/mL).

The doses, administration route, and premedication timing were based on published pharmacokinetic profiles and were chosen to be safe with clinically relevant effects. The rationale for different administration times was discussed in the first publication of the trial.[9]

2.4 | Randomization and blinding

Eligible children were randomly assigned in a 1:1:1: ratio to one of the three study groups. The study was randomized using sequentially numbered opaque envelopes containing group assignments. An independent statistician generated a randomization list with a block size of 15 using the randomization function in Microsoft Excel. Randomization of children and administration of the study drugs were performed by a nurse independent of the research team and data collection. The patients, parents, department staff, and researchers were blinded to the interventions.

Sixty minutes before the planned induction of anesthesia, all included children were orally administered a fluid containing clonidine (CLO-group) or sterile water (MID- and DEX-groups). Twenty minutes later, a fluid was administered intranasally using a mucosal atomization device (MAD Nasal™, Teleflex, USA) containing dexmedetomidine (DEX-group) or 0.9% NaCl (CLO- and MID-groups), followed by an orally administered fluid containing midazolam (MID-group) or sterile water (CLO- and DEX-groups) (Table 1).

2.5 | Endpoints and assessment

The main endpoint for this secondary analysis was recovery time in the PACU. We used the Post Anaesthestic Discharge Scoring System (PADSS) and considered a PADSS-score of ≥9 as recovered.[10] Explanatory endpoints were conceivable postoperative outcomes affecting recovery time, including vital signs, sedation levels, ED events, anxiety, pain, and PONV.

An independent observer (ÅB), not responsible for providing anesthesia or postoperative care to the children, documented the baseline assessments and evaluated the children in the PACU every 15 min for 2 h after arrival in the PACU. The observer was trained to read, learn, and test the instruments during normal clinical encounters, followed by pilot runs of the complete protocol. None of the questions were directly addressed to the children.

2.5.1 | Recovery/readiness for discharge/PADSS

The PADSS has high validity and reliability and is a tool for providing a safe discharge from the PACU.[10] The PADSS is based on the following five main domains: vital signs, activity and mental status, pain/PONV, surgical bleeding, and intake/output. The maximum score on the PADSS is 10, with a maximum of two points in each subdomain (Appendix S1).

The five domains of the PADSS-score were assessed using standard monitoring in the PACU and validated observational instruments. The domain *vital signs* included assessments of respiratory rate, peripheral oxygen saturation, heart rate, capillary refill time, and body temperature. *Activity and mental status* were assessed using the Ramsay Sedation Scale (RSS), and a PADSS-score of two was achieved when the RSS-score was 2 or 3 (awake or drowsy).[10] *Pain* was assessed using the Face Legs Activity Cry Consolability scale (FLACC) and *PONV* as observations of nausea, retching, or vomiting. When FLACC score was ≤3 in the absence of PONV, a PADSS-score of two (2) was achieved for the domain. *Input/output* was assessed as oral intake (one point) and the ability to void (one point).

Time to readiness for discharge/recovery was defined as the time from arrival at the PACU to when the PADSS score was 9 or 10 on two consecutive assessments, and the only sub-score allowed to remain unfulfilled was the ability to void.

2.5.2 | Sedation/RSS

Sedation levels were assessed using the Ramsay Sedation Scale (RSS). High scores denote high levels of sedation, including the following states of consciousness: 1, anxious, restless, or agitated; 2, cooperative; 3, responds to commands only; and 4–6, different levels of unconsciousness, where 6 indicates no response to a light glabellar tap or loud auditory stimulus.[11] The children were considered recovered from anesthesia at an RSS score of 2 or 3 (awake or drowsy); hence, RSS levels 1 and 4–6 were synonymous with not having recovered from anesthesia.

TABLE 1 Administration and blinding of the study drugs according to the allocation.

	60 min before surgery Oral administration	40 min before surgery Oral administration	40 min before surgery Intranasal administration
MID-group	Placebo	Midazolam 0.5 mg/kg	Placebo
CLO-group	Clonidine 4 μg/kg	Placebo	Placebo
DEX-group	Placebo	Placebo	Dexmedetomidine 2 μg/kg

2.5.3 | Emergence delirium/PAED

The Paediatric Anaesthesia Emergence Delirium scale (PAED) was used to define ED events and is considered a reliable and valid measure of ED in children.[12,13] The PAED scale has been applied in efforts to differentiate between ED and pain in children aged 2–6 years in the early postoperative period after tonsillectomy, adenoidectomy, or both.[14] The PAED scale consists of five characteristics (the child makes eye contact with a caregiver, makes purposeful actions, is aware of their surroundings, is restless, and is inconsolable), each of which is scored using a 5-point Likert scale. The individual scores for each item were added to determine the composite score at a particular moment. For the presence of pediatric ED, we defined the threshold score as a PAED score ≥10, which has 64% sensitivity and 86% specificity for ED, whereas a score >12 yielded 100% sensitivity and 94.5% specificity for ED.[12]

2.5.4 | Anxiety/mYPAS

Anxiety levels were assessed using a validated Swedish version of the modified Yale Preoperative Anxiety Scale (mYPAS). The instrument contains 27 items in the following five categories (representing five domains of anxiety): activity, emotion, expressivity, state of arousal, vocalization, and parental use.[15,16] The scale ranges from 0 to 100, and the score is normalized for different numbers of steps in each item. High scores denote high levels of anxiety, and based on prior characterization of the scale, an mYPAS ≤30 is classified as not anxious.[15] The instrument has good-to-excellent observer reliability, with high concurrent and construct validity for assessing children's anxiety during the perioperative period.[15,16]

2.5.5 | Pain/FLACC

The FLACC is recommended for evaluating postoperative pain in children aged 1–6 years as young children might have difficulties in expressing their level of pain.[17] With this observational tool (instead of self-valid measurements) we could identify signs of pain in sedated and drowsy children.

Each of the five behavioral categories in the FLACC—facial expression, leg movement, bodily activity, crying or verbalization, and consolability—was rated on a scale of 0 to 2 to provide an overall pain score ranging from 0 to 10. Merkel et al.[18] suggested the following overall interpretations based on the score: 0, relaxed and comfortable; 1–3, mild discomfort; 4–6, moderate pain; and 7–10, severe discomfort or pain.

2.5.6 | Nausea/vomiting

Since nausea is a subjective phenomenon, small children may not be able to address and describe this symptom. Thus, objective symptoms of retching and vomiting were used as the endpoints. Situations in which children verbally expressed nausea were also considered as events of PONV.

2.6 | Concomitant medication

2.6.1 | Induction and anesthesia

Anesthesia was administered according to a standardized protocol. Initially, a bolus of atropine (0.01 mg/kg) was injected, followed by a 1-min infusion of remifentanil (2–3 μg/kg) and a bolus injection of propofol (3–5 mg/kg) until the child was asleep. If an intravenous line could not be established for technical reasons or because of the child's discomfort, mask induction was initiated by inhalation of oxygen/nitrous oxide (1:1) mixed with 8% sevoflurane. Volatile agents were discontinued immediately after establishing an intravenous line. Anesthesia was maintained with intravenous infusions of remifentanil (50 μg/mL) at 0.5 μg/kg/min and propofol (10 mg/mL) at 15 mg/kg/h during the first 15 min, 12 mg/kg/h for the next 15 min, and 9 mg/kg/h at 30 min and thereafter.

2.6.2 | Pain and PONV preventive drug treatment

To prevent postoperative pain, all children received preoperative analgesic medications 60 min before surgery (per oral (p.o.) paracetamol 24 mg/mL, 30 mg/kg, and p.o. ibuprofen 20 mg/mL, 10 mg/kg). Perioperatively, local anesthetic was injected in the surgical area, and intravenous morphine (1 mg/mL, 0.1 mg/kg) was administered at the end of surgery. Betamethasone (4 mg/mL, 0.2 mg/kg) was administered intravenously at the induction of anesthesia to prevent PONV.

2.7 | Statistical analysis

No specific sample size calculation was performed for this planned secondary analysis as the size of the cohort in this clinical trial was based on the primary analysis.[9]

Statistical analyses were performed using SPSS Statistics for PC, version 26.0 (IBM Corporation, Armonk, NY, USA, released 2018). Categorical variables are presented as numbers with percentages, normally distributed continuous variables as mean ± standard deviation (SD), and non-normally distributed variables as medians with interquartile ranges (IQR) and minimal and maximal values.

To assess the overall differences among the three treatment groups, Pearson's chi-square test with Yates correction was used for categorical variables, and Kruskal–Wallis test was used for continuous variables (non-normal distribution). Significance level was set to 5%. To describe the effect size of continuous variables, Hodge–Lehman method was used to estimate differences in medians, including the 95% confidence interval (pairwise comparison of the groups).[19]

To compare the treatment groups in recovery and behavioral measures in the PACU, we used logistic regression with a mixed model approach to account for repeated measurements. Measures were observed/sampled at every 15th minute of an observation period of 120 min, and each measure was categorized as recovered or not recovered in the model. If a child was discharged from the PACU within 120 min, the child was considered to have recovered at the missing time points in the model. Main outputs from the model were as follows: (1) a regression model, where the intercept is common for all groups and slope is relative to the MID-group and (2) effect size described as estimated marginal means (EMM), where the effect size is relative to a standardized value of 0.5 standing for "no effect." Values are presented as 95% confidence intervals, and the significance level was set at 5% in the model. The details of the model are provided in the Appendix S2.

3 | RESULTS

A total of 239 children scheduled for ENT surgery were screened for eligibility, and 90 were enrolled in the study. Eight children were excluded from this secondary analysis: six refused the study drugs (CLO-group, $n=3$; MID-group, $n=3$), one child in the CLO-group received sevoflurane for the maintenance of anesthesia, and one child in the MID-group had surgical complications. The final study cohort comprised 82 children (Figure 1).

The characteristics of the children and their perioperative management are presented in Table 2.

3.1 | Recovery/readiness for discharge assessed by PADSS

There were no differences between the study groups in terms of time to readiness for discharge (PADDS-score ≥9) (Table 3). Differences were found between the groups in the domain *vital signs*, where children in the MID-group could maintain a normal peripheral oxygen saturation without supplementary oxygen earlier than those in the CLO- and DEX-groups (MID-group, 40 min [IQR 24 min] vs. CLO-group, 48 min [IQR 32 min] and DEX-group, 62 min [IQR 24 min]; $p<.001$).

3.2 | Sedation in the PACU

After 60 min in the PACU, 38% of children ($n=31$) recovered from sedation (RSS-score of 2 or 3), and there were no differences between the study groups (Table 4).

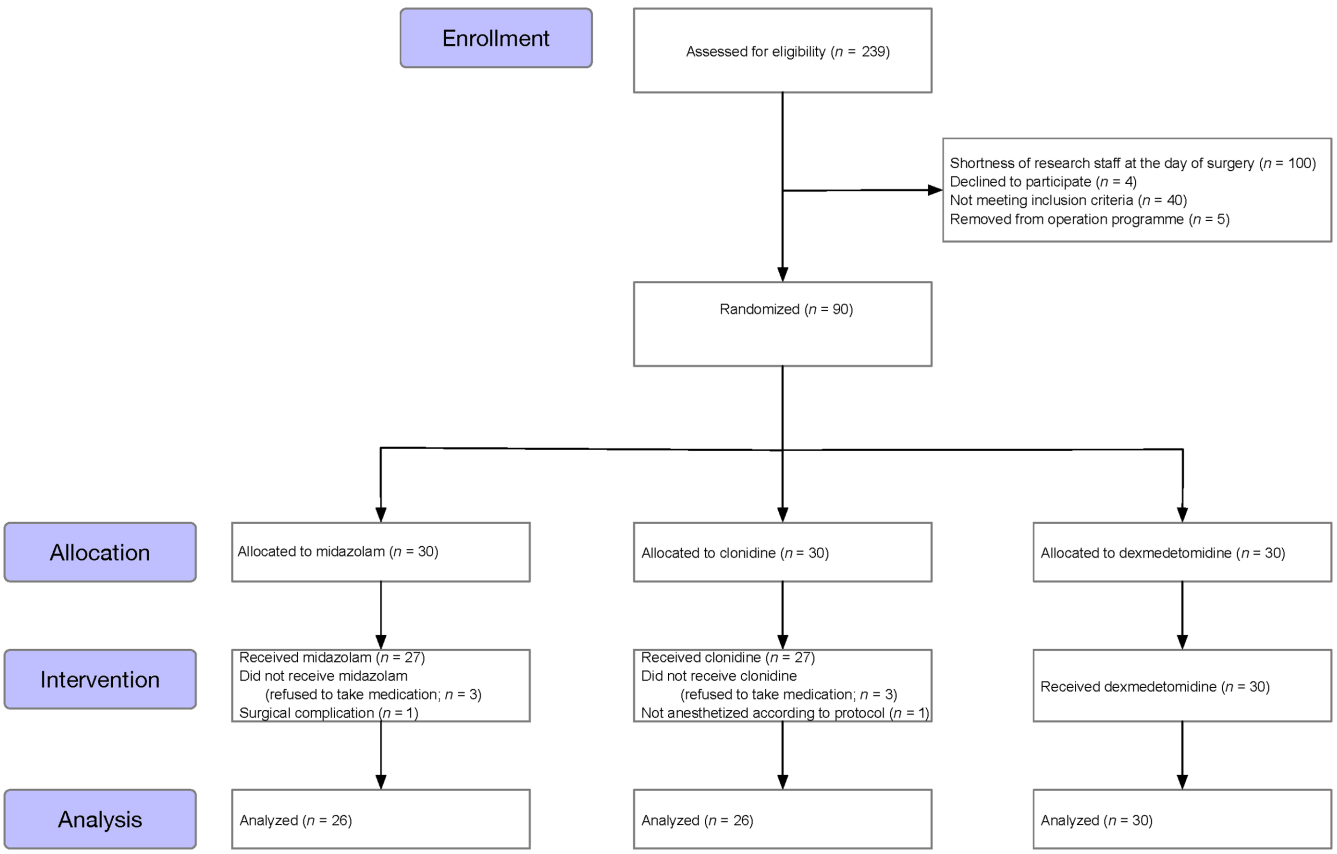

FIGURE 1 Consort diagram.

TABLE 2 Patient and perioperative characteristics.

Characteristics	Study group		
	MID $n=26$	CLO $n=26$	DEX $n=30$
Sex			
Boys	16 (62%)	15 (58%)	17 (57%)
Girls	10 (38%)	11 (42%)	13 (43%)
Age (years)	4.2 ± 0.9	4.5 ± 0.9	4.2 ± 1.0
Weight (kg)	18.3 ± 3.8	19.0 ± 3.9	17.0 ± 2.1
ASA-PS			
I	21 (81%)	20 (77%)	25 (83%)
II	5 (19%)	6 (23%)	5 (17%)
Level of care			
Outpatient surgery	24 (92%)	22 (85%)	24 (80%)
Inpatient surgery	2 (8%)	4 (15%)	6 (20%)
Previous anesthesia	2 (8%)	5 (19%)	4 (13%)
Method for anesthetic induction			
Propofol/remifentanil	24 (92%)	23 (88%)	26 (87%)
Volatile (sevoflurane/N_2O)	0 (0%)	1 (4%)	1 (3%)
Volatile/propofol/remifentanil	2 (8%)	2 (8%)	3 (10%)
Anesthetics, total doses			
Propofol, mg	221 ± 37.5	221 ± 75.4	204 ± 54.1
Remifentanil, μg	384 ± 105	416 ± 253	371 ± 118
I.v. morphine, mg	1.3 ± 0.4	1.0 ± 0.5	1.1 ± 0.3
Type of surgery			
Tonsillectomy	1 (4%)	0 (0%)	1 (3%)
Tonsillectomy and adenectomy	2 (8%)	1(4%)	2 (7%)
Tonsillotomy	0 (0%)	0 (0%)	1 (3%)
Tonsillotomy and adenectomy	20 (77%)	19 (73%)	22 (73%)
Adenectomy	2 (8%)	3 (12%)	3 (10%)
Other ENT surgery[a]	1 (4%)	3 (12%)	1 (3%)
Duration of surgery, minutes	28.5 ± 12.4	25.4 ± 10.7	28.9 ± 13.3
Duration of anesthesia, minutes	65.2 ± 16.3	58.2 ± 16.6	63.4 ± 15.4

Note: The values are presented as the numbers (percent) or as the mean ± the SD.

Abbreviations: ASA-PS, American Society of Anaesthesiologists Physical Status Classification; CLO, clonidine; DEX, dexmedetomidine; ENT, ear, nose, and throat; i.v., intravenous; MID, midazolam; N_2O, nitrous oxide.

[a]Extirpation of dermal affections in the ENT-region.

3.3 | Emergence delirium in the PACU

Fifteen percent of children ($n=12$) had ED in the PACU (PAED-score ≥10). The MID-group had significantly more ED (31%, $n=8$) than the DEX-group ($n=1$). None of the children experienced ED after the first hour in the PACU (Table 4).

3.4 | Anxiety in the PACU

Thirty-four percent of the children ($n=28$) had anxiety in the PACU (mYPAS score >30). There was significantly more anxiety in the MID-group (46%, $n=12$) than in the CLO-group (27%, $n=7$) or DEX-group (30%, $n=9$) (Table 4).

3.5 | Pain in the PACU

Eighteen percent of the children ($n=15$) had signs of clinically significant pain in the PACU (FLACC score >3). There were significant differences between the MID- and DEX-group ($p=.03$). Nine children (35%) had a FLACC-score >3 in the MID-group, five (19%) in CLO-group, and one (3%) in DEX-group. No differences were found in the number of children who were administered rescue opioids ($p=.19$). After the first 60 min in the PACU, only one child had a FLACC score >3 (CLO-group, $n=1$) (Tables 4 and 5).

3.6 | PONV in the PACU

Four children showed signs of vomiting, retching, or nausea in the PACU. There were no significant differences between the groups ($p=.52$) (Table 5).

4 | DISCUSSION

This randomized study investigated the characteristics of postoperative recovery in children aged 2–6 years premedicated with midazolam, clonidine, or dexmedetomidine. We did not find any major differences in the recovery time in the PACU. However, more ED and pain was experienced with midazolam than with dexmedetomidine, and more anxiety with midazolam than with both dexmedetomidine and clonidine.

We found no differences in the overall recovery time from the PACU between the groups. A recent randomized controlled study comparing premedication with midazolam or dexmedetomidine in preschool-aged children also found no differences in PACU length of stay.[20] The authors concluded that the delayed emergence from anesthesia might be associated with a smoother overall recovery with fewer episodes of ED. Consistent with that study, we found a better recovery profile with dexmedetomidine and clonidine.

ED is reported to affect every fifth child after general anesthesia.[21] Preoperative anxiety, pain, and volatile anesthesia (sevoflurane) are associated with ED in children,[1] but the evidence for the risk estimate is weak. Compared to no premedication at all, previous studies have shown that midazolam reduces the risk of ED.[22] However, more recent studies report that α_2-agonists are superior to midazolam in reducing the risk of ED in young children.[6,20] In congruous with these reports, we found that both dexmedetomidine and clonidine were associated with lower risk of ED (3% and 12%, respectively) than midazolam (31%).

TABLE 3 Time to recovery (minutes) in the PACU using the Post Anaesthesia Discharge Scoring System (PADDS) and in the different subdomains evaluated.

	Study group				Median differences (95% CI)		
All values are minutes	MID $n=26$	CLO $n=26$	DEX $n=30$	p-value	CLO vs. MID	DEX vs. MID	CLO vs. DEX
Time to fulfill PADSS ≥9	90.0 (48.0; 38–162)	80.0 (46; 45–150)	100.5 (42; 60–325)	.211	−4 (−22; 17)	11 (−6; 28)	−14 (−30; 4)
PADSS domains							
Vital parameters, recovery to preoperative values							
Oxygenation	40.5 (23.5; 12–77)	47.5 (32.0; 0–139)	62.0 (24.5; 40–108)	<.001	6 (−5; 18)	22.5 (13; 32)	−17 (−28; −5)
Respirator rate	17.0 (10.2; 4–103)	20.0 (16.2; 9–79)	24.0 (36.0; 9–78)	.153	2 (−3; 7)	5 (0; 12)	−4 (−10; 2)
Heart rate	33.5 (54.5; 8–162)	20.0 (11.2; 9–79)	20.0 (43.0; 6–183)	.124	−9.5 (−26; −1)	−5 (−19; 5)	−3 (−12; 3)
Capillary refill	15.0 (8.0; 7–35)	17.0 (6; 9–79)	17.5 (9.0; 6–78)	.564	2 (−1; 5)	1 (−2; 5)	0 (−3; 4)
Body temperature	15.0 (11.0; 4–58)	20.0 (13.5; 9–79)	19.0 (11.0; 9–78)	.075	5 (0; 10)	4 (0; 9)	0 (−4; 5)
Activity and mental status							
Sedation (RSS-score of 2–3)	75.5 (47.5; 24–133)	75.5 (48.8; 31–150)	87.5 (44.0; 41–183)	.205	13 (−6; 30)	15 (−2; 30)	−3 (−19; 15)
Pain and PONV							
FLACC ≤3 and no PONV	75.5 (44.0; 38–148)	73.5 (51.0; 31–140)	90.5 (38.0; 41–183)	.224	5 (−12; 22)	15 (−3; 30)	−8 (−26; 8)
Bleeding	No bleeding	No bleeding	No bleeding				
Intake or output							
Time to oral intake	82.5 (46.5; 12–147)	72.5 (52.8; 30–135)	89.5 (43.0; 35–325)	.123	9.5 (−13; 29)	19 (0; 38)	−11 (−32; 7)

Note: Effect size is described with pairwise comparisons of the median differences.

The values are presented as medians (IQR; min-max). The Kruskal–Wallis test was used to test differences between groups. The Hodge–Lehman estimator was used to calculate the median difference between the groups, including the 95% confidence interval.

Abbreviations: CI, confidence interval; CLO, clonidine; DEX, dexmedetomidine; FLACC, Face Legs Activity Cry Consolability scale; MID, midazolam; N.A., not applicable; PACU, post anesthesia care unit; PADSS, Post Anaesthesia Discharge Scoring System; PONV, postoperative nausea and vomiting; RSS, Ramsay Sedation Scale.

TABLE 4 Postoperative recovery and behavioral measures in the PACU.

Numbers of children not recovered in the domain		MID $n=26$	CLO $n=26$	DEX $n=30$
Sedated (RSS-score 1 or 4–6) [numbers RSS = 1; numbers RSS = 4–6]				
Arrival to PACU		24 (92%) [2; 22]	25 (96%) [2; 23]	30 (100%) [0; 30]
15 min		18 (69%) [2; 16]	23 (88%) [1; 22]	29 (97%) [0; 29]
30 min		16 (62%) [3; 13]	21 (81%) [2; 19]	24 (80%) [0; 24]
45 min		13 (50%) [3; 10]	14 (54%) [0; 14]	19 (63%) [0; 19]
60 min		9 (35%) [2; 7]	9 (35%) [0; 9]	13 (43%) [0; 13]
75 min		7 (27%) [0; 7]	8 (31%) [0; 8]	11 (37%) [0; 11]
90 min		5 (19%) [0; 5]	4 (15%) [0; 4]	7 (23%) [0; 7]
105 min		4 (15%) [0; 4]	2 (8%) [0; 2]	4 (13%) [0; 4]
120 min		2 (8%) [0; 2]	1 (4%) [0; 1]	1 (3%) [0; 1]
Estimated marginal mean (95% CI)		0.48 (0.41; 0.55)	0.42 (0.37; 0.48)	0.42 (0.37; 0.47)
Coefficients in model (95% CI)	Intercept (β_0): −0.092 (−0.39; 0.20)			
	Slope (β_1)	Reference	−0.21 (−0.58; 0.161)	−0.23 (−0.59; 0.13)
	p-value		.265	.204
Emergence delirium (PAED score ≥10p)				
Any time		8 (31%)	3 (12%)	1 (3%)
Arrival to PACU		4 (15%)	2 (8%)	0 (0%)
15 min		5 (19%)	1 (4%)	0 (0%)
30 min		3 (12%)	0 (0%)	0 (0%)
45 min		3 (12%)	0 (0%)	0 (0%)
60 min		2 (8%)	0 (0%)	1 (3%)
75 min		0 (0%)	0 (0%)	0 (0%)
90 min		0 (0%)	0 (0%)	0 (0%)
105 min		0 (0%)	0 (0%)	0 (0%)
120 min		0 (0%)	0 (0%)	0 (0%)
Estimated marginal mean (95% CI)		0.026 (0.01; 0.07)	0.006 (0.002; 0.02)	0.001 (0.0002; 0.008)
Coefficients in model (95% CI)	Intercept (β_0): −3.62 (−4.60; −2.65)			
	Slope (β_1)	Reference	−1.54 (−3.10; 0.02)	−2.99 (−5.07; −0.92)
	p-value		.053	.005
Anxiety (mYPAS score >30p)				
Any time		12 (46%)	7 (27%)	9 (30%)
Arrival to PACU		5 (19%)	2 (8%)	0 (0%)
15 min		8 (31%)	3 (12%)	0 (0%)
30 min		8 (31%)	3 (12%)	3 (10%)
45 min		6 (23%)	2 (8%)	4 (13%)
60 min		4 (15%)	0 (0%)	4 (13%)
75 min		1 (4%)	0 (0%)	0 (0%)
90 min		2 (8%)	0 (0%)	1 (3%)
105 min		2 (8%)	0 (0%)	0 (0%)
120 min		0 (0%)	1 (4%)	2 (7%)
Estimated marginal mean (95% CI)		0.13 (0.07; 0.23)	0.043 (0.02; 0.09)	0.041 (0.02; 0.08)
Coefficients in model (95% CI)	Intercept (β_0): −1.90 (−2.59; −1.22)			
	Slope (β_1)	Reference	−1.19 (−2.26; −0.12)	−1.26 (−2.21; −0.30)
	p-value		.029	.010

(Continues)

TABLE 4 (Continued)

Numbers of children not recovered in the domain		MID $n=26$	CLO $n=26$	DEX $n=30$
Pain (FLACC score >3p)				
Any time		9 (35%)	5 (19%)	1 (3%)
Arrival to PACU		4 (15%)	2 (8%)	0 (0%)
15 min		4 (15%)	1 (4%)	0 (0%)
30 min		4 (15%)	1 (4%)	0 (0%)
45 min		3 (12%)	0 (0%)	0 (0%)
60 min		2 (8%)	0 (0%)	1 (3%)
75 min		0 (0%)	0 (0%)	0 (0%)
90 min		0 (0%)	0 (0%)	0 (0%)
105 min		0 (0%)	0 (0%)	0 (0%)
120 min		0 (0%)	1 (4%)	0 (0%)
Estimated marginal mean (95% CI)		0.038 (0.02; 0.08)	0.014 (0.01; 0.03)	0.002 (0.0003; 0.01)
Coefficients in model (95% CI)	Intercept (β_0): −3.23 (−4.08; −2.39)			
	Slope (β_1)	Reference	−1.06 (−2.31; 0.20)	−3.03 (−5.00; −1.05)
	p-value		.098	.03

Note: Values are the number of children (%) not recovered in a specific domain every 15th minute during the first 2 h in the PACU. Differences between the study groups were analyzed using logistic regression with a mixed model approach to account for the repeated measurements. In the model, intercept is common for the three groups, but the slope is relative to the reference (MID-group). Children discharged from PACU were considered fully recovered and remained in the model as recovered.

Abbreviations: CLO, clonidine; DEX, dexmedetomidine; FLACC, Face Legs Activity Cry Consolability scale; MID, midazolam; mYPAS, Modified Yale Preoperative Anxiety Scale; PACU, Post Anaesthesia Care Unit; PAED, Pediatric Anesthesia Emergence Delirium scale; RSS, Ramsey Sedation Scale.

TABLE 5 Postoperative rescue analgesia and PONV at PACU.

	Study group			
	MID $n=26$	CLO $n=26$	DEX $n=30$	*p*-value
Rescue-opioids given, numbers (morphine 0.1 mg/kg i.v.)	5 (19%)	1 (4%)	1 (3%)	.19
Children with events of PONV. numbers	1 (5%)	0 (0%)	3 (10%)	.52
Recue-antiemetics given, numbers (ondansetron 0.1 mg/kg i.v.)	0 (0%)	0 (0%)	1 (3%)	.88

Note: Values are numbers (percent). Differences between groups tested with Pearson's Chi-2 test including Yate's correction.

Abbreviations: CLO, clonidine; DEX, dexmedetomidine; i.v., intravenous; MID, midazolam; PACU, post anesthesia care unit; PONV, postoperative nausea and vomiting.

High levels of preoperative anxiety have been reported to be a risk for postoperative anxiety.[1] In our previous analysis of the cohort, we found that midazolam resulted in better preoperative anxiolysis compared to both clonidine and dexmedetomidine.[9] Despite better preoperative anxiolysis after midazolam, we found an increased risk for early delirium and anxiety in the midazolam group compared with dexmedetomidine group. A possible explanation is that the short duration of midazolam causes rapid emergence from anesthesia, whereas dexmedetomidine and clonidine provide an extended and smoother emergence.[20]

Postoperative pain is known to be associated with adverse postoperative outcomes and delayed recovery,[23] and children with a high level of preoperative anxiety experience more postoperative pain.[1] In contrast, we found that children who received α_2-agonists experienced higher levels of preoperative anxiety[9] but lower levels of postoperative pain than those who received short-acting benzodiazepine. However, several studies have reported that premedication with α_2-agonists decreases the requirement for postoperative opioids, indicating their analgesic properties.[24]

Midazolam, clonidine, and dexmedetomidine have been described as having antiemetic properties.[20] In our study, only four children (5%) experienced PONV in the PACU, with no differences between the groups. Generally, the risk of PONV in children is estimated to be 30%.[25] The low risk in our study might reflect the fact that all children received propofol as part of the total intravenous anesthesia and that all children also received PONV prophylaxis with betamethasone. No further nausea was observed after the first postoperative oral dose.

4.1 | Strengths and limitations

This study was a preplanned secondary analysis of a clinical trial. A major limitation is the sample size, as the size of the study cohort was justified for the previously published primary report.[9] However, for this secondary analysis, we must be cautious in the conclusions, as the sample size might not be appropriate. We found no evidence

for a difference in the primary objective for this analysis (time to recovery), but future studies must challenge our conclusion and might use our data to estimate a proper study size.

This study had few strengths. First, the blinding process, which allowed us to administer the premedications through different routes and at different time points. Second, the use of validated observational instruments that were adapted and developed for use in children during the postoperative period. Third, the study cohort of children aged 2–6 years who underwent ENT surgery is a clinically common, challenging, and relevant group of patients. However, the single-center study design with a limited number of children reduces the generalizability of the results. Additionally, dose–response relationships of the interventions were not examined in this study, but the doses used were standard and based on previous studies and clinical routines.

4.2 | Conclusions

Our study showed no differences in the postoperative recovery time in the PACU between the premedication regimens. Given the small sample size, our results indicate that premedication with midazolam results in a more rapid emergence from anesthesia compared with premedication with clonidine or dexmedetomidine, as children administered midazolam had more episodes of postoperative delirium, anxiety, and pain than those administered clonidine or dexmedetomidine. For smoother emergence and recovery after anesthesia, the use of clonidine or dexmedetomidine as premedication might be a better option than midazolam.

ACKNOWLEDGMENTS

We gratefully acknowledge statistician Robert Lundqvist, the Clinical Trial Unit, Umeå, and our research nurse team—Anna Lindström, Anders Pulkkinen and Ulrika Sundström—for their support.

FUNDING INFORMATION

This work was supported by grants from Region Norrbotten (NLL-485451, NLL-486841, RN-785981) and Region Västerbotten (RV-940554, RV-865681).

CONFLICT OF INTEREST STATEMENT

JW has received lecture fees from AbbVie Sweden AB. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The study protocol followed Good Clinical Practice and was approved by the Regional Ethic Review Board in Umeå (Dnr 2016-46-31 M, March 30, 2016, chair: A Iacobæus) and the Swedish Medical Products Agency (Dnr 5.1-2016-17 854, May 13, 2016).

PATIENT CONSENT STATEMENT

Written informed consent was obtained from parents on the day of the procedure.

CLINICAL TRIAL REGISTRATION

The trial protocol was registered in the European Union Drug Regulation Authorities' Clinical Trials Database (EudraCT 2015-003676-70).

ORCID

Åsa Bromfalk https://orcid.org/0000-0002-4585-8786
Magnus Hultin https://orcid.org/0000-0003-2935-7161
Tomi Myrberg https://orcid.org/0000-0002-8802-2321
Åsa Engström https://orcid.org/0000-0001-6244-6401
Jakob Walldén https://orcid.org/0000-0002-8171-5184

REFERENCES

1. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. *Pediatrics*. 2006;118:651-658.
2. Davidson A, McKenzie I. Distress at induction: prevention and consequences. *Curr Opin Anaesthesiol*. 2011;24:301-306.
3. Manso MA, Guittet C, Vandenhende F, Granier LA. Efficacy of oral midazolam for minimal and moderate sedation in pediatric patients: a systematic review. *Paediatr Anaesth*. 2019;29:1094-1106.
4. Bergendahl H, Lonnqvist PA, Eksborg S. Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. *Acta Anaesthesiol Scand*. 2006;50:135-143.
5. Kawai M, Kurata S, Sanuki T, et al. The effect of midazolam administration for the prevention of emergence agitation in pediatric patients with extreme fear and non-cooperation undergoing dental treatment under sevoflurane anesthesia, a double-blind, randomized study. *Drug des Devel Ther*. 2019;13:1729-1737.
6. Dahmani S, Brasher C, Stany I, et al. Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. *Acta Anaesthesiol Scand*. 2010;54:397-402.
7. Chandler JR, Myers D, Mehta D, et al. Emergence delirium in children: a randomized trial to compare total intravenous anesthesia with propofol and remifentanil to inhalational sevoflurane anesthesia. *Paediatr Anaesth*. 2013;23:309-315.
8. Bromfalk A, Hultin M, Wallden J, Myrberg T. Cardiorespiratory response to sedative premedication in preschool children: a randomized controlled trial comparing midazolam, clonidine, and Dexmedetomidine. *J Perianesth Nurs*. 2023;38:454-460.
9. Bromfalk A, Myrberg T, Wallden J, Engstrom A, Hultin M. Preoperative anxiety in preschool children: a randomized clinical trial comparing midazolam, clonidine, and dexmedetomidine. *Paediatr Anaesth*. 2021;31:1225-1233.
10. Chung F, Chan VW, Ong D. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. *J Clin Anesth*. 1995;7:500-506.
11. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J*. 1974;2:656-659.
12. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology*. 2004;100:1138-1145.
13. Ringblom J, Wahlin I, Proczkowska M. A psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Paediatr Anaesth*. 2018;28:332-337.

14. Somaini M, Sahillioglu E, Marzorati C, Lovisari F, Engelhardt T, Ingelmo PM. Emergence delirium, pain or both? A challenge for clinicians. *Paediatr Anaesth*. 2015;25:524-529.
15. Kain ZN, Mayes LC, Cicchetti DV, Bagnall AL, Finley JD, Hofstadter MB. The Yale preoperative anxiety scale: how does it compare with a "gold standard"? *Anesth Analg*. 1997;85:783-788.
16. Proczkowska-Bjorklund M, Gimbler Berglund I, Ericsson E. Reliability and validity of the Swedish version of the modified Yale preoperative anxiety scale. *Acta Anaesthesiol Scand*. 2012;56:491-497.
17. Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. *Am J Crit Care*. 2010;19:55-61.
18. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997;23:293-297.
19. Staffa SJ, Zurakowski D. Calculation of confidence intervals for differences in medians between groups and comparison of methods. *Anesth Analg*. 2020;130:542-546.
20. Yao Y, Sun Y, Lin J, Chen W, Lin Y, Zheng X. Intranasal dexmedetomidine versus oral midazolam premedication to prevent emergence delirium in children undergoing strabismus surgery: a randomised controlled trial. *Eur J Anaesthesiol*. 2020;37:1143-1149.
21. Nair S, Wolf A. Emergence delirium after paediatric anaesthesia: new strategies in avoidance and treatment. *BJA Educ*. 2018;18:30-33.
22. Ko YP, Huang CJ, Hung YC, et al. Premedication with low-dose oral midazolam reduces the incidence and severity of emergence agitation in pediatric patients following sevoflurane anesthesia. *Acta Anaesthesiol Sin*. 2001;39:169-177.
23. Vaughn F, Wichowski H, Bosworth G. Does preoperative anxiety level predict postoperative pain? *AORN J*. 2007;85:589-604.
24. Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simoes CM, Auler JO Jr. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. *Paediatr Anaesth*. 2007;17:667-674.
25. Robb PJ, Ewah BN. Post-operative nausea and vomiting following paediatric day-case tonsillectomy: audit of the Epsom protocol. *J Laryngol Otol*. 2011;125:1049-1052.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bromfalk Å, Hultin M, Myrberg T, Engström Å, Walldén J. Postoperative recovery in preschool-aged children: A secondary analysis of a randomized controlled trial comparing premedication with midazolam, clonidine, and dexmedetomidine. *Pediatr Anesth*. 2023;33:962-972. doi:10.1111/pan.14740