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Research

Cardiorespiratory Response to Sedative Premedication in Preschool Children: A Randomized Controlled Trial Comparing Midazolam, Clonidine, and Dexmedetomidine

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A B S T R A C T

Purpose: Sedative premedication in children may negatively impact their cardiorespiratory status during the perioperative course, and no clear consensus exists on the optimal premedication treatment for pediatric patients. The objective was to compare the perioperative cardiorespiratory responses to sedation using three different sedative premedication regimens in preschool children scheduled for surgery with total intravenous anesthesia.

Design: A single-center randomized controlled trial.

Methods: This is a planned secondary analysis of a study conducted at a 200-bed tertiary referral hospital. Ninety children participated in the study. They were aged 2–6 years and scheduled for ear, nose, and throat surgery with propofol/remifentanil anesthesia. Participants were randomly assigned to receive oral midazolam 0.5 mg/kg^{-1} (MID), oral clonidine 4 mcg/kg^{-1} (CLO), or intranasal dexmedetomidine 2 mcg/kg^{-1} (DEX). The main outcome measures were the sedation level, based on the Ramsay Sedation Scale (RSS), and cardiorespiratory status, monitored during the perioperative period.

Findings: The final cohort had 83 children (MID, *n*=27; CLO, *n*=26; DEX, *n*=30), with similar intergroup patient characteristics. RSS scores were lower in the MID group than in the CLO and DEX groups before induction and within 30 min postsurgery ($P<0.001$ and $P=0.006$, respectively). A negative correlation existed between the RSS and heart rate (HR) ($r=-0.570$, $P<0.001$). Before anesthesia induction, the respiratory rate was lowest in the DEX group (MID 21.5±1.7 min^{-1}, CLO 20.6±2.6 min^{-1}, DEX 20.2±1.7 min^{-1}; $P=0.042$). The HR was lower in the CLO and DEX groups than in the MID group (MID, 102.8±10.0 min^{-1}; CLO, 87.4±9.6 min^{-1}; DEX, 87.6±7.9 min^{-1}; $P<0.001$). The HR was lower immediately after induction ($P=0.009$) and intraoperatively ($P=0.025$) in the CLO and DEX groups than in the MID group.

Conclusions: When used as premedication before propofol/remifentanil anesthesia, clonidine and dexmedetomidine provided deeper preoperative sedation compared to midazolam. From a clinical perspective, all three study drugs provided essentially stable cardiovascular and respiratory conditions during the entire perioperative period.

Preparation for anesthesia and surgery can be stressful, particularly for children.[1] Stress evokes an endocrine response and stimulates the sympathetic nervous system, thereby leading to increased arterial blood pressure (BP), heart rate (HR), and oxygen consumption. Children are particularly vulnerable to this surgical stress response because of their limited energy reserves; larger brain mass, compared to body size; and obligatory glucose requirements.[2,3] Thus, controlling and preventing perioperative stress responses is crucial in modern pediatric anesthesia.

The benzodiazepine midazolam has traditionally been used to relieve preoperative stress and provide sedation in pediatric patients; however, in higher doses, it has an increased risk of respiratory depression.[4] In addition, stress-induced hypertension is reported as an unwanted reaction in midazolam-treated adult patients, which may be

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a concern also in pediatric clinical practice.[5] Two alpha$_2$-agonists, clonidine and dexmedetomidine, have emerged as alternatives to midazolam and have effective sedative properties, and the hypertensive response to stress is attenuated.[5] They induce minimal respiratory depression and decrease perioperative catecholamine concentrations, thereby promoting perioperative hemodynamic and adrenergic stability.[6,7] Dexmedetomidine has an even more favorable safety profile than does clonidine, with increased hamodynamic stability.[8] However, high plasma levels of intravenous dexmedetomidine may cause hypotension, sometimes paradoxically preceded by hypertension.[9] A recent meta-analysis[5] revealed similar respiratory and hemodynamic responses to dexmedetomidine and midazolam. However, no current clear consensus exists on the ideal premedication for pediatric patients.

The aim of this study was to compare the perioperative cardiorespiratory responses to sedation using three different sedative premedication regimens in preschool children scheduled for surgery with total intravenous anesthesia. We hypothesized a similar level of sedation between the interventions and that the alpha$_2$-agonists; clonidine and dexmedetomidine, would have fewer respiratory effects and a greater hemodynamic impact, compared to midazolam.

Methods

This is a planned secondary analysis of a randomized controlled trial that was conducted in accordance with Good Clinical Practice (GCP) and was approved by the Regional Ethics Review Board in Umeå, Sweden (approval number: 2016-46-31M; approval date: 30 March 2016; chairperson: A Iacobæus), and the Swedish Medical Products Agency (approval number: 5.1-2016-17854; approval date: 13 May 2016). Data on preoperative sedation and anxiety was recently published in a separate study.[10]

Written informed consent was obtained from both guardians of each enrolled child, with one parent present during the perioperative process, including anesthesia induction. The study involved no deviations or risks beyond those of the clinical routines, and the children were continuously monitored during anesthesia.

Events meeting the criteria and definition of adverse events (AEs) were assessed, classified according to GCP regulations, and followed up by the principal investigator (MH before 16 November 2018 and TM thereafter) until resolved. An AE was defined as any untoward, unfavorable, or unintended medical occurrence, whether it was or was not related to the drug used. The AE intensity was graded as 'mild', 'moderate' or 'severe'; mild or moderate events were considered acceptable, and severe events were considered an unacceptable interference with the participants' daily activities. This study adheres to the consolidated standards of reporting trials (CONSORT) guidelines.

Study Design

This is a planned secondary analysis of data from a phase II double-blind randomized clinical trial conducted at Sunderby Hospital (Luleå, Sweden), a 200-bed general tertiary referral hospital, and the trial design was published with the primary analysis.[10] Briefly, the trial included 90 children (3×30) in three arms. The inclusion criteria were age 2–6 years; either sex; weight, ≤30 kg, an American Society of Anesthesiologists (ASA) risk score of I–II, and scheduled for elective ear, nose, and throat (ENT) surgery with total intravenous anesthesia with propofol and remifentanil. The exclusion criteria were an ASA risk score >II; heart, lung, neurological, or central nervous system disorders (hypotension, hypovolemia, severe bradyarrhythmia, atrioventricular block II or III, acute cerebrovascular events, impaired consciousness, respiratory disorders with hypoventilation, myasthenia gravis and central sleep apnoea syndrome); use of psychotropic medication; or recent surgery (within a year).

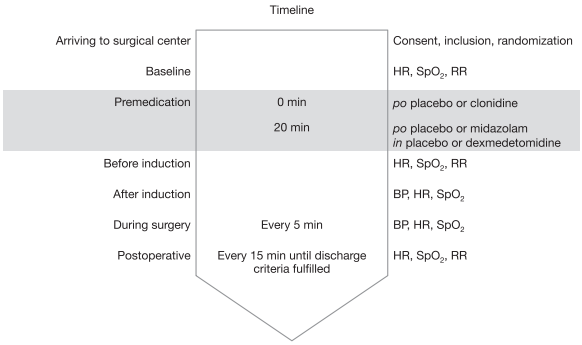

Figure 1. Timeline for premedication and measurements.
BP, blood pressure; HR, heart rate; RR, respiratory rate; SpO_2, peripheral oxygen saturation.

The children were randomized to one of the three sedative premedication interventions: oral midazolam 0.5 mg/kg^{-1} (MID; Apotek, Produktion & Laboratorier, APL, Stockholm, Sweden; 1 mg/ml^{-1} 40 min before surgery), oral clonidine 4 mcg/kg^{-1} (CLO; APL; 20 mcg/ml^{-1} 60 min before surgery), or intranasal dexmedetomidine 2 mcg/kg^{-1} (DEX; Dexdor®; Orion Pharma, Espoo, Finland; 100 mcg/ml^{-1} administered 40 min before surgery). Owing to the different times and routes of administration for the three interventions, a placebo was used to enable double-blinding. The participants first received an oral fluid (i.e. CLO or sterile water) and 20 min later intranasal fluid was administered with a mucosal atomization device (MAD Nasal™; Teleflex, Wayne, PA, USA; DEX or 0.9% saline), followed by oral fluid (MID or sterile water; Figure 1).

Routes of administration, doses and the timing of the interventions were based on published pharmacokinetic profiles and chosen to be of clinically relevant effect and safe. The rationales are discussed in the primary study.[10]

Data Collection and Outcome Measures

To minimize inter-rater variability, one member of the research team (ÅB) observed and collected all data. The observer was not involved in the medical or nursing care of the children.

The primary outcome in the present study was the sedation level, and the secondary outcome was the cardiorespiratory effects of the sedative premedication during the perioperative period. The measurement timeline is shown in Figure 1.

Sedation Level

The sedation level was measured using the Ramsay Sedation Scale (RSS), at baseline, 60 min after the first premedication, and every 15 min in the postanesthesia care unit (PACU) until the cardiorespiratory baseline was reached. Higher scores on the RSS denote higher sedation levels. The levels were '1' for anxious, restless, or agitated; '2' for cooperative; '3' for response to commands only; and '4'–'6' for different levels of unconsciousness ('6' indicated no response to a light glabellar tap or loud auditory stimulus.[11,12]

Cardiorespiratory Response

In the daycare unit, the HR (measured via ECG), capillary refill time (CRT), peripheral oxygen saturation (SpO_2, measured with pulse oximetry), and respiratory rate (RR, measured during a 1-min observation) were assessed as the baseline data, and then re-assessed 60 min after the first premedication.

In the surgical setting, HR, SpO_2, and noninvasive BP were assessed immediately after anesthesia induction and tracheal intubation. HR and SpO_2 were documented using ECG and pulse oximetry, and noninvasive BP was measured using an oscillometer with a

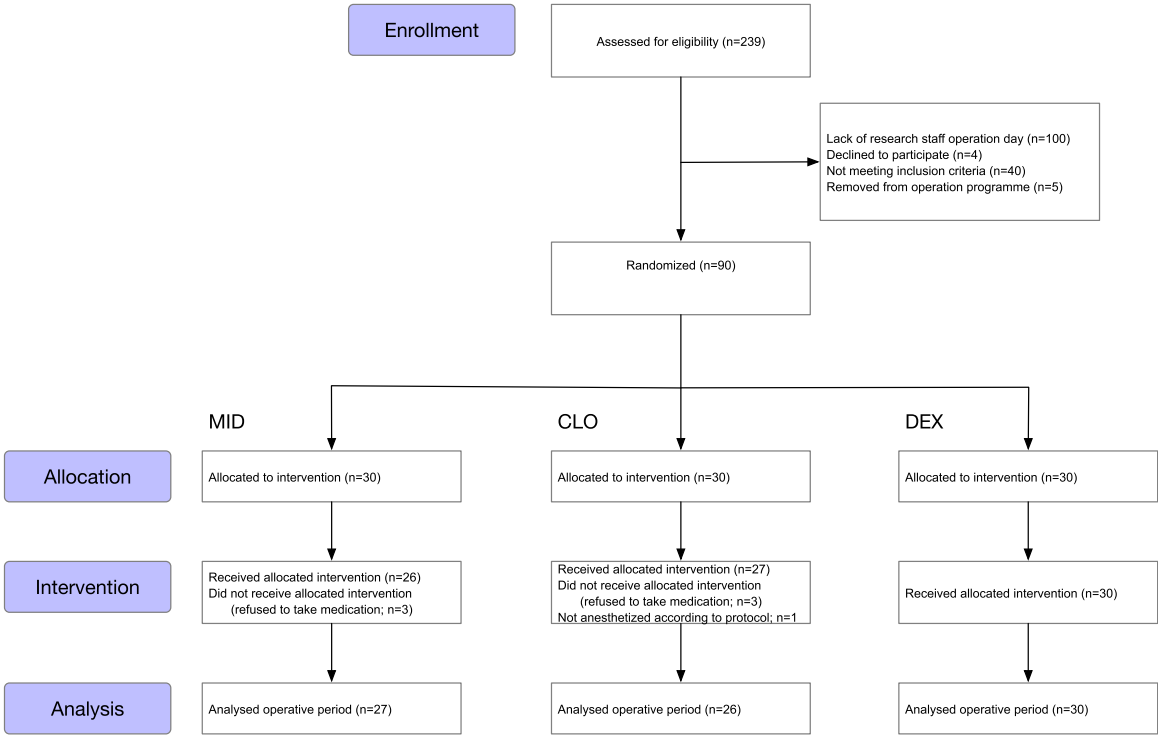

Figure 2. The CONSORT diagram.
CLO, clonidine; CONSORT, Consolidated Standards of Reporting Trials; DEX, dexmedetomidine; MID, midazolam.

properly sized cuff. The variables were continuously recorded and acquired every 5 min, and the mean blood pressure (MBP)was determined using a standard electronic physiologic monitor (Infinity® M540; Dräger, Lübeck, Germany) throughout the anesthetic period.

In the PACU, the HR, SpO_2, and RR were assessed every 15 min until reaching the values, based on the postanesthesia scoring system, of the recommended discharge criteria (HR and RR = baseline ± 20% and $SpO_2 \geq 92\%$).[13] Recovery time was as the period from admission to the PACU until reaching the target values for the different variables (i.e. HR, SpO_2, and RR).

In line with the standard operating protocol at the clinic, BP was not measured at baseline or at the PACU. Valid measurement of BP is difficult in small children and might cause discomfort and stress to the child. In addition, young children compensate for hemodynamic decrease mainly with an increase in HR, and guidelines instead recommend the use of CRT as part of the routine assessment of children (press on the finger for 5 seconds using moderate pressure at an ambient temperature of 20°C-25°C. A capillary refill time of 3 seconds or more should be considered abnormal).[14]

Anesthesia

A standardized protocol for total intravenous anesthesia was used. All children were intubated. For induction, a bolus dose of atropine (0.01 mg/kg^{-1}) was administered, followed by a 60-second infusion of remifentanil (2–3 mcg/kg^{-1}) and propofol (3–5 mg/kg^{-1}) for 2 min simultaneously, until the child was asleep. During surgery, anesthesia was maintained using a standardized protocol: propofol, 15 mg/kg^{-1} $/h^{-1}$during the first 15 min of surgery, 12 mg/kg^{-1} $/h^{-1}$ for the next 15 min of surgery, 9 mg/kg^{-1} $/h^{-1}$ after 30 min and

Table 1
Participants' Characteristics (N = 83)

	Treatment			
Characteristics	MID	CLO	DEX	*P*-Value
Number of patients	27 (32.5)	26 (31.3)	30 (36.1)	*.442*
Sex				
Male	17 (63.0)	16 (61.5)	17 (56.7)	*.877*
Female	10 (37.0)	10 (38.5)	13 (43.3)	
Age (y)	4.2 ± 0.9	4.4 ± 0.9	4.2 ± 1.0	*.623*
Weight (kg)	18.3 ± 3.8	18.7 ± 3.9	17.0 ± 2.1	*.116*
ASA-PS				
I	21 (77.8)	20 (76.9)	25 (83.3)	*.808*
II	6 (22.2)	6 (23.1)	5 (16.7)	
Hospitalization				
Outpatient surgery	25 (92.6)	22 (84.6)	24 (80.0)	*.397*
Inpatient surgery	2 (7.4)	4 (15.4)	6 (20.0)	

The values are presented as the number (percent) or as the mean ± the SD. To test differences between groups, the χ square test was used for categorical variables and ANOVA for continuous variables.
ASA-PS, American Society of Anesthesiologists Physical Status score; CLO, clonidine; DEX, dexmedetomidine; MID, midazolam.

Table 2
Anesthesia, Surgical Variables, and Adverse Events (N = 83)

Variables	Treatment			*P*-Value
	MID (n = 26)	CLO (n = 26)	DEX (n = 30)	
Induction				
Propofol/remifentanil	25 (92.6)	24 (92.3)	26 (86.7)	*.692*
Volatile (Sevoflurane/N_2O)	2 (7.4)	2 (7.7)	4 (13.3)	
Dose (mg)				
Total dose of propofol	221.4 ± 36.7	220.1 ± 76.6	203.9 ± 54.1	*.457*
Total dose of remifentanil	0.4 ± 0.1	0.4 ± 0.3	0.4 ± 0.1	*.729*
Total dose of atropine	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	*.084*
Morphine IV.	1.3 ± 0.4	1.0 ± 0.5	1.2 ± 0.3	*.058*
Glucose (ml)	60.7 ± 53.2	64.1 ± 46.9	60.1 ± 43.3	*.927*
Surgical procedure				
Tonsil/adenoid	27 (100)	23 (88.5)	29 (96.7)	*.131*
Other ENT surgery	0	3 (11.5)	1 (3.3)	
Time of surgery (min)	29.2 ± 12.7	25.4 ± 10.6	28.9 ± 13.3	*.466*
Adverse events (mild)				
No adverse events	23 (85.2)	23 (88.5)	28 (93.3)	*.161*
Bradycardia	0	2 (7.7)	0	
Obstructive/desaturation	4 (14.8)	1 (3.8)	2 (6.7)	

The values are presented as the number (percent) or as the mean ± the SD. To test differences between groups, the χ square test was used for categorical variables and ANOVA for continuous variables.
CLO, clonidine; DEX, dexmedetomidine; ENT, ear, nose, and throat; IV, intravenous; MID, midazolam; N_2O, nitrous oxide.

thereafter, and remifentanil 0.5 mcg/kg^{-1}/min^{-1} throughout the surgery.[1,15] At the end of the surgery, all children received intravenous morphine (0.1 mg/kg^{-1}) to prevent postoperative pain.

Rescue Medication

If an intravenous line could not be established, anesthesia was induced by inhalation of oxygen/nitrous oxide (50:50) + sevoflurane (8%). Inhalation induction was considered a rescue medication in this study. Furthermore, if the inhalational method was used for induction, sevoflurane and nitrous oxide were discontinued immediately after establishing an intravenous line, and anesthesia was further maintained with propofol/remifentanil, based on the protocol.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for PC, version 26.0 (IBM Corporation, Armonk, NY; released 2018). To assess differences between groups, binominal data were analyzed using Pearson's chi-square test, whereas nonparametric data were analyzed using the Kruskal–Wallis test. Normally distributed parametric data were analyzed using ANOVA with post-hoc tests. Student's *t*-test was used to compare the mean values, when appropriate. Nominal data are presented in the tables as the number (*n*) and percentage (%), and binominal data are presented as the mean ± the SD. Statistical significance was set at $P<0.05$.

Findings

As previously published, ninety children were enrolled in the study between February 2017 and May 2019.[10] Of the enrolled children, six children were excluded because their parents/guardians refused the study drug (CLO, *n*=3; MID, *n*=3), and one child was excluded because of receiving volatile anesthetics instead of total intravenous anesthesia during surgery (CLO, *n*=1). The final cohort consisted of 83 children (Figure 2). Of these, one prestudy closure (MID, *n*=1) occurred because of a surgical complication and no postoperative data were collected.

Participants, Anesthesia, and Surgical Variables

The mean age of the included children was 4.3±0.9 years. Boys and girls were equally distributed, and no difference existed in demographic characteristics between the groups (Table 1).

The time from administration of the interventional study drugs until anesthesia induction was 60±18 min for MID, 84±20 min for CLO, and 56±18 min for DEX. In eight children, anesthesia was induced by inhalation to establish an intravenous line (rescue medication: MID, *n*=2; CLO, *n*=2; DEX, *n*=4). No differences between the groups existed in terms of the anesthesia method, surgical procedure, or time of surgery (Table 2).

Table 3
Postoperative Sedation Level by Ramsay Sedation Scale (RSS*) (N = 82)

Sedation (RSS)	Treatment			*P*-Value
	MID	CLO	DEX	
On arrival	4.6 ± 1.3	4.5 ± 1.2	5.1 ± 0.6	*.116*
At 15 min	3.9 ± 1.3	4.2 ± 1.1	4.9 ± 0.7	*.001*
At 30 min	3.2 ± 1.3	3.8 ± 1.2	4.3 ± 1.0	*.006*
At 45 min	2.8 ± 1.1	3.4 ± 1.0	3.5 ± 1.0	*.056*
At 60 min	2.8 ± 1.1	3.0 ± 1.0	3.1 ± 1.0	*.737*
Time to reach RSS 2–3 (min)	74.3 ± 29.3	87.2 ± 32.7	89.2 ± 30.5	*.166*

The values are presented as the mean ± the SD. *P-value*, Kruskal–Wallis independent test (RSS) or ANOVA (time).
CLO, clonidine; DEX, dexmedetomidine; MID, midazolam; PACU, postanesthesia care unit; RSS, Ramsay Sedation Scale.
*RSS: 1, anxious and agitated and/or restless; 2, cooperative, oriented, and tranquil; 3, responds to commands only; and 4, brisk response to light glabellar tap or loud auditory stimulus; 5, sluggish response to light glabellar tap or loud auditory stimulus; 6, no response.

Table 4
Cardiorespiratory Outcomes (N = 83; Postoperative Data N = 82)

Variable	Treatment			*P*-Value
	MID	CLO	DEX	
Respiratory rate (min^{-})				
Baseline	21.8 ± 1.5	21.5 ± 1.7	21.1 ± 1.9	*.296*
Before induction	21.5 ± 1.7	20.6 ± 2.6	20.2 ± 1.7	*.042*
Time to reach baseline for RR at PSACU (min)	27.2 ± 19.8	28.7 ± 16.0	33.9 ± 18.1	*.351*
Peripheral oxygen saturation (%)				
Baseline	98.3 ± 0.9	98.6 ± 0.7	98.1 ± 1.2	*.173*
Before induction	97.5 ± 2.1	97.6 ± 1.2	97.0 ± 1.7	*.338*
After induction	98.6 ± 1.1	98.8 ± 1.2	98.4 ± 1.8	*.560*
During surgery	98.4 ± 0.9	98.8 ± 1.0	98.3 ± 1.1	*.180*
Time to reach baseline for SpO_2 in the PACU (min)	45.1 ± 18.1	52.9 ± 23.2	67.8 ± 16.6	*.000*
Heart rate (min^{-})				
Baseline	99.5 ± 9.3	92.9 ± 10.2	100.6 ± 9.7	*.010*
Before induction	102.8 ± 10.0	87.4 ± 9.6	87.6 ± 7.9	*.000*
After induction	97.4 ± 18.8	83.5 ± 10.6	88.4 ± 17.3	*.009*
During surgery	97.7 ± 14.6	90.9 ± 9.8	88.4 ± 13.0	*.025*
Time to reach baseline for HR at PACU (min)	50.9 ± 41.1	29.3 ± 17.9	42.9 ± 35.1	*.063*
Systolic blood pressure (mmHg)				
After induction	90.1 ± 10.0	88.8 ± 7.2	89.5 ± 9.2	*.862*
During surgery	98.6 ± 20.1	91.7 ± 11.7	93.5 ± 8.1	*.196*
Diastolic blood pressure (mmHg)				
After induction	45.2 ± 10.0	46.2 ± 8.0	47.4 ± 8.6	*.657*
During surgery	51.7 ± 11.2	52.6 ± 9.0	51.9 ± 9.0	*.935*
Mean arterial blood pressure (mmHg)				
After induction	65.1 ± 10.3	63.4 ± 7.2	64.5 ± 7.2	*.759*
During surgery	70.9 ± 10.8	69.4 ± 8.4	70.1 ± 7.1	*.817*

The values are presented as the mean ± the SD. *P-value*, ANOVA
CLO, clonidine; DEX, dexmedetomidine; HR, heart rate; MID, midazolam; PACU, postanesthesia care unit; RR, respiratory rate; SpO_2, peripheral oxygen saturation.

Sedation Level

The preoperative sedation level at 60 min, as measured with RSS, was significantly different between the groups (MID (2.3±0.4) vs. CLO (3.5±1.1) and DEX (4.0±0.7), *P*<0.001; and DEX vs. CLO, *P*=0.045). At 60 min, high RSS scores were associated with low HR frequencies (*r*=-0.570 and *P*<0.001). During the postoperative period, the differences in the RSS scores between the groups remained within the first 30 min after arriving to the PACU (Table 3). The post-hoc analysis showed that DEX provided a higher sedation level 15 min after arrival at the PACU compared to MID and CLO (DEX vs. CLO; *P*=0.032, DEX vs. MID; *P*=0.001). At 30 min after arrival at the PACU, DEX still had a higher RSS score compared to MID (*P* =0.003), but thereafter no other differences could be detected in sedation between the groups.

Cardiorespiratory Response

At baseline, no differences in RR or SpO_2 existed between the groups. However, before anesthesia induction, significant differences in RR were observed (*P*=0.042; Table 4). Post-hoc analysis revealed differences in RR before anesthesia induction in the comparison of DEX versus MID (-1.4±0.5 min^{-1}; *P*=0.034), but not between CLO and MID (-0.9±0.6 min^{-1}; *P*=0.260) or DEX versus CLO (-0.5±0.5 min^{-1}; *P*=0.659). However, when comparing the decrease in RR from baseline to before induction, no significant changes were detected (*P*=0.670). In the postoperative ward, patients in the MID and CLO groups reached the SpO_2 discharge criteria faster than did patients in the DEX group (*P*<0.001; Table 4). The MID and CLO groups were not significantly different (45 min and 53 min; *P*=0.321). Short periods (i.e. <5 min) of obstructive breathing and desaturation were observed in eight patients immediately after endotracheal extubation (MID, *n*=4; CLO, *n*=2; DEX, *n*=2; *P*=0.161; Table 2).

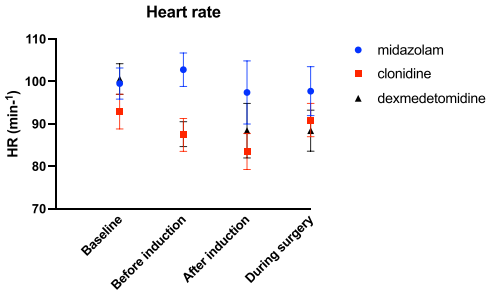

Figure 3. Heart rate (HR) at baseline, before induction, after induction and during surgery. (N = 83).
Clonidine is indicated by red squaresss; dexmedetomidine, black triangles; and midazolam, blue circles.

All children had a CRT under 2 seconds at baseline, and all through the perioperative period. Significant differences existed in HR at baseline, before and after induction, and during surgery among the three study groups (Table 4, Figure 3). No differences in postoperative HR-recovery were observed between the groups. Patients in the MID group maintained the baseline HR throughout the procedure compared to patients in the CLO and DEX groups in whom decreases in HR were observed (CLO vs. MID: -15.38±2.54 min-1; *P*<0.001; and DEX vs. MID: -15.18±2.43 min^{-1}; *P*<0.001). No difference was found between the CLO and DEX groups (*P*=0.997). A significant difference existed between the groups when the decrease in HR was compared from baseline to the value after induction (CLO -9.5±13.8 min^{-1}, DEX-12.1±16.2 min^{-1}, and MID -2.1±15.5 min^{-1}; *P*=0.047). The difference between MID and DEX was significant (*P*=0.042), but it was not different between MID and CLO (*P*=0.196) or CLO and DEX (*P*=0.791). In addition, the intraoperative HR was continuously lower in the DEX group than in the MID group (*P*=0.042), but it was not different between the CLO and DEX groups (*P*=0.791) or between the MID and CLO groups (*P*=0.196). No differences were observed in systolic, diastolic, or mean BP immediately after induction or during surgery among the groups (Table 4). Two mild AEs with bradycardia (CLO) occurred during anesthesia induction; however, they responded promptly to atropine administration. No significant

differences in the occurrence of AEs were detected among the groups (Table 2).

Discussion

Comparing the cardiorespiratory responses after sedative premedication with midazolam, clonidine, and dexmedetomidine indicated that children that received clonidine and dexmedetomidine reached deeper level of sedation and a decrease in RR and HR, compared to children receiving midazolam. No differences in adverse events were detected, but as this is a rather small cohort, it cannot be ruled out that there might be clinically relevant differences between the premedications from a safety-perspective.

Cardiorespiratory Responses to the Interventions

Midazolam has been associated with respiratory depression at high doses, above 0.5 mg/kg^{-1}.[4] In the present study, the group receiving midazolam 0.5 mg/kg^{-1} maintained the respiratory baseline throughout the anesthesia and surgical process. Compared to the use of midazolam, the RR showed a minor decrease after dexmedetomidine when measured immediately before anesthesia induction. In a recent study on the sedative and anxiolytic effects in this study cohort, oral midazolam (0.5 mg kg^{-1}) did not provide deep sedation in pediatric patients, whereas dexmedetomidine (2 mcg kg^{-1}) provided the deepest sedation level among all groups,[10] which indicated that respiratory depression may be highly associated with the sedation level.[16] Furthermore, after anesthesia, children receiving midazolam recovered faster from the required oxygen supplementation than did children receiving dexmedetomidine. This finding is inconsistent with the findings of a previous study suggesting that, after midazolam treatment, prolonged postoperative oxygen supplementation is needed in children.[17]

Endotracheal tube placement during anesthesia may increase HR and BP. Numerous strategies, including pre-treatment with clonidine, have been devised to inhibit catecholamine release and minimize stress-induced increases in HR and BP. Off-label use of clonidine and dexmedetomidine is considered safe, with an even greater increase in hemodynamic stability during laryngoscopy and tracheal intubation for dexmedetomidine than that of clonidine.[18] Consistent with previous study results in adults and children, a decreased HR was observed after treatment with alpha$_2$-agonists in our study. No decrease in HR or BP was detected after midazolam administration. Thus, the potential synergistic interaction of the gamma-amino butyric acid (GABA) receptor agonists midazolam and propofol, leading to a lower stress-induced adrenergic response with lower perioperative HR,[19,20] a hemodynamic decrease was not observed in the midazolam group in our study. However, the stress response to tracheal intubation is brief and of limited magnitude in young patients, as indicated by the lack of neuropeptide Y release, why strategies to attenuate the stress response in otherwise healthy children have been debated.[7] Furthermore, a decreased HR may be related to the degree of sedation and/or anesthesia depth.[21] When compared to midazolam, deeper sedation was observed when alpha$_2$-agonists were administered before induction.[10] In the present study, intraoperative anesthesia management was standardized without differences in the administered anesthetics. Thus, compared to midazolam, a decreased HR was observed during surgery with clonidine and dexmedetomidine, which suggests that alpha$_2$-agonists may provide deeper sedation when combined with propofol/remifentanil anesthesia. Morris et al.[22] examined the effects of premedication on anesthesia depth using bispectral index (BIS) and suggested that clonidine might reduce the requirement for propofol. The authors of the study[22] considered that this finding was a pharmacokinetic effect rather than a pharmacodynamic central sedative effect. Nevertheless, the present results suggested that alpha$_2$-agonists may be better than midazolam in preventing induction-induced and intubation-induced stress responses.

Safety of the Interventions

Nine mild AEs were recorded in the study, and no significant differences were observed between the groups. The cases of obstructive breathing immediately after extubation were brief, and mild bradycardia during anesthesia induction responded promptly to atropine administration. Clonidine may induce hypotension and bradycardia, although no serious adverse effects have been reported in children with clonidine doses <10 mcg/ kg^{-1}.[23] However, in the present trial, a minor reduction in HR occurred after treatment with clonidine (4 mcg/kg^{-1}). The present study results alone do not justify recommending atropine administration after clonidine; however, remaining vigilant and closely monitoring the HR at induction may be advisable. No bradycardia AEs were detected after dexmedetomidine treatment. Iirola et al.[24] suggested that the intranasal administration of dexmedetomidine may avoid high peak plasma levels, and thus contribute to the reported complex hemodynamic effects of dexmedetomidine. The minor and mild recorded AEs are in line with those in previous studies suggesting that off-label oral clonidine and intranasal dexmedetomidine may be safely used as premedications in children, as previously reported in adults.[25,26]

Limitations and Future Research

The study groups were homogenous in terms of patient characteristics (sex, age, weight, and baseline parameters), as well as anesthesia and surgical variables (e.g. anesthesia protocol, drug doses, procedure, and time of surgery). However, the anesthesia depth was not monitored. BIS may have enabled a more reliable comparison of the hemodynamic responses during anesthesia and surgery by ensuring comparable anesthesia depths. However, in this study, other biases may have been introduced such as greater fluctuations in anesthesia depth. The present study was a single-center study with relatively small sample size, thereby making obtaining any deductive evidence regarding the safety of the interventions difficult. However, the purpose of this study was not to establish the safety profile of the interventions as larger randomized controlled trials would be required.

Conclusion

Compared to midazolam, deeper sedation and minor cardiorespiratory effects were observed after clonidine and dexmedetomidine. Dexmedetomidine as a premedication may cause a mild decrease in RR, and clonidine and dexmedetomidine can both cause a decrease in the HR, compared to midazolam. Midazolam appeared to maintain the cardiorespiratory baseline throughout the perioperative process, and to have a rapid cardiorespiratory recovery profile. Even though this is based on a rather small cohort, midazolam, clonidine and dexmedetomidine appear to be safe to use for premedication of preschool children with an ASA of I–II who are scheduled for routine ENT surgery with remifentanil/propofol anesthesia.

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