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ORIGINAL RESEARCH

Preoperative Anxiolytic and Sedative Effects of Intranasal Remimazolam and Dexmedetomidine: A Randomized Controlled Clinical Study in Children Undergoing General Surgeries

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Purpose: Remimazolam, an ultra-short-acting and fast-metabolized sedative, has only been sporadically investigated in children. This study was performed to determine the beneficial effects of intranasal remimazolam or dexmedetomidine on preoperative anxiety in children undergoing general surgeries.

Patients and Methods: Ninety children were randomly and equally assigned to Group R (intranasal remimazolam 1.5mg kg^{-1}), Group D (intranasal dexmedetomidine 2 mcg kg^{-1}), and Group C (intranasal distilled water). The primary outcomes were the preoperative anxiety scores using the modified Yale preoperative anxiety scale (m-Ypas). The secondary outcomes included the cooperation behaviour of intranasal drug application, preoperative sedation levels, parental separation anxiety scores (PSAS), and mask acceptance scores (MAS).

Results: Group R showed a significant low anxiety at 10 min after intranasal premedication (vs group C, P=0.010; vs group D, P = 0.002) and at anaesthesia induction (vs group C, P = 0.004). Group D showed a significantly low anxiety score only prior to anaesthesia induction (vs group C, P = 0.005). Most children in group R achieved mild sedation at 10 min (vs group C, P < 0.001; vs group D, P < 0.001), with a few progressing to deep sedation afterwards, while group D tended toward deep sedation. Compared to Group C, patients in Group R performed significantly better on the MAS (P = 0.014) and PSAS (P = 0.008). However, remimazolam did cause poor cooperation behavior to the intranasal application due to its mucosal irritation (vs group C, P = 0.001; vs group D, P = 0.010).

Conclusion: Both intranasal remimazolam and dexmedetomidine can effectively alleviate preoperative anxiety in children. While intranasal remimazolam has a rapid onset, it produces only mild sedation and causes substantial nasal irritation.

Trial Registration: NCT 04720963, January 22, 2021, ClinicalTrials.Gov.

Keywords: dexmedetomidine, paediatrics, preoperative anxiety, premedication, remimazolam

Introduction

Preoperative anxiety is a psychological and physiological stress syndrome in response to upcoming surgeries. It has a profound influence on anesthesia performance and surgical outcomes, such as longer hospitalization period, more pain, and long-term behavioral problems.[1] Pharmacological approach is the most commonly used method for mitigating preoperative anxiety.

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In pediatric patients, premedication via oral/nasal route is preferred for its needle-free advantage, and on the top of that, the intranasal approach has higher bioavailability because of its bypass of hepatic metabolism.[2] Intranasal dexmedetomidine at 2mcg kg^{-1} is widely used for preoperative anxiolysis in children due to its ability to provide adequate sedation, no amnesia, lower incidence of emergence delirium, and fewer perioperative respiratory adverse events.[3] However, its slow onset of sedative action, prolonged recovery time, and other adverse effects (eg, bradycardia) have served as limitations, restricting its broader application.[4,5]

Remimazolam is an ultra-short-acting benzodiazepine. It can be rapidly metabolized to inactive compounds by tissue esterase enzyme.[6] This drug is made by combining midazolam and remifentanil and incorporating carboxylic ester linkage.[7] Unlike other benzodiazepines, intravenous administration of remimazolam has a faster onset time with a shorter elimination half-life. In addition, remimazolam causes less respiratory and hemodynamic depression and its sedation effect can be quickly reversed with flumazenil if necessary.[8] A pharmacokinetic study in healthy adult volunteers showed that the bioavailability of intranasal remimazolam is approximately 25–50%.[9] A recent dose-exploration study has reported that the intranasal remimazolam can rapidly and effectively alleviate preoperative anxiety levels in children.[10] However, there is currently a lack of randomized controlled trials (RCTs) to verify the sedative effect of intranasal remimazolam in this specific population. This study was performed to determine the beneficial effects of intranasal remimazolam or dexmedetomidine on preoperative anxiety in children undergoing general surgeries.

Materials and Methods

Study Design

This prospective, double-blind, randomized controlled trial was performed at the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University between February 7, 2021, and February 28, 2022. The study was approved by the Institutional Review Board (IRB) of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (No.LCKY 2020-426, December 22, 2020) and written informed consent was obtained from the parents or legal guardians of all subjects participating in the study. The trial was registered prior to patient enrolment at ClinicalTrials.Gov (NCT 04720963, January 22, 2021). This study followed the principles of the Declaration of Helsinki and Consolidated Standards of Reporting Trials (CONSORT) Guidelines.[11] We have obtained approval from our Hospital Ethics Committee to conduct a remimazolam study in pediatric patients, given that the use of this drug in this population is considered off-label in China. Relevant national laws and regulations were strictly followed in this research project.

Study Population

Inclusion Criteria

Male and female children with American Society of Anesthesiologists (ASA) physical status I or II, aged 2–5 years old, weight for age between the 25th and 75th percentiles[12] who were scheduled for general surgery under general anesthesia were eligible in this clinical trial.

Exclusion Criteria

Children who had gastrointestinal, cardiovascular, or endocrine dysfunction, had a contraindication to preoperative sedation or had a known allergy or a hypersensitive reaction to either remimazolam or dexmedetomidine or has any nasal pathology, organ dysfunction; Children who recently had a respiratory infection (2 weeks), mental disorder, and developmental delay. Additionally, children may be excluded if they were under specialized care or lived in social welfare institutions, or any other factors that could affect their ability to participate in the study.

Data Collection

A CRF (case report form) was designed for registration of clinical data. Data were stored in a password-protected computer for the concealment of patients' confidentiality. The guidelines of GCP (good clinical practice) were closely followed during the study. One investigator was specifically assigned to the job for data collection, filing, and transfer and another one verified the data's accuracy and safety.

Randomization and Study Blindness

Randomization sequences were generated by researcher via computer program, and group allocation was sealed in opaque envelopes. Ninety children were randomly and equally divided into the groups of remimazolam (R), dexmedetomidine (D), and distilled water (C).

Personnel involved in this study included: (1) A well-trained anesthesiologist, who only administrated intranasal medicines and evaluated the drug acceptance in pediatric patients. (2) An independent assessor was well-trained and was responsible for measuring different scales, including the modified Yale preoperative anxiety scale (m-Ypas) and Ramsay Sedation Scale (RSS), parental separation anxiety scale (PSAS), mask acceptance score (MAS) and post-anesthesia emergence delirium (PAED). This assessor was instructed not being present at and 5 minutes after drug administration to minimize the potential of un-blinding the study caused by remimazolam-induced nasal irritation. Baseline data for the m-Ypas and Ramsay Sedation Scale were obtained prior to drug administration. (3) A data recorder was designated for entering data into the CRF in real time. (4) Another anesthesiologist who only performed the anesthesia during surgeries. (5) A designated investigator who prepared and labelled the medication was not involved in any other study steps. All above individuals and the patient and their families were totally blinded to the grouping of patients.

Study Doses and Preparation of Remimazolam and Dexmedetomidine

Intranasal remimazolam at 1.5 mg kg^{-1} was used in this study based on our pilot study. This selected dose was also validated by recent results from an intranasal remimazolam dose-finding study.[10] Dexmedetomidine 2 mcg kg^{-1} has been used in our daily clinical practice as it provides adequate anxiety reduction and sedation.[13]

The applying volume of intranasal drug or distilled water was set to 0.03mL per kg. All the study drugs (remimazolam, dexmedetomidine) or the distilled water were prepared by an independent pharmacist. Stock solutions of the drugs were prepared as follows. The powder of remimazolam besylate (Yichang Humanwell Pharmaceutical Co., Ltd) was dissolved in water to 50mg.mL^{-1} referred to the previous study.[9] The stock solution of dexmedetomidine (100 mcg mL^{-1}) was diluted with distilled water by 1:2 ratio to 66.7 mcg mL^{-1}. Children in Group C were treated similarly with 0.03 mL kg^{-1} distilled water as a control treatment. Allocated medication was added to numbered participant packs by pharmacists independent of the team. In this way, the study medication was identical in color, and shape and was dispensed in identical containers to conceal the identity of the study drug.

Study Protocol

Children and their families were informed in detail about this study, and a written informed consent was obtained from the parents or legal guardians of enrolled children in the trial. All children were confirmed to meet ASA fasting guideline.

The time course from premedicated administration to anesthesia induction was set to about 30 min based on a study by Pesic M,[9] which showed that the peak effects of remimazolam via the intranasal administration route in healthy adult volunteers were achieved within 10 to 20 minutes for lower doses and over 30 minutes for higher dose (40 mg). Previous studies have confirmed the onset time for intranasal dexmedetomidine was approximately 25 min.[14]

Approximately 30 min prior to anesthesia induction, patients received intranasal 2% lidocaine in a volume of 0.2mL per nostril to alleviate the possible burning sensations inflicted by intranasal medication.[15,16] Then, intranasal pre-meds in a volume of 0.03mL kg^{-1} (1.5 mg kg^{-1} for remimazolam; 2 mcg kg^{-1} for dexmedetomidine) or distilled water were given according to the group assignment. All children were allowed to watch cartoon videos accompanied by one of parents or guardians after being pre-medicated.[17] Heart rate (HR) and pulse oximetry were monitored during the period of premedication.

Continuous electrocardiography and pulse oximetry, blood pressure, and HR were monitored and recorded every 5 min starting from anesthesia induction to the end of anesthesia. Anesthesia was induced with 8% sevoflurane in 100% oxygen at flow rate of 6 L min^{-1} and then, peripheral IV access was established. Intravenous fentanyl (2–3 mcg kg^{-1}), propofol (2.0 mg kg^{-1}) and rocuronium (0.6 mg kg^{-1}) were administered to facilitate tracheal intubation or laryngeal mask airway (LMA) insertion. The mode of pressure controlled mechanical ventilation was started to achieve an end-tidal level of $PaCO_2$ at 35 to 45 mmHg. The depth of anesthesia was maintained at 1–1.5 MAC with sevoflurane in 50% oxygen/air mixture at a constant 2 L min^{-1} flow rate. Additional fentanyl 1–2 mcg kg^{-1} was administered if needed at the discretion of the anesthesiologist.

At the end of surgery, sevoflurane was discontinued, and oxygen flow was increased to 5 L min^{-1}. The muscle blockade was reversed with neostigmine 0.02 $mg.kg^{-1}$ and atropine 0.01 $mg.kg^{-1}$. When patients regained regular and spontaneous breathing and voluntary body movement, the endotracheal tube or LMA was removed. Then, the children were transferred to the post-anesthesia care unit (PACU).

Patients were discharged from PACU once the discharge criteria were met (Aldrete score 9 had been reached).

Hypotension (SBP < 70mmHg + 2 times age in years) was treated with Ephedrine, and bradycardia (HR <70 $beats.min^{-1}$) was treated with atropine.

Primary Outcome

Anxiety Assessment

Preoperative anxiety was assessed by Modified Yale Preoperative Anxiety Scale (m-Ypas)[18] at the time before premedication, 10 min and 20 min after intranasal premedication, and at the time prior to anesthesia induction. The m-Ypas consists of 27 items in five categories, including activity, emotional expressivity, state of apparent arousal, vocalizations, and use of parents.[18] All m-Ypas categories have good validity and good to excellent inter- and intra-observer reliability. Because the number of items are different among categories (either four or six), partial weights were calculated and then added to a total score, and the final adjusted score range is from 23.3 to 100, with a higher score indicating higher anxiety.[18] The "satisfactory" m-Ypas score was defined as less than 30.[19]

Secondary Outcomes

Sedation Assessment

Preoperative sedation was assessed by the scores of Ramsay Sedation Scale (RSS) (Supplementary Table S1) and the observation times were same as the anxiety assessment. A score of RSS 2–3 is defined as light sedation and a satisfactory status as anesthesia premedication, while RSS≥4 indicates asleep status.[20,21]

The Acceptance of Intranasal Medications; Parental Separation Anxiety and Mask Acceptance Scale

The 4-point behavior score (BS) reflexed the degree of cooperation to intranasal premed administration in a child (Supplementary Table S1).[22] The 4-point parental separation anxiety scale (PSAS) was used to assess the children's response when they were taken away from parents (Supplementary Table S1).[23] A four-point mask acceptance score (MAS) was used to grade the behavior when a face mask was placed over the patient's nose and mouth at the beginning of inhalation induction (Supplementary Table S1), a score of 1 and 2 were considered "satisfactory".[23] A survey rating the premedication outcomes respectively by parents and attending anesthesiologist were assessed by a 3-point scale: very satisfied, satisfied, dissatisfied.[24,25]

Emergence Agitation from Anesthesia

An incidence of emergence agitation (EA) or delirium during anesthesia recovery was diagnosed when a score on the scale of post-anesthesia emergence delirium (PAED) (Supplementary Table S2) was ≥10.[26] EA was treated with fentanyl 0.5 $\mu g.kg^{-1}$ or propofol 1 $mg.kg^{-1}$ whenever necessary.

The Emergence Time and Recovery Time, and Other Side Effects

The emergence time (defined as from the end of anesthesia to spontaneous eye opening in PACU) and the recovery time (defined as from the end of anesthesia to the point of discharge from the PACU) were recorded. Post-operative nausea and vomiting were also documented.

Statistical Analysis

Sample Size

Previous study showed that the average scores of m-Ypas in children without premeds before anesthesia induction was 57.4 ± 18.1.[27] We assumed a 15-point reduction in m-Yas between the intervention and control groups. With a significance level of 0.05 ($\alpha = 0.05$) and a statistical power of 80% ($\beta = 0.20$), it was necessary to include a minimum of 27 patients in each group. For a potential 10% drop-out, the final sample size should be 30 in each group for a total of 90 patients in this clinical trial.

Data Analysis

The data were analyzed using SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality and homogeneity of variances of data were tested by using Shapiro–Wilk test and Levene's test respectively. Continuous variables with normal distribution were presented as mean ± standard deviation (SD); nonnormal variables were reported as median (interquartile range (IQR)). If variances were homogeneous, comparison of multiple groups was performed by one-way ANOVA, followed by Bonferroni post-hoc analysis; otherwise, data were analyzed with a Welch-ANOVA, followed by a Games-Howell post-hoc analysis. Non-normally distributed variables were analyzed using the Kruskal–Wallis test, followed by the Dunn's post-hoc test. Categorical variables are presented as number and percentage and their inter-group comparison was performed by Chi-square test or Fisher's exact test. The preoperative pre-dosing baseline data was compared with post-dosing data by repeated measures ANOVA. For continuous variables, mean difference or median difference were calculated. Median differences with 95% CI were calculated using Hodges-Lehmann estimates. For categorical outcomes, logistic regression models were computed with odds ratio (OR) and 95% CI. All statistical tests were two-sided, and a P value of <0.05 was considered significant. For pair-wise comparisons between the three groups, the Bonferroni correction was adopted, and the corrected P value was 0.0167 (corrected P = 0.05/3≈0.0167).

Results

The patients in the study were consecutively recruited from February 2021 to February 2022. Ninety children were randomly allocated and were included for the final analysis (Figure 1), and all children were categorized as ASA I. The premedication course (median [interquartile range]) for Group R, Group D, and Group C were 23.50 [21.00, 27.00], 25.00 [22.00, 30.00], and 23.50 [21.75, 25.00] minutes, respectively. No statistically significant differences in premedication times were found between the groups (*P*=0.076). The surgical type, including hernia repair, hydrocele, superficial

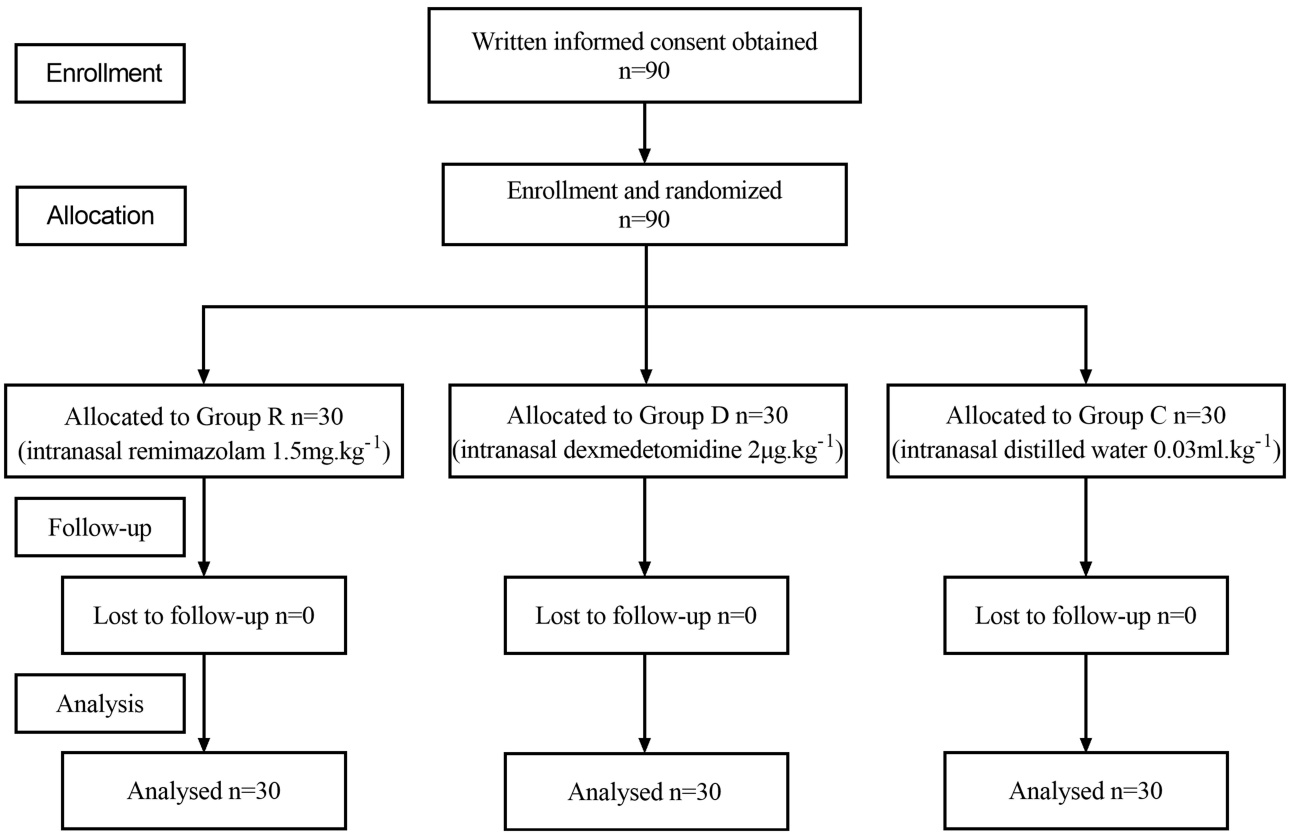

Figure 1 Consort flow diagram.

Table 1 Subject Characteristics and Clinical Data

	Group R (n=30)	Group D (n=30)	Group C (n=30)
Sex (Male/Female)			
Male n, %	25 (83.33%)	24 (80%)	23 (76.67%)
Female n, %	5 (16.67%)	6 (20%)	7 (23.33%)
Age (yr)	3.82 (2.68, 4.71)	3.48 (2.87, 4.64)	4.01 (2.88, 4.57)
Weight (kg)	16.00 (14.75, 17.25)	16.45 (13.75, 19.63)	16.50 (14.95, 19.40)
Type of surgery			
Inguinal hernia repair n, %	11 (36.67%)	15 (50%)	10 (30%)
Hydrocele n, %	12 (40%)	10 (33.33%)	7 (23.33%)
Superficial benign masses n, %	3 (10%)	2 (6.67%)	3 (10%)
Orchidopexy n, %	1 (3.33%)	2 (6.67%)	5 (16.67%)
Others n, %	3 (10%)	1 (3.33%)	5 (16.67%)
Anesthesia time (min)	42.50 (29.75, 52.25)	42.00 (35.00, 53.50)	41.50 (29.00, 80.50)
Surgery time (min)	23.50 (16.75, 34.25)	28.50 (23.00, 33.25)	24.50 (14.50, 50.00)
Premedication time (min)	23.50 (21.00, 27.00)	25.00 (22.00, 30.00)	23.50 (21.75, 25.00)
Fentanyl consumption (mcg)	40.00 (39.50, 45.00)	40.00 (35.00, 50.00)	40.00 (40.00, 50.00)

Note: Data are expressed as median (IQR [range]) or number (proportion).

benign masses, concealed penis and orchidopexy etc., were not significantly different among the three groups. There were no significant differences among groups as concerns of demographic characteristics or baseline data. (Table 1).

Primary Outcome

Anxiety Assessed by m-Ypas

Results of m-Ypas score (median [interquartile range]) are depicted in Figure 2. At 10 minutes after drug administration, patients in group R showed a lowed m-Ypas scores (23.33 [23.33–31.66]) compared to Group D (36.67 [23.33–41.67]; median difference, −10.00; 95% CI, −13.34 to −1.66; *P*=0.002) and Group C (35.84 [23.33–45.42]; median difference, −6.66; 95% CI, −13.34 to 0.00; *P*=0.010), and maintained a lower anxiety level (23.33 [23.33–28.33]) up till the anesthesia induction (vs group C; 34.17 [23.33–43.75]; median difference, −8.34; 95% CI, −13.34 to 0.00; *P*=0.004). While, only at prior to anesthesia induction did group D (23.33 [23.33–23.33]) exhibit a statistically significant lower m-Ypas scores compared to Group C (34.17 [23.33–43.75]; median difference, −8.34; 95% CI, −13.34 to 0.00; *P*=0.005). No other statistically significant differences in m-Ypas scores were observed between Group R and Group D at any other time points during the study.

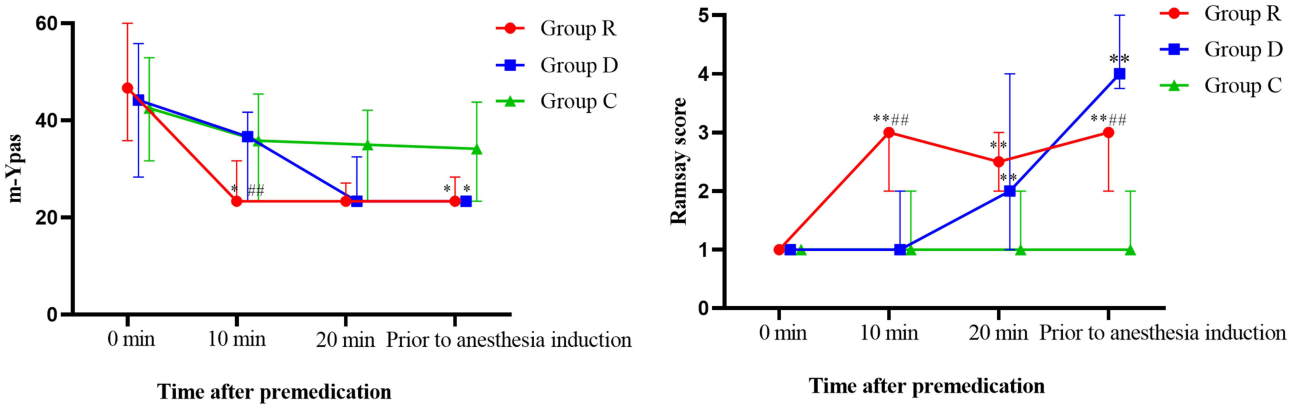

Figure 2 Ramsay score and m-Ypas after drug administration. Compared with Group C, *P<0.05/3, **P<0.01/3; compared with Group D, ##P<0.01/3.

The Group R had higher proportions of satisfactory m-Ypas scores than the Group C at 10 minutes after drug administration (73.33% vs 40%; odds ratio, 4.13; 95% CI, 1.39 to 12.27; $P = 0.010$) until anesthesia induction (80% vs 40%; odds ratio, 6.00; 95% CI, 1.89 to 19.04; $P=0.001$). In contrast, only at prior to anesthesia induction Group D showed higher proportions of satisfactory m-Ypas scores than Group C (83.33% vs 40%; odds ratio, 7.50; 95% CI, 2.24 to 25.06; $P<0.001$). The Group R had significantly higher proportions of satisfactory m-Ypas scores than the Group D (73.33% vs 30%; odds ratio, 6.42; 95% CI, 2.08 to 19.76; $P=0.001$) at 10 minutes after drug administration, with no significant difference between the two groups for the rest of the premedication period. Detailed information is included in Table 2.

Secondary Outcomes

Sedation Assessed by RSS

The results of RSS (median [interquartile range]) were presented in Figure 2. At 10 minutes after drug administration, patients in group R quickly showed a significant deeper sedation level (3.00 [2.00, 3.00]) compared to Group C (1.00 [1.00, 2.00]; mean difference, 1.00; 95% CI, 1.00 to 2.00; $P<0.001$), and maintained a mild sedation level (3.00 [2.00, 3.00]) up till the anesthesia induction (vs group C; 1.00 [1.00, 2.00]; mean difference, 1.00; 95% CI, 1.00 to 2.00; $P<0.001$). While, the difference in sedation levels between group D (2.00 [1.00, 4.00]) and group C (1.00 [1.00, 2.00]; mean difference, 1.00; 95% CI, 0.00 to 2.00; $P<0.001$) was observed starting at 20 minutes after drug administration. Group R (3.00 [2.00, 3.00]) had higher RSS scores than group D (1.00 [1.00, 2.00]; mean difference, 1.00; 95% CI, 1.00 to 2.00; $P<0.001$) at 10 minutes after administration, but lower scores (3.00 [2.00, 3.00]) than group D (4.00 [3.75, 5.00]; mean difference, −2.00; 95% CI, −2.00 to −1.00; $P<0.001$) at prior to anesthesia induction.

The results for sedation depth are reported in Table 2. After intranasal drug administration, most patients in group R had achieved a level of mild sedation at 10 min compared to other two groups (group R vs group C, odds ratio, 11.90; 95% CI, 3.46 to 40.92; $P<0.001$; group R vs group D, odds ratio, 10.23; 95% CI, 3.02 to 34.70; $P<0.001$), and remained at mild sedation level to the point of anesthesia induction (group R vs group C, odds ratio, 16.43; 95% CI, 4.47 to 60.42; $P=0.001$) except a few had slipped into deep sedation. Only one-third of patients in group D achieved mild sedation at 10 min, and many quickly converted into deep sedation at 20 min. More than 75% of patients in group D fell into the category of deep sedation at the time of anesthesia induction (group D vs group C, odds ratio, 81.28; 95% CI, 15.11 to 437.11; $P<0.001$; group R vs group D, odds ratio, 0.07; 95% CI, 0.02 to 0.24; $P<0.001$).

The Acceptance of Intranasal Medications; Parental Separation Anxiety and Mask Acceptance Scores

Patients had significantly lower scores of the behavior score during intranasal medications in group R (30%) than those in group D (63.33%; odds ratio, 0.25; 95% CI, 0.08 to 0.73; $P=0.010$) and C (73.33%; odds ratio, 0.16; 95% CI, 0.05 to 0.48; $P=0.001$). Patients in both R (86.67%) and D (80%) groups showed higher satisfaction rate on PSAS, with only group R reaching statistical significance compared to group C (56.67%; odds ratio, 4.97; 95% CI, 1.39 to 17.82; $P=0.008$).

Table 2 Ramsay Score (RSS) and m-Ypas After Drug Administration

	Group R (n=30)	Group D (n=30)	Group C (n=30)	*P*	Odds Ratio (95% CI)		
					Group R vs D	Group R vs C	Group D vs C
Satisfactory m-Ypas (n, %)							
0min	4 (13.33%)	8 (26.67%)	6 (20%)	0.488	0.42 (0.11, 1.60)	0.62 (0.16, 2.45)	1.45 (0.44, 4.86)
10min	22 (73.33%)*##	9 (30%)	12 (40%)	0.002	6.42 (2.08, 19.76)	4.13 (1.39, 12.27)	0.64 (0.22, 1.87)
20min	24 (80%)**	20 (66.67%)	12 (40%)	0.005	2.00 (0.62, 6.47)	6.00 (1.89, 19.04)	3.00 (1.05, 8.60)
Prior to anesthesia induction	24 (80%)**	25 (83.33%)**	12 (40%)	<0.001	0.80 (0.22, 2.97)	6.00 (1.89, 19.04)	7.50 (2.24, 25.06)
RSS (No/Mild/Deep)[a]							
0min	27/3/0	26/4/0	26/4/0	1.000	0.72 (0.15, 3.55)	0.72 (0.15, 3.55)	1.00 (0.23, 4.43)
10min	5/24/1**##	20/10/0	21/9/0	<0.001	10.23 (3.02, 34.70)	11.90 (3.46, 40.92)	1.17 (0.39, 3.47)
20min	4/23/3**	10/8/12**	19/11/0	<0.001	0.74 (0.28, 1.95)	12.14 (3.38, 43.60)	5.50 (1.94, 15.59)
Prior to anesthesia induction	4/22/4**##	2/5/23**	21/9/0	<0.001	0.07 (0.02, 0.24)	16.43 (4.47, 60.42)	81.28 (15.11, 437.11)

Notes: Data are expressed as median (IQR [range]) or number (proportion). Compared with Group C, *$P<0.05/3$, **$P<0.01/3$; compared with Group D, ##$P<0.01/3$. [a]RSS 1 is defined as NO sedation, RSS 2–3 is defined as Mild sedation, RSS≥4 is defined as Deep sedation.

Patients in group R and D had recorded better MAS when a face mask was placed to patient's nose and mouth than group C (group R vs group C, odds ratio, 3.71; 95% CI, 1.38 to 10.00; *P*=0.014; group D vs group C, odds ratio, 3.69; 95% CI, 1.40 to 9.73; *P*= 0.005), while no significant difference between the R and D groups was founded. Detailed information is included in Table 3.

Emergence Agitation (EA) by PAED Scale; Emergence Time; Recovery Time

In contrast to groups R and C, children in group D exhibit a trend toward a reduced incidence of EA, but experience prolonged emergence time (group R vs group D, median difference, −16.00; 95% CI, −26.00 to −9.00; *P*<0.001; group D vs group C, median difference, 16.00; 95% CI, 8.00 to 25.00; *P*=0.001, Table 4) and significantly delayed anesthesia recovery (group R vs group D, median difference, −16.00; 95% CI, −25.00 to −8.00; *P*<0.001; group D vs group C, median difference, 15.00; 95% CI, 5.00 to 24.00; *P*=0.003, Table 4).

Preoperative HR

There was no significant change of HR in group R compared to group C after intranasal premed was given. HR in group D had dropped at 10 min after premedication (group R vs group D, mean difference, 12.90; 95% CI, 5.85 to 19.95; *P*<0.001) and continued lowering further at the time starting anesthesia induction (group R vs group D, mean difference, 19.17; 95% CI, 12.73 to 25.60, *P*<0.001; group D vs group C, mean difference, −19.03; 95% CI, −25.29 to −12.77; *P*<0.001). Detailed information is included in Supplementary Table S3.

Table 3 Perioperative Assessments

	Group R (n=30)	Group D (n=30)	Group C (n=30)	*P*	Odds Ratio (95% CI)		
					Group R vs D	Group R vs C	Group D vs C
Satisfactory BS n,%	9 (30%)**#	19 (63.33%)	22 (73.33%)	0.002	0.25 (0.08, 0.73)	0.16 (0.05, 0.48)	0.63 (0.21, 1.88)
Satisfactory PSAS n,%	26 (86.67%)*	24 (80%)	17 (56.67%)	0.023	1.63 (0.41, 6.47)	4.97 (1.39, 17.82)	3.06 (0.97, 9.66)
MAS n,%				0.010	0.82 (0.32, 2.06)	3.71 (1.38, 10.00)	3.69 (1.40, 9.73)
Excellent	6 (20%)*	11 (36.67%)*	2 (6.67%)				
Good	16 (53.33%)*	8 (26.67%)*	10 (33.33%)				
Fair	5 (16.67%)*	9 (30%)*	11 (36.67%)				
Poor	3 (10%)*	2 (6.67%)*	7 (23.33%)				
Satisfactory score of anesthesiologists n, %				0.004	1.22 (0.74, 3.18)	5.41 (1.87, 15.70)	3.57 (1.32, 9.64)
Very satisfied	13 (43.33%)**	13 (43.33%)*	4 (13.33%)				
Generally satisfied	14 (46.67%)**	11 (36.67%)*	14 (46.67%)				
Dissatisfied	3 (10%)**	6 (20%)*	12 (40%)				
Satisfactory score of parents n,%				0.095	0.74 (0.27, 2.00)	2.14 (0.80, 5.74)	2.93 (1.07, 8.05)
Very satisfied	15 (50%)	17 (56.67%)	10 (33.33%)				
Generally satisfied	13 (43.33%)	12 (40%)	15 (50%)				
Dissatisfied	2 (6.67%)	1 (3.33%)	5 (16.67%)				

Notes: Data are expressed as number (proportion). Compared with Group C, *P<0.05/3, **P<0.01/3; compared with Group D, #P<0.05/3.
Abbreviations: BS, behavior score; PSAS, parental separation anxiety scores; MAS, mask acceptance scale.

Table 4 Postoperative Assessments

	Group R (n=30)	Group D (n=30)	Group C (n=30)	P
Emergence delirium n, %	9 (30%)	5 (16.67%)	10 (33.33%)	0.412
Emergence time (min)	22.00 (17.50, 37.75)##	44.50 (30.00, 55.25)	25.00 (21.75, 30.25)##	<0.001
Recovery time (min)	34.50 (28.00, 44.75)##	56.00 (39.00, 64.00)	37.00 (29.75, 40.75)##	0.001

Notes: Data are expressed as median (IQR [range]) or number (proportion). Compared with Group D, ##P<0.01/3.

Premedication Satisfaction Scores and Other Adverse Effects

Both the group R and D had higher satisfactory scores for anesthesiologists than the group C (group R vs group C, odds ratio, 5.41; 95% CI, 1.87 to 15.70; P=0.002; group D vs group C, odds ratio, 3.57; 95% CI, 1.32 to 9.64; P=0.009), but there was no difference between the groups R and D. There were no differences in satisfactory scores of parents among the three groups. Twenty-four children (80%) in Group R reported discomfort or burning sensation during intranasal premedication, significantly higher than the other two groups, where no such discomfort was reported (group R vs group D, P<0.001; group R vs group C, P<0.001). One child developed vomiting during premedication in Group R. Two patients in group R experienced postoperative nausea and vomiting (PONV), compared with one in group D and two in group C. Two children developed bradycardia in Group D and one of them was treated with atropine when HR was below 65 bpm. No psychological, psychiatric, and other side effects were observed.

Discussion

Compared to the control group, both intranasal remimazolam and dexmedetomidine can effectively alleviate preoperative anxiety in children. This study showed intranasal remimazolam dosed at 1.5mg kg^{-1} provides rapid onset of anxiolysis, with its main pharmacological effects being mild sedation and improved perioperative cooperation in pediatric patients. However, it's worth noting that intranasal remimazolam may lead to nasal irritation, resulting in poor compliance during intranasal administration. In comparison, intranasal dexmedetomidine of 2 mcg kg^{-1} has a slightly delayed onset of anxiolysis and elicits deeper sedation. However, intranasal dexmedetomidine may prolong emergence from anesthesia and delay post-anesthesia care unit (PACU) discharge.

Preoperative anxiety, as the primary outcome in our study, was measured by m-Ypas. Compared with the "gold standard", State-Trait Anxiety Inventory for Children (STAIC), the advantages of m-Ypas are its good reliability and validity data, and it can be applied both in the preoperative holding area and during induction of anesthesia, and the measurement can be completed in less than one minute.[18] m-Ypas has been validated among children aged 2–12 years by several clinical studies.[28,29]

In this study, we chose a dosage of 1.5 mg kg^{-1} for the intranasal administration of remimazolam, which was based on our preliminary pilot study. The selected dose was supported by recent results from a dose-finding study on intranasal remimazolam.[10] The study suggested that the ED95 of intranasal remimazolam for relieving preoperative anxiety was 1.57 and 1.09 mg kg^{-1} in early childhood children and pre-school children, respectively.

Compared to intranasal dexmedetomidine, intranasal remimazolam has a faster onset time, approximately 10 minutes. A dose exploration study of intranasal remimazolam in children reported similar results.[10] This is consistent with the pharmacokinetic data of intranasal remimazolam in adults, which indicates a T_{max} of 10 minutes.[9] The rapid onset of action observed with intranasal remimazolam is likely due to its pharmacologic properties. The rapid onset of anxiolytic medications is particularly beneficial for children suffering with high preoperative anxiety. Moreover, it can partially alleviate the anxiety felt by the families due to extended preoperative periods. The shorter the preparation, the better it is for children and parents, and anesthesiologist.

Our study revealed that patients in remimazolam group mainly presented mild sedation and rarely displayed an asleep state, while patients in dexmedetomidine group often slipped from mild sedation into deep sedation. Similar phenomena can also be found in another short-acting benzodiazepine, midazolam. A study conducted by Bromfalk et al found that midazolam was more effective of anxiolysis and less of sedation compared to intranasal dexmedetomidine.[30] This may also be attributed to the distinct types of sedation induced by benzodiazepines and dexmedetomidine. Although the depth of sedation with remimazolam was not as deep as dexmedetomidine, both medications showed notable improvements in mask acceptance scores and increased satisfaction rates of PSAS. In this study, the good performance of children in the control group may be attributed to the fact that all groups of children watched cartoons after administration to reduce preoperative anxiety.

In terms of postoperative recovery, there was no difference in the incidence of EA between the remimazolam group and the control group. This may be associated with the short half-life of remimazolam, as the elimination half-life of intranasal remimazolam has been reported to range from 0.7 to 1.2 hours in healthy adults.[9] However, there is a lack of pharmacokinetic data for intranasal remimazolam in children. Continuous infusion of remimazolam in the pediatric population indicated a half-life time of approximately 1.1 hours.[31] These findings suggest that the pharmacological

impact of remimazolam may not persist into the recovery phase in children. In contrast, our study aligns with previous research, emphasizing that preoperative intranasal dexmedetomidine correlates with a reduced incidence of postoperative delirium.[32]

In our study, it was observed that the dexmedetomidine group exhibited a prolonged postoperative emergence time and recovery time. In contrast, intranasal remimazolam does not prolong postoperative recovery time in children, which is another advantage of using remimazolam for preoperative sedation. The delay in emergence from anesthesia caused by dexmedetomidine could be attributed to the relatively long half-life of dexmedetomidine (approximately 2 hours),[33,34] as well as the fact that the majority of surgeries included in this study were minor procedures. The prolonged effect of dexmedetomidine in the recovery area may not be as significant during longer procedures, as it has more time to wear off. Further studies are warranted to clarify the impact of intranasal dexmedetomidine on recovery profiles in pediatric surgical patients undergoing procedures of varying durations.

A prior study in adult volunteers reported that intranasal administration of remimazolam caused some nasal irritation.[9] To mitigate this side effect, this current study applied a topical intranasal smear of lidocaine before intranasal dosing. However, despite this measure, most pediatric patients still experienced nasal discomfort and exhibited poor compliance to intranasal administration. Intranasal remimazolam can cause significant nasal irritation, which might limit its use in children despite its efficacy in relieving anxiety within 10 minutes. This discomfort could be a consideration for healthcare providers when choosing anxiolytic treatments. Additionally, such irritation posed challenges for blinding in the study design. To achieve blinding and reduce subjective bias, this study had the anesthesiologist who only administered intranasal medications and evaluated drug acceptance be present during administration, while the independent assessor responsible for measuring different scales was instructed to not be present within 5 minutes after drug administration. In this study, no statistical differences in satisfactory score of parents were observed among the three groups of pediatric patients. This may be attributed to the rapid onset of action of remimazolam, which could offset any dissatisfaction from parents regarding the nasal irritation caused by remimazolam. Additionally, the uniform strategy of allowing children from all groups to watch cartoons after nasal administration could have increased parents' satisfaction, thereby reducing the differences between groups.

Antonik et al[35] and Schuttler et al[36] have demonstrated that IV remimazolam could increase HR, which was not the case in our intranasal study. HR was trending down in dexmedetomidine group, and treatment was not required since other vital signs remained stable in most scenarios. Two children developed bradycardia in Group D, and only one of them received atropine. One child developed mild nausea and vomiting 5 minutes after intranasal remimazolam and the symptoms went away without intervention. We were unable to root out a clear cause for it since it was alone incident.

Based on the results, intranasal remimazolam showed rapid onset and anxiolytic effect but tended to induce mild sedation, seemingly more suitable for procedures where a quick anxiolytic and less invasive is desired. However, intranasal discomfort with remimazolam administration remains to be resolved before wider clinical application. Notably, the risks of accidental overdose, misuse, and abuse should not be overlooked as intranasal remimazolam can elicit mild sedation. In contrast, intranasal dexmedetomidine exhibited longer half-life and deeper sedative actions, deeming it more appropriate for lengthy surgery or procedures necessitating substantial sedation. Although dexmedetomidine could mitigate postoperative delirium to some degree, delayed arousal following its administration should be heeded when utilized for pre-sedation in minor surgery.

Limitation

The study has some limitations. First, a fixed premedication time course in our protocol may be not an ideal fit because two intranasal pre-meds have different times of onset and the peak action. Secondly, due to the nasal irritability of remimazolam, and participants' family members having been informed of the potential risk of nasal irritation, blinding the participants in this study presents challenges. Nevertheless, this study still tries to achieve double-blind by not disclosing the grouping to the participants' family members and by keeping the assessors absent during drug administration and for 5 minutes after administration. Thirdly, due to the lack of monitoring of muscle relaxation in this study, we cannot rule out the possibility of a sedative effect caused by hypercapnia. Finally, we only focused on clinical events, and future studies of pharmacodynamics and pharmacokinetics should be conducted to substantiate our clinical observations. Also, multiple doses with a range could provide better understanding of the wider spectrum of clinical effects by intranasal remimazolam and dexmedetomidine.

Conclusion

Both intranasal remimazolam and dexmedetomidine can effectively alleviate preoperative anxiety and improve mask compliance young children undergoing inhalational induction of anesthesia. Intranasal remimazolam has a rapid onset, it produces only mild sedation and causes substantial nasal irritation. Intranasal dexmedetomidine provides deeper sedation but slower onset of effect and longer emergence and recovery times.

Abbreviations

ANOVA, Analysis of variance; ASA, American Society of Anesthesiologists; BS, Behavior score; CI, Confidence interval; CRF, Case report form; EA, Emergence agitation; GCP, Good clinical practice; HR, Heart rate; IN, Intranasal; IQR, Interquartile range; IV, Intravenous; LMA, Laryngeal mask airway; MAC, Minimum alveolar concentration; MAS, Mask acceptance scores; MD, Median difference; m-Ypas, Modified Yale Preoperative Anxiety Scale; OR, Odds ratio; PACU, Post-anesthesia care unit; PAED, Post-anesthesia emergence delirium; PSAS, Parental separation anxiety scores; RSS, Ramsay Sedation Scale; SD, Standard deviation.

Data Sharing Statement

The data are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This randomized, double-blind, placebo-controlled clinical trial was approved by the Institutional Review Board (IRB) of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (No.LCKY 2020-426, December 22, 2020) and written informed consent was obtained from the parents or legal guardians of all subjects participating in the study.

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Disclosure

The authors declare that they have no competing interests.

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