Preoperative anxiety in preschool children: A randomized clinical trial comparing midazolam, clonidine, and dexmedetomidine

Åsa Bromfalk1 | Tomi Myrberg1 | Jakob Walldén2 | Åsa Engström3 | Magnus Hultin4

Abstract

Introduction: Anxiety in pediatric patients may challenge perioperative anesthesiology management and worsen postoperative outcomes. Sedative drugs aimed to reducing anxiety are available with different pharmacologic profiles, and there is no consensus on their effect or the best option for preschool children. In this study, we aimed to compare the effect of three different premedications on anxiety before anesthesia induction in preschool children aged 2–6 years scheduled for elective surgery. The secondary outcomes comprised distress during peripheral catheter (PVC) insertion, compliance at anesthesia induction, and level of sedation.

Patients and methods: In this double-blinded randomized clinical trial, we enrolled 90 participants aged 2–6 years, who were scheduled for elective ear-, nose- and- throat surgery. The participants were randomly assigned to three groups: those who were administered 0.5 mg/kg oral midazolam, 4 µg/kg oral clonidine, or 2 µg/kg intranasal dexmedetomidine. Anxiety, distress during PVC insertion, compliance with mask during preoxygenation, and sedation were measured using the modified Yale Preoperative Anxiety Scale, Behavioral Distress Scale, Induction Compliance Checklist, and Ramsay Sedation Scale, respectively.

Results: Six children who refused premedication were excluded, leaving 84 enrolled patients. At baseline, all groups had similar levels of preoperative anxiety and distress. During anesthesia preparation, anxiety was increased in the children who received clonidine and dexmedetomidine; however, it remained unaltered in the midazolam group. There were no differences in distress during PVC insertion or compliance at induction between the groups. The children in the clonidine and dexmedetomidine groups developed higher levels of sedation than those in the midazolam group.

Conclusions: In preschool children, midazolam resulted in a more effective anxiolysis and less sedation compared to clonidine and dexmedetomidine.
1 | INTRODUCTION

Many preschool children experience significant anxiety during the preoperative period. This may cause distress to the child during the preoperative period, which, in turn, may have a negative impact on their postoperative recovery and cause long-term impairment in cognition. Preoperative anxiety can increase stress-induced hemodynamic instability and pose as a challenge to smooth anesthesia induction. Thus, an optimal drug for premedication in young children is crucial.

The benzodiazepine midazolam has long been the most commonly used drug for premedication in children. It has been shown to alleviate anxiety and provide adequate sedation with an onset duration of ∼40 min. However, midazolam has untoward side effects with increased risk of respiratory depression, amnesia, and paradoxical reactions. Two alpha-2-agonists, clonidine and dexmedetomidine, have emerged as alternatives to midazolam. These drugs have good sedative, analgesic, and anxiolytic properties with minimal respiratory depression and better perioperative hemodynamic stability. Among these two alpha-2-agonists, clonidine has been used more frequently. One major downside of clonidine is a longer duration of onset, requiring administration 60 min before anesthesia induction. Compared with clonidine, dexmedetomidine has been suggested to have a more favorable safety profile, with anxiolysis and sedation achieved in 40 min following intranasal administration. There are only a few published randomized controlled studies using validated tools for the measurement of preoperative anxiety in preschool children, comparing the effect of dexmedetomidine, clonidine and midazolam. Neville et al. and Linares et al. reported that the dexmedetomidine groups showed less preoperative anxiety as compared to the groups receiving midazolam. These results are in contrast to studies from Fazi et al., and Kumari et al., showing that the midazolam was superior in reducing anxiety as compared to clonidine and dexmedetomidine. In sum, the literature on reducing preoperative anxiety in preschool children is sparse with diverging results.

In this study, we aimed to compare the effect of three different premedication regimens on preoperative anxiety and sedation in preschool children scheduled for elective ear, nose, and throat (ENT) surgery. We hypothesized that midazolam is superior in reducing preoperative anxiety compared to alpha-2-agonists and that the three groups have equal ability to provide sedation in preschool children.

2 | METHODS

2.1 | Study design

A double-blinded randomized clinical trial of pediatric patients was conducted according to the Good Clinical Practice (GCP) (Guideline for GCP E6(R2) EMA/CHMP/ICH/135/1995) (Products, 2018). The study 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 5.1-2016-17854, May 13, 2016), and registered as EudraCT 2015-003676-70. The complete protocol is available upon request from the authors. This paper adheres to the consolidated standards of reporting trials (CONSORT) guidelines.

2.2 | Participants

The trial was planned to include 150 children and was conducted at Sunderby Hospital, Luleå, Sweden. The inclusion criteria comprised: age, 2–6 years; both sexes; American Society of Anesthesiologists Physical Status (ASA-PS) I–II; weight, ≤30 kg; scheduled for elective ENT surgery; primarily tonsillectomies/adenotonsillectomies and adenotonsillectomies; and written informed consent obtained from their parents. The exclusion criteria comprised: ASA-PS >II; heart, lung, neurologic, or central nervous system disorders; use of psychotropic medication; or history of recent surgery.

2.3 | Investigated medical products and regime

The participants were randomized into three intervention groups: oral midazolam (MID) 0.5 mg/kg 40 min preoperatively (Midazolam, APL Stockholm, 1 mg/ml), oral clonidine (CLO) 4 µg/kg 60 min preoperatively (Klonidin, APL Stockholm, 20 µg/ml), or intranasal dexmedetomidine (DEX) 2 µg/kg 40 min preoperatively (Dexdor®, Orion Pharma, 100 µg/ml). The doses, route of administration, and timing were chosen based on previously published pharmacokinetic data and were chosen to be within a safe and clinically relevant window. Compared with intranasal administration, oral administration of dexmedetomidine has poor bioavailability (65% vs. 16%). Both oral midazolam and intranasal dexmedetomidine have a faster onset, compared with...
oral clonidine (30–40 min vs. 60 min, respectively). Therefore, clonidine was administered 20 min earlier than midazolam and dexmedetomidine.

2.4 | Consent, randomization, and blinding

Signed informed consent was obtained from the parents upon the child’s arrival at the day care unit. All children were accompanied by a parent throughout the preoperative period and one parent was allowed to attend during induction of anesthesia.

Randomization was performed by opening a sequentially numbered envelope containing the group assignment. The envelopes were prepared by an independent statistician using the randomization function in Microsoft Excel, with randomization in blocks of 15.

A nurse, independent from the research team and data collection, administered the study drugs. All children first received oral fluid (clonidine or sterile water); 20 min later, intranasal fluid was administered using a mucosal atomization device (MAD Nasal™, Teleflex, USA; dexmedetomidine or 0.9% NaCl), followed by oral fluid (midazolam or sterile water; Figure 1). The interventions were triple-blinded; that is, blinded for the patient, care providers, and researchers.

2.5 | Background and baseline

Immediately after inclusion, the patients’ background information was collected, and baseline assessments were performed. No questions were addressed directly toward the child. The parents were asked about their child’s anesthetic experience, in what way they had prepared their child for anesthesia (preoperative information, dichotomized into “yes” or “no”), and to grade their child’s anxiety level at home due to surgery, using a self-devised four-grade scale (not worried, somewhat worried, worried, and very worried; dichotomized into “not worried” or “worried” [“somewhat” to “very”]).

2.6 | Endpoints and timing

The primary endpoint was anxiety at anesthesia preparation, and the secondary endpoints were distress during peripheral venous catheter (PVC) insertion, compliance at induction, and level of sedation. The timing of the measurement is shown in Figure 1.

2.7 | Data collection and tools

To minimize interrater variability, one person in the research team (ÅB) collected all data. The researcher was not responsible for administering clinical anesthesia or providing care for the patients. The researcher was trained through reading, learning, and testing the instruments during normal clinical encounters, followed by pilot runs of the complete protocol.

2.8 | Anxiety as measured by mYPAS

Anxiety was measured at the time of arrival in the day care unit (baseline) and during anesthesia preparation in the operating theater. The level of anxiety was assessed using the validated Swedish version of the modified Yale Preoperative Anxiety Scale (mYPAS), containing 27 items in five categories (activity, emotional, expressivity, state of arousal, vocalization, and use of parents), representing five domains of anxiety.17,18 The mYPAS scale ranges from 0 to 100 points, with higher scores signifying higher levels of anxiety. The score is normalized for the different number of steps in the items and also accounts for non-observable items. The instrument assesses the children’s anxiety during the perioperative period, has good-to-excellent observer reliability, with high concurrent and construct validity.17,18 Before the mYPAS was developed, the State-Trait Anxiety Inventory for Children (STAI-CH) was used as the golden standard. A validation study showed that in children aged 5–12 years, an mYPAS score >30 for anxiety had a positive predictive value of 79%, which corresponded to an STAI-CH score of >37, with only 6% false-positives and 4% false-negatives.18
2.9  |  Distress during PVC insertion as measured by BDS

Distress during PVC insertion was assessed on a five-point behavioral distress scale (BDS), with zero denoting no response. To minimize the pain associated with PVC insertion, all children received a topical anesthetic (EMLA® 25 mg/25 mg, Astra Zeneca, Stockholm) that was applied 60 min before needle insertion.

2.10  |  Compliance at induction as measured using the induction compliance checklist (ICC)

The child’s compliance to the face mask during pre-oxygenation before anesthesia induction was measured using the ICC. The ICC observational scale has shown good reliability, containing 10 negative behavioral items, with 0 representing a perfect induction with no negative behaviors due to fear or distress.

2.11  |  Sedation as measured by RSS

Sedation status was measured using the Ramsay sedation scale (RSS) at baseline, at 40, 50, and 60 min after the first premedication, and during anesthesia preparation for the surgery. This scale includes the following categories: 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. Higher scores denote higher levels of sedation.

2.12  |  Induction of anesthesia

Anesthesia was induced using a standardized protocol. First, a bolus of atropine (0.01 mg/kg) was administered, continued by a 1-min infusion of remifentanil (2–3 µg/kg), and a 2-min infusion of propofol 3–5 mg/kg infused for 2 min until the child was asleep. If an intravenous line could not be established, either for technical reasons, or due to child discomfort (BDS >3), an alternative rescue anesthesia induction was initiated with inhalation of oxygen/nitrous oxide (1:1) mixed with 8% sevoflurane using a face mask.

2.13  |  Statistical analysis

A sample size of minimum 102 participants was calculated using the mean (27.30) and standard deviation (6.24) from the method reported by Wright et al. and was modeled to detect a mean difference of ≥4 in the mYPAS among the three groups (F-test, omnibus, one-way, alpha = 0.05%; power =80%) using the G*Power software. To adjust and compensate for uncertainties in the power calculation and to account for drop-outs, the study was designed to include 150 participants. As the initial power calculation was based upon uncertain data, the protocol included an interim analysis to analyze the variance in the primary outcome variable after more than half of the patients were included. During the study period, the procedure was relocated to another hospital, which severely impeded recruitment for the study. After the inclusion of 90 patients (six randomization blocks), an interim analysis was performed in collaboration with an independent statistician and the three study groups were compared. The variance in the primary endpoint variable was <70% of the variance on which the power analysis was based upon. The analysis concluded that the primary study objectives could be answered, and after a discussion with the monitoring authority, a decision was taken to conclude the study.

After all study data were entered in the database and had been validated according to the GCP guidelines, the study database was locked, and the complete randomization code was broken.

Data are reported as numbers, means ± standard deviation, or medians (interquartile range, IQR). For the nominal and ordinal variables, the Kruskal–Wallis test was used to analyze the differences between the groups, and one-way analysis of variance (ANOVA) was used for the continuous variables. After the Kruskal–Wallis test, pairwise comparison between the groups was performed using the SPSS procedure that adjusts the significance level using the Bonferroni correction for multiple tests. For repeated measurements of the RSS and mYPAS, within-group differences over time were analyzed with using the Related-Samples Wilcoxon Signed Rank test. The Pearson’s correlation was used to analyze the correlations among age, mYPAS, and RSS. Statistical analyses were performed using SPSS (IBM Corp. Released 2018. IBM SPSS Statistics for Mac, Version 26.0. Armonk, NY: IBM Corp.).

3  |  RESULTS

3.1  |  Participant recruitment

Two hundred and thirty-nine children scheduled for ENT surgery were screened for eligibility; among them, 90 children were enrolled in the study from February 2017 to May 2019. Six children were excluded from the analysis due to a refusal to the study drugs (CLO: n = 3; MID: n = 3). The final study cohort consisted of 84 children (Figure 2).

The patient characteristics are summarized in Table 1. The average age of the included children was 4.3 ± 0.9 years. There were no differences among the three groups in the distribution of boys and girls, demographic characteristics, preoperative training, or the parental rating of the children’s worry and concern regarding the upcoming surgery. The time from administration of the study drug to the initiation of anesthesia induction was 60 ± 18 min, 84 ± 20 min, and 56 ± 18 min in the MID, CLO, and DEX groups, respectively.
3.2 | Primary outcome: anxiety

There were no differences in the mYPAS score at baseline between the groups (Figure 3, Table 2). During anesthesia preparation, the mYPAS score increased compared to the baseline in both the CLO \( (p = 0.016) \) and DEX \( (p = 0.007) \) groups, while no change was observed in the MID group. None of the five categories/domains of anxiety in the mYPAS showed any significant differences when comparing the groups at baseline or at anesthesia preparation (Table S1).

In the entire study population \( (n = 84) \), a negative correlation was observed between age and mYPAS during anesthesia preparation \( (r = -0.26, p = 0.019) \), indicating that the high mYPAS scores were predominately among the younger children.

3.3 | Secondary outcome: distress during PVC and induction compliance

Neither the BDS \( (MID, 1.4 \pm 0.6; CLO, 1.3 \pm 0.7; DEX, 1.2 \pm 1.0; p = 0.17) \) nor ICC \( (MID, 0.4 \pm 1.3; CLO, 1.6 \pm 1.7; DEX, 0.6 \pm 1.6; p = 0.87) \) showed any significant differences between the groups. During PVC insertion, >80% of the children had a BDS score of 0 \( (MID n = 21, 78%; CLO n = 22, 81%; DEX n = 25, 83\%) \), and >80% had an ICC score of 0 during preoxygenation \( (MID, n = 23, 85\%; CLO, n = 22, 81\%; DEX, n = 24, 80\%) \).

3.4 | Secondary outcome: sedation

The baseline assessment of the RSS showed no significant differences between the groups. Sixty minutes after the first study intervention (clonidine or placebo), with all participants given an active premedication, the CLO and DEX groups had a higher RSS score compared to the MID group \( (MID, 2.26 \pm 0.45; CLO, 3.56 \pm 1.12; DEX, 4.03 \pm 0.72; p < 0.001; Figure 4) \). Compared to the observations at 60 min, seven (26\%) children in the CLO group and four (13\%) in the DEX group had a decreased RSS score from 4 to 2 during anesthesia preparation in the operating theater. These children had a higher median mYPAS score compared with those who did not have a decrease in the RSS score \( (50 [IQR, 15] vs. 23 [IQR, 0]; p < 0.001) \). There was a positive correlation between age and RSS at 40 min \( (r = -0.248; p = 0.023) \); however, no correlation was observed at 50 min, 60 min, or at anesthesia preparation.

3.5 | Rescue induction of anesthesia

In 75 children, anesthesia was induced intravenously according to the study protocol, while in nine children, the rescue inhalational method was required \( (MID, n = 2; CLO, n = 3; and DEX, n = 4; not significant) \).
In this randomized study evaluating anesthetic premedication in preschool children (2–6 years), midazolam was better in reducing preoperative anxiety, while sedation, as secondary outcome, was better achieved with clonidine and dexmedetomidine. The compliance with administration of premedication was best with the intranasal route (dexmedetomidine) with no child refusal, while one out of 10 children rejected the oral route (midazolam and clonidine).

In our study, the children that received midazolam had no increase in anxiety from baseline until anesthesia preparation, while the children in both the clonidine and dexmedetomidine groups experienced an increase in anxiety. Fazi et al. used the mYPAS to estimate preoperative anxiety in children aged 4–12 years and observed a similar result, with higher levels of anxiety following 4 µg/kg clonidine administration, compared with administration of 0.5 mg/kg midazolam. However, these results are in contrast with those in the reports from Segovia et al. and Neville et al., who observed that premedication with intranasal dexmedetomidine was more effective than oral midazolam in reducing preoperative anxiety, measured using the mYPAS, in pediatric patients (2–12 years and 1–5 years, respectively). The discrepancy between the studies might have been due to the differences in the age of the population, or in the timing of the protocols.

As noted by Doughty in 1959, a smooth anesthesia induction depends on the likelihood of the establishment of a rapport between the anesthesiologist and patient. In younger patients with inadequate sedation and anxiolysis, this interaction might be
impeded. Around 80% of the children in our study showed no distress and were completely compliant at anesthesia induction, with no differences between the premedication used in the study, even though the mYPAS scores were significantly increased in the children who had received dexmedetomidine or clonidine. However, we observed that younger preschoolers had higher mYPAS scores compared with older preschoolers. This might have been due to differences in the pharmacokinetics and pharmacodynamics, or an interaction with the nonpharmacological components of the preanesthetic milieu.

Both the alpha-2-agonists clonidine and dexmedetomidine were superior in achieving sedation before anesthesia, compared with midazolam. We observed that the children who received midazolam remained cooperative and were not sedated, while both clonidine and dexmedetomidine induced sedation. In a meta-analysis, Pasin et al. used the data from 1033 children in 13 randomized trials to compare the level of satisfactory sedation and observed no difference between dexmedetomidine and midazolam.28 However, the average age of the included children was 6 years (range 2−14 years), compared to that of 4 years (2−6 years) in our study. Further, Schmidt et al. enrolled 60 preschool children (7−12 years old) in an open-label randomized study comparing the effect of dexmedetomidine, clonidine and midazolam.29 The study showed no differences between the groups regarding preanesthesia anxiety or sedation. However, notably, their study had significantly older children as compared to our study. Thus, the results reported here indicate that alpha-2-agonists provides better sedation in children aged 2−6 years.

The differences between the drug’s potential to induce sedation and relieve anxiety might be important, as dexmedetomidine is rapidly becoming the drug of choice for pediatric procedural sedation, such as for intravenous cannulations, magnetic resonance imaging, and computed tomography examinations. Furthermore, in this study, children who had received either clonidine or dexmedetomidine and were still sedated after preparing for induction, had low mYPAS scores. However, some of these children woke up during the transfer

**TABLE 2** Primary and secondary outcomes

| Variable                  | Midazolam | Clonidine | Dexmedetomidine | p-Value |
|---------------------------|-----------|-----------|-----------------|---------|
| mYPAS                     | Median (IQR; min-max; n) | Median (IQR; min-max; n) | Median (IQR; min-max; n) | Kruskal-Wallis test |
| Baseline                  | 23 (0; 23–37; n = 30) | 23 (0; 23–45; n = 30) | 23 (0; 23–43; n = 30) | .818 |
| Anesthesia preparation    | 23 (0; 23–87; n = 27) | 23 (15; 23–87; n = 27) | 23 (11; 23–82; n = 30) | .061 |
| Delta                     | 0 (0; −13–77; n = 27) | 0 (13; −8–67; n = 27) | 0 (6; −13–63; n = 30) | .036 |
| p-value: Baseline vs Anesthesia preparation | .733 | .016 | .007 |
| BDS 60 min                | 1 (1; 1–3; n = 27) | 1 (1; 0–3; n = 27) | 1 (0; 0–6; n = 30) | .173 |
| ICC anesthesia preparation| 0 (0; 0–5; n = 27) | 0 (0; 0–7; n = 27) | 0 (0; 0–7; n = 30) | .871 |

**RSS**

| Variable                  | Midazolam | Clonidine | Dexmedetomidine | p-value: Baseline vs 40 min | p-value: Baseline vs 50 min | p-value: Baseline vs 60 min | p-value: Baseline vs Anesthesia preparation |
|---------------------------|-----------|-----------|-----------------|---------------------------|---------------------------|---------------------------|-----------------------------------|
| Baseline                  | 2 (0; 2–2; n = 30) | 2 (0; 2–2; n = 30) | 2 (0; 2–2; n = 30) | .025 | .014 | .008 | .025 |
| 40 min                    | 2 (0; 2–3; n = 27) | 2 (0; 3–5; n = 27) | 2 (1; 2–4; n = 30) | .026 | .001 | .000 | .000 |
| 50 min                    | 2 (0; 2–3; n = 27) | 3 (1; 1–5; n = 27) | 4 (1; 2–5; n = 30) | .002 | .000 | .000 | .000 |
| 60 min                    | 2 (1; 2–3; n = 27) | 4 (0; 1–5; n = 27) | 4 (0; 2–5; n = 30) | .000 | .000 | .000 | .000 |
| Anesthesia preparation    | 2 (0; 2–3; n = 27) | 3 (2; 2–5; n = 27) | 4 (1; 2–5; n = 30) | .000 | .000 | .000 | .000 |

Note: IQR denotes the interquartile range, that is, the difference between the 75th percentile and the 25th percentile. p-value: Baseline vs [...] is the p-value of the related-samples Wilcoxon Signed Rank test of the difference within the group compared to baseline.

**FIGURE 4** Sedation as measured by Ramsey’s Sedation Scale (RSS) in the daycare unit at baseline, 40, 50, and 60 min after the first medication, and in the operating room before induction. * indicates p < .05 compared to midazolam.
from the preoperative holding area to the operating room or during anesthesia preparation and had increased anxiety as measured with the mYPAS. Previous studies have shown that patients receiving alpha-2-agonists, particularly dexmedetomidine, are easily aroused from sedation through external stimulation.\textsuperscript{27,30} Furthermore, Yuen et al. showed that after intranasal administration of 1 \( \mu g/kg \) dexmedetomidine, sedation peaked at 60 min after administration and satisfactory behavior decreased after this peak,\textsuperscript{14} indicating that when the sedative effect of dexmedetomidine wears off, so does the calming effect on the child.

The differences in acceptance between the studied drugs, with 10\% rejection of oral clonidine and midazolam and no rejection of intranasal dexmedetomidine, is in line with previous publications. Intranasal dexmedetomidine is generally accepted by children, and several authors have reported no rejections.\textsuperscript{8,14} Almenrader et al.\textsuperscript{5} compared the effectiveness of midazolam per os and clonidine per os before mask induction and observed that 14\% of the children rejected midazolam, whereas none of them rejected clonidine. This contrasts with our findings that both drugs had a similar rejection rate.\textsuperscript{8,14} Flavored preparations of the drugs might be used to increase compliance for the oral premedications.\textsuperscript{31}

\subsection*{4.1 Strength, limitations, and future research}

To increase the generalizability of our results, we included children from among the normal patient influx at a county hospital. Furthermore, we used block randomization; therefore, the study groups had similar characteristics (Table 1). The strengths of our study also include the narrow age spectrum of population and the use of validated instruments, adapted and developed for use in children, to validate the interventions in the perioperative period. Further, we used the mYPAS as it is an observation instrument developed specifically to enable measurement of preoperative anxiety in children.\textsuperscript{18} Kain et al. compared the mYPAS against the STAI-CH, which is the golden standard, in children aged 5–12 years and showed an acceptable concurrent validity between the two (\( r = .01 \); \( r = .79 \)) and good inter- and intra-observer reliability. In addition to being reliable and validated, the mYPAS has several other important features. First, it can be applied to all children aged >2 years. Second, because it is a structured instrument that comprises five domains of anxiety, it is much more sensitive to changes in anxiety levels than global instruments.

The limitations of this study include its single-center study design, early termination, and a sample size of only 90 children. However, there were uncertainties regarding the calculated sample size prior to the start of the study, and an interim analysis was incorporated in the study protocol. We observed significant differences between the groups in this analysis and combined with limited resources, we decided to terminate the study early. It would have been appropriate to complete the study; however, we were unable to do so. Nonetheless, as we were able to draw conclusions from the patients included, we believe that our findings should be reported.

Furthermore, the parents were not separated from the child until the child was anesthetized. The transfer from the daycare unit to the operating room, and being moved to the operation table aroused some of the children, as noted with the increase in the mYPAS scores and decrease in the RSS scores. An optimal premedication would help overcome these challenges.

As the perioperative settings differ between hospitals and countries, a more optimal premedication routine can be established in the specific context through an increased knowledge of the drugs used. The results from our study contribute to this knowledge by adding information from a Swedish perspective. Further, international multi-center studies on the optimal timing and doses for sedation and anxiety relief in children are warranted.

\section*{5 CONCLUSIONS}

In preschool children aged 2–6 years, premedication with midazolam resulted in a more effective anxiolysis, thereby requiring less sedation compared with premedication with clonidine and dexmedetomidine. If deeper sedation is required, dexmedetomidine, due to its easy administration and faster duration of onset, might be preferable to clonidine in clinical use.

\section*{ACKNOWLEDGEMENTS}

We would like to thank Robert Lundqvist for statistical support, the Clinical Trial Unit, Umeå and our research nurse team; Anna Lindström, Anders Pulkkinen and Ulrika Sundström. This work was supported by grants from Region Norrbotten (NLL-485451, NLL-486841) and Region Västerbotten (RV-865681, RV-932836, RV-940554).

\section*{CONFLICT OF INTEREST}

The study was conducted with public funding from Region Norrbotten and Region Västerbotten. JW has received lecture fees from AbbVie Sweden AB. All authors declare no conflicts of interest.

\section*{ETHICAL APPROVAL}

The study 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), and registered as EudraCT 2015-003676-70.

\section*{DATA AVAILABILITY STATEMENT}

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

\section*{ORCID}

Åsa Bromfalk \url{https://orcid.org/0000-0002-4585-8786}

Tom Myrberg \url{https://orcid.org/0000-0002-8802-2321}

Jakob Walldén \url{https://orcid.org/0000-0002-8171-5184}

Åsa Engström \url{https://orcid.org/0000-0001-6244-6401}

Magnus Hultin \url{https://orcid.org/0000-0003-2935-7161}
REFERENCES

1. Watson AT, Visram A. Children’s preoperative anxiety and postoperative behaviour. Pediatr Anaesth. 2003;13(3):188-204.
2. McCann ME, Kain ZN. The management of preoperative anxiety in children: an update. Anesth Analg. 2001;93(1):98-105.
3. Barends CR, Absalom A, van Minnen B, Vissink A, Visser A. Dexmedetomidine and Midazolam in procedural sedation: A systematic review of efficacy and safety. PLoS One. 2017;12(1):e0169525.
4. Bergendahl H, Lönnqvist P-A, Eksborg S. Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. Acta Anaesth Scand. 2006;50(2):135-143.
5. Almenrader N, Passariello M, Coccetti B, Haiberger R, Pietropaoli P. Premedication in children: a comparison of oral midazolam and oral clonidine. Pediatr Anesth. 2007;17(12):1143-1149.
6. Plambech M, Afshari A. Dexmedetomidine in the pediatric population: a review. Minerva Anestesiol. 2015;81(3):320-332.
7. Larsson P, Nordlinger A, Bergendahl HTG, et al. Oral bioavailability of clonidine in children. Pediatr Anesth. 2010;21(3):335-340.
8. Cimen ZS, Hanci A, Sivrikaya GU, Kilinc LT, Erol MK. Comparison of buccal and nasal dexmedetomidine premedication for pediatric patients. Pediatr Anesth. 2013;23(2):134-138.
9. Neville DNW, Hayes KR, Ivan Y, McDowell ER, Pitetti RD. Double-blind Randomized Controlled Trial of intranasal dexmedetomidine versus intranasal midazolam as anxiolysis prior to pediatric laceration repair in the Emergency Department. Acad Emerg Med. 2016;23(8):910-917.
10. Segovia BL, Cuevas MAG, Casillas ILR, et al. Medicación preanestésica con dexmedetomidina intranasal y midazolam oral como ansiolítico. Un ensayo clínico. Anales De Pediatr. 2014;81(4):226-231.
11. Fazi L, Jantzec EN, Rose JB, Kurch CD, Watcha MF. A comparison of oral clonidine and oral midazolam as preanesthetic medications in pediatric tonsillectomy patients. Anesthesia Analgesia. 2001;92(1):56-61.
12. Kumari S, Agrawal N, Usha G, Talwar V, Gupta P. Comparison of oral clonidine, oral dexmedetomidine, and oral midazolam for premedication in pediatric patients undergoing elective surgery. Anesth Essays Res. 2017;11(1):185-191.
13. Yuen V. Dexmedetomidine: perioperative applications in children. Pediatr Anaesth. 2010;20(3):256-264.
14. Yuen VM, Hui TW, Irwin MG, Yuen MK. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. Anaesthesia. 2010;65(9):922-929.
15. Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. Brit J Clin Pharmac. 2003;56(6):691-693.
16. Iirola T, Vilo S, Manner T, et al. Bioavailability of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol. 2011;67(8):825-831.
17. Proczkowska-Björklund M, Berglund IG, Ericsson E. Reliability and validity of the Swedish version of the modified Yale Preoperative Anxiety Scale. Acta Anaesth Scand. 2012;56(4):491-497.
18. Kain ZN, Mayes LC, Cichetti DV, Bagnall AL, Finley JD, Hofstadter MB. The Yale Preoperative Anxiety Scale: how does it compare with a “gold standard”? Anesth Analg. 1997;85(4):783-788.
19. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. Arch Dis Child. 2000;82(4):309-310.
20. Lander J, Weltman B, So S. EMLA and amethocaine for reduction of children’s pain associated with needle insertion. Cochrane Database Syst Rev. 2006;3:CD004236.
21. Varughese AM, Nick TG, Gunter J, Wang Y, Kurth DC. Factors predictive of poor behavioral compliance during inhaled induction in children. Anest Analg. 2008;107(2):413-421.
22. Ramsay M, Savege T, Simpson B, Goodwin R. Controlled sedation using alphaxalone-alphadolone. BMJ. 1974;2(5920):656.
23. Manson KP, Michna E, Zurakowski D, et al. Value of bispectral index monitor in differentiating between moderate and deep Ramsay Sedation Scores in children. Pediatr Anesth. 2006;16(12):1226-1231.
24. Wright KD, Eisner A, Stewart SH, Finley AG. Measurement of preoperative anxiety in young children: self-report versus observer-rated. J Psychopathol Behav Assess. 2010;32(3):416-427.
25. Faull F, Einfeld E, Buchner A, Lang A-G. Statistical power analyses using G’Power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149-1160.
26. Doughty AG. The evaluation of premedication in children. J Roy Soc Med. 1959;52(10):823-834.
27. Pasin L, Febres D, Testa V, et al. Dexmedetomidine vs midazolam as preanaesthetic medication in children: a meta-analysis of randomized controlled trials. Pediatr Anesth. 2015;25(5):468-476.
28. Schmidt AP, Valinetti EA, Ndeira D, Bertacchi MF, Simônés CM, Auler JC. Effects of preanaesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Pediatr Anesth. 2007;17(7):667-674.
29. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blind randomized controlled trial. Anest Analg. 2008;106(6):1715-1721.
30. Keating GM. Dexmedetomidine: a review of its use for sedation in the intensive care setting. Drugs. 2015;75(10):1119-1130.
31. Yuen VM, Bailey CR. Premedication in children: does taste matter? Anaesthesia. 2018;73(12):1453-1456.

SUPPORTING INFORMATION

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

How to cite this article: Bromfalk Å, Myrberg T, Waldén J, Engström Å, Hultin M. Preoperative anxiety in preschool children: A randomized clinical trial comparing midazolam, clonidine, and dexmedetomidine. Pediatr Anaesth. 2021;31:1225–1233. https://doi.org/10.1111/pan.14279