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Original work

EFFICACY AND SAFETY OF INTRANASAL MIDAZOLAM, S-KETAMINE, AND DEXMEDETOMIDINE AS PREMEDICATION FOR PEDIATRIC TONSILLECTOMY: A COMPARATIVE STUDY

(PREMEDICATION IN PEDIATRIC TONSILLECTOMY STUDY)

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Abstract

Introduction: *More than 50% of children experience significant preoperative anxiety, which adversely affects anesthetic management and postoperative behavior. Premedication in pediatric patients should facilitate parental separation, venous cannulation, and smooth induction, while minimizing respiratory depression, particularly relevant in children undergoing tonsillectomy for airway obstruction. Intranasal administration offers rapid absorption, predictable effects, and non-invasive delivery. The main goal of this study is to compare the efficacy and safety of intranasal midazolam, S-ketamine, and dexmedetomidine as premedication in children undergoing tonsillectomy under general anesthesia.* ***Methods:*** *In this prospective, randomized study, 90 children aged 1-7 years (ASA I–II) were allocated to three groups (n=30 each) receiving intranasal midazolam (0.2 mg/kg), S-ketamine (0.1 mg/kg), or dexmedetomidine (1 μg/kg), 30 minutes preoperatively. Sedation (Ramsay scale), separation anxiety, and mask acceptance (MAS scale) were assessed. Intraoperative hemodynamics and opioid consumption were recorded. Postoperative sedation (Ramsay), pain (FLACC/FACES scales), and postoperative excitation (PAED scale) were evaluated. Children with sleep apnea or drug allergies were excluded.* ***Results****: No significant differences were observed between groups in separation anxiety or mask acceptance. Intraoperative fentanyl consumption differed significantly, with lower requirements in the S-ketamine group. Significant intergroup differences were also found in systolic blood pressure and heart rate after induction. Postoperative pain scores were significantly lower in children receiving S-ketamine compared with midazolam and dexmedetomidine.* ***Conclusion:*** *Intranasal premedication is effective and safe in pediatric tonsillectomy. S-ketamine provides superior analgesia and reduces intraoperative opioid requirements without compromising sedation or anxiolysis, suggesting it may be a preferable option in this population.*

Key words*: premedication; ORL surgery; S-ketamine; midazolam; dexmedetomidine; intranasal application*

Introduction

Tonsillectomies in children are most often indicated by breathing problems and airway obstruction during a sleep, so as in many other indications[1-3], becoming the one of the most common interventions in children. Absolute indications for tonsillectomy are as follows: hypertrophy of the palatine tonsils causing shortness of breath, recurrent acute infections of the palatine tonsils. Relative indications are: streptococcal germs, recurrent peritonsillar abscesses, chronic/cryptic tonsillitis, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome, tonsillar asymmetry.[4] This kind of ORL surgery in children is very challenging because of sleep apnea being a frequent disturbance, requiring serious supervision and very cautious anesthesia technique. In anxious children, postoperative bleeding is more frequent, which could additionally endanger the child. This is a reason of premedication significance in these children, because of the psychological

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trauma reduction, calm introduction to anesthesia enabling and also a safe awakening preventing the possible complications, primarily related to breathing and bleeding.[5,6] Anxiety and psychological trauma as a result of separation from the mother and new, often painful experiences, are a major challenge in pediatric anesthesia and more than 50% of children show signs of significant preoperative fear and anxiety. Since contact with unknown persons is often traumatic for children, potentiated by an unfamiliar and "threatening" environment, it is important not only to choose the proper medicine, but also the application and person who will perform it. The best choice is for the parent to give this medicine, under the control of the medical staff, because the child trusts him and for the administration to be minimally traumatic.[7] Although the focal point in perioperative phase is a psychological trauma in children, it could also significantly affect the course of anesthesia and postoperative behaviour. Premedication in children is more complicated than in adults, because it should ensure separation from parents, the possibility of placing a venous cannula, which is usually the biggest challenge and a calm introduction to anesthesia.[8] In children, the oral route is often used for premedication, but anatomically adapted nasal applicators enables the nasal route of application also,[9] enabling smaller drug doses and the effect is achieved faster. The anxiolytic and sedative component of the drug is important, but it often coincides with postoperative respiratory depression.[10,11] Accordingly, the most widely used drug is midazolam, orally. The oral route of administration can be unpredictable (uncontrolled), because children can throw out the medicine. Due to stress, resorption can be slowed down and the effect delayed or even undesirably delayed postoperatively.

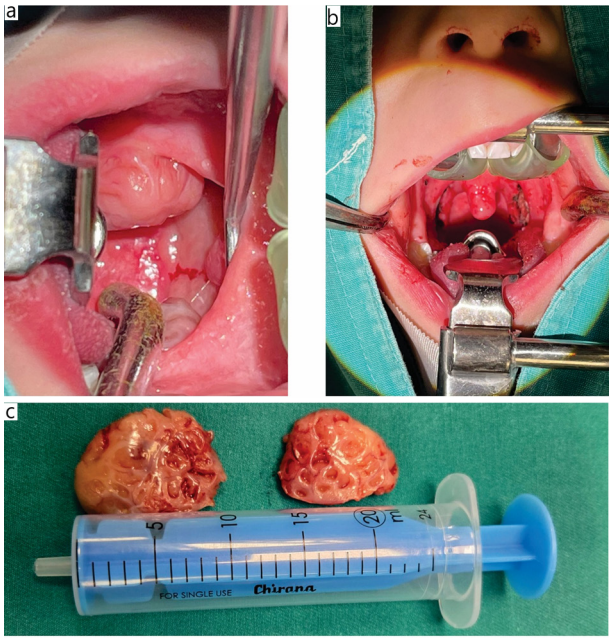
The choice of surgical technique for tonsillectomy depends on the indications for the operation, the age of the patient and the goals of postoperative recovery. Traditionally, tonsillectomy was performed using electrocautery and liquid nitrogen (cryogenic tonsillectomy), which allow for efficient excision of the tonsils, but are associated with significant postoperative pain and slower recovery.[12] The illustration of the tonsillectomy procedure is presented at the Figure 1.

Anesthesiological approach and preparation for tonsilloadenoidectomy

Perioperative preparation in ORL surgery is not only limited to the operation, but also to the patient's overall health condition, implementing individual approach and consistent following of valid guidelines. In preoperative risk assessment, the American Society of Anesthesiologists (ASA) classification provides a general overview of health status. For ORL surgery, the risk is usually low, but in patients with comorbidities, the individual risk must be carefully assessed.[13]

In children who are being prepared for adenotonsillectomy, anesthesia is most often performed with edotracheal intubation, while in isolated adenoidectomies, a laryngeal mask (LMA) is sometimes used. Due to the increased risk of complications in children with obstructive sleep apnea (OSA), a detailed clinical evaluation and insight into possible findings indicating the consequences of OSA (pulmonary hypertension, left ventricular hypertrophy) is recommended. Physical examination must include airway assessment and the possibility of difficult intubation due to macroglossia, retro/micrognathia, hypoplasia of the jaw, limited mobility of the cervical spine, as well as auscultatory examination of the lungs to rule out acute

Figure 1.



a. Pre-tonsillectomy b. Post-tonsillectomy c. Macroscopic view of the tonsiles after the tonsilectomy (author's photo-archive)

respiratory infection. Hospitalization after surgery is advised in children under three years of age, in patients with severe OSA, coagulation disorders, significant comorbidities, or those whose families live far from the hospital. Upper respiratory tract infections are common in children and significantly increase the risk of perioperative respiratory complications (laryngospasm, bronchospasm, hypoxemia). The decision to postpone or perform the procedure in case of more severe symptoms of an upper respiratory tract infection is made by the anesthesiologist in agreement with the surgeon, the patient and the family.[14]

Among the numerous arguments for and against the use of premedication and sedative drugs in children, the principle of reducing the psychological trauma associated with anesthesia and surgery stands out. Premedication must be adapted to each child according to age, body mass, health condition, cognitive abilities, and psychological profile. Relative contraindications for the use of premedication are a problematic airway, central and obstructive sleep apnea, increased intracranial pressure, altered Glasgow coma score, liver or kidney insufficiency, cyanogenic heart defects, neuromuscular diseases.[15] Premedication with midazolam and ketamine are often used and provide adequate sedation in the pediatric population. Midazolam has the advantage of faster onset and shorter recovery, while ketamine shows slightly better separation from the parent with a higher frequency of side effects. Intranasal application enables effective sedation without the need for intravenous access. Alternative drugs, such as α2-agonists (clonidine and especially dexmedetomidine), are gaining more importance, because they provide sedation similar to natural sleep, without impairing memory, with a more stable postoperative course.[16]

The aim of this study was to estimate and compare the efficacy and safety of nasal premedication in children 1-7 years of age, for tonsillectomy under general anesthesia. Midazolam, S-ketamine and dexmedetomidine are used in equivalent doses as nasal premedication drugs. The main hypothesis of our study is that intranasal premedication with midazolam, S-ketamine, and dexmedetomidine differs in efficacy and safety in children aged 1–7 years undergoing tonsillectomy under general anesthesia.

Material and methods

Patients

This prospective, randomized, comparative clinical study included 90 subjects who underwent tonsils surgery under general anesthesia at the Mother and Child Health Care Institute of Serbia "Dr Vukan Čupić" (Belgrade, Serbia). The institutional Ethical Board has approved the protocol in May 2024 (No. of the Ethical Approval 8/157) and also approved the manuscript publication in January 2026 (No. of the Ethical Approval 8/12). Written informed consent was obtained from the parents/caregivers of all study participants, after the main investigator has explained them the goal and methodology of the study.

In accordance with the goal of evaluating the effectiveness and safety of different types of premedication used because of the control of preoperative anxiety, postoperative sedation and pain, all subjects were divided into three groups (n = 30 each), according to the type of nasal premedication: midazolam (0.2 mg/kg BW), S-ketamine (0.1 mg/kg BW) and dexmedetomidine (1 μg/kg BW). Participants were randomly assigned to one of the three study groups using a computer-generated randomization sequence with a 1:1:1 allocation ratio. Group allocation was performed using sequentially numbered opaque sealed envelopes opened immediately before premedication administration.

The children's respiratory and hemodynamic stability after drug administration and the risk of postoperative apnea and occurrence of postoperative excitation were monitored. The inclusion criteria was: age, ASA I and II physical status, absence of allergy-related medical history to prescribed drugs, that the intervention is the first in the child's life, that the intervention is elective and that the parent signs consent for the intervention. Children with proven sleep apnea, were not included in the study because premedication with midazolam is contraindicated for them.

All children were pre-medicated while they were with their parents, 30 minutes before the intervention. A special nasal applicator was used to administer the medicine. We previously instructed the parents about the method of drug administration. Midazolam at a dose of 0.2 mg/kg BW, S-ketamine at a dose of 0.1 mg/kg BW, and dexmedetomidine

1 μg/kg BW were used for premedication. Before drug administration, oxygen saturation and heart rate were measured with a pulse oximeter. About 30 minutes after giving the medicine, the child was separated from the parents and transfer to operating room. Sedation was measured using the Ramsey sedation scale [17], while separation anxiety was also measured using the parental scale[18], as well as the Mask acceptance scale (MAS)[19], which measured the acceptance of the mask for preoxygenation, before introduction to anesthesia. For all interventions general, endotracheal anesthesia was used. Several drugs were used at the end of the intervention to control postoperative pain (propofol, fentanyl, rocuronium bromide and ketoprofen at a dose of 1 mg/kg BW. Hemodynamic parameters and total use of opioids for analgesia were monitored perioperatively. Postoperatively, after extubation, the child was monitored in the recovery room. Postoperative sedation of the child was measured also by the Ramsey scale, immediately after being brought to the recovery room, and then after 10, and 20 minutes. The level of postoperative pain was estimated by using an age-appropriate scale before the child was transferred to the parents.

The Face, Legs, Activity, Cry, and Consolability (FLACC) pain scale for children up to 3 years[20], while FACES scale was used for children from 3 to 7 years.[21] It was noted whether the child had apnoeic crises postoperatively, and the presence and level of postoperative excitation was also noted using the Pediatric Anaesthesia Emergence Delirium (PAED) scale.[22] Patients who did not complete the protocol for any reason were excluded from the study, and all adverse events related to the safety of the drugs used was reported.

The sample size was highly effective for measuring analgesic efficacy, specifically showing that S-ketamine significantly reduced intraoperative fentanyl consumption ($p < 0.001$ with high statistical power (> 99%). Older Children Subgroup (n = 76): For children aged 3–7, the study had sufficient power (88%) to confirm S-ketamine's superiority in pain suppression (FACES scale). Younger Children Subgroup (n = 12): For children under 3, the power was very low (< 50%) due to the small number of participants, making results for this age group less conclusive. The justification of this result is based on vulnerability of this patients' population.

Statistical analysis

The statistical software SPSS (IBM® SPSS®Statistics, version 22, Chicago, USA) and a set of statistical tests was used for statistical data processing. The normality of the distribution was checked by using Shapiro-Wilks test. Different statistical test such as Student's t-test, ANOVA with post-hoc Tukey test, Mann-Whitney U test and Kruskal-Wallis test for continuous and Chi-square test for categorical data were used. Statistical significance is determined at the $p < 0.05$ level.

Results

Between the analysed groups of subjects with different intranasal premedication, no statistically significant difference was observed in the representation of children with different indications for ORL surgery. In all three groups, subjects who underwent tonsillotomy were represented with 83.3% in midazolam premedication group, 80% of children with S-ketamine premedication and 73.3% of children who received dexmedetomidine. Three therapy subgroups didn't differ by gender ratio, with boys' predominance in every group. There were also no significant difference neither in age, nor in BMI, in therapy subgroups (Table 1). The absence of difference in socio-demographic and anthropometric measures enables good groups matching and stronger statistical data validity.

The dose of given muscle relaxant rocuronium bromide, ranging from 0.3 mg/kg - 0.6 mg/kg, didn't differ between the groups of subjects with different nasal premedication. The similar result was for propofol medication, while fentanyl dose in S-ketamin group was significantly lower, compared to the other two groups (Table 1). Presented confidence intervals for fentanyl doses confirmed that the lowest doses were in S-ketamin group (there is no overlapping between these doses in S-ketamin and two other groups). The reduction of fentanyl in the **S-ketamine group** is the most significant result with Cohen's d = 2.1 (large effect size).

Adverse reactions occurrence was homogeneous in three premedication therapy groups, as was the rate of post-surgery apnea incidence and the post-surgery time of apnea occurrence. It is worth mentioning that there were a low incidence of adverse reactions and also low incidence of apnea. Also, it is important to stress that no adverse reactions were noted in the dexmedetomidine group.

Adverse reactions occurred in two children (6.7%) premedicated with midazolam, while in the group with S-ketamine, adverse reactions occurred in four children (Table 1).

Parental separation anxiety and mask acceptance scale were measured with appropriate scales, results are presented at the Table 2 (Table 2).

Results of this part of study didn't confirmed any significant difference in the level of the parental separation anxiety, neither in mask acceptance behaviour. It is important to emphasize that in all three intranasal premedication groups the percent of excellent/good separation behaviour was higher than 70% of children. Midazolam group showed about 23% of children had poor separation anxiety behaviour, but this was not statistically significant. Also about 60% of chidren accepted the mask showing calm/cooperative or after the some reassurance in all three premedication groups. But, about 26%, 23% and 20% children in midazolam,

Table 1. Basic demographic, antropometric and surgery-related clinical patients' data in premedication therapy subgroups

Variable		Midazolam (n = 30)	S-ketamine (n = 30)	Dexmedetomidin (n = 30)	P
ORL surgery indication	Tonsillectomy, n (%)	5 (16.7)	6 (20.0)	8 (26.7)	0.627a
	Tonsillotomy, n (%)	25 (83.3)	24 (80.0)	22 (73.3)	
Gender	Boys, n(%)	21 (70.0)	17 (56.7)	20 (66.7)	0.532a
	Girls, n(%)	9 (30.0)	13 (43.3)	10 (33.3)	
Age (years)		4,1 ± 1,3	4.6 ± 1.5	4.6 ± 1.9	0.290
BMI (kg/m2)		17,9 ± 5,0	17.2 ± 5.1	18.0 ± 3.0	0.346
Surgery duration (minutes)		22.3 ± 6.8	23.83 ± 9.26	21.50 ± 9.84	0.501
Drugs' dosage during surgery					
Propofol bolus (mg/kg)		3.0 ± 0	3.0 ± 0	3.07 + 0.25	0.132
Fentanyl (μg/kg) (95th % confidence interval CI)		3.13 + 0.35 3.01–3.25	2.27 + 0.45*** 2.11–2.43	3.20 + 0.48### 3.03–3.37	<0.001
Rocuronium bromide (mg/kg)		0.47 ± 0.08	0.44 ± 0.12	0.43 ± 0.11	0.192
Adverse reactions	Yes	2 (6.7)	4 (13.3)	0 (0)	0.117a
	No	28 (93.3)	26 (86.7)	30 (100)	
Post-surgery apnea	Yes	0 (0)	3 (10.0)	3 (10.0)	0.200a
	No	30 (100)	27 (90.0)	27 (90.0)	
Post-surgery period of apnea occurrence	Early post-surgery time	0 (0)	3 (100)	2 (66.7)	0.999[a]
	Late post-surgery time	0 (0)	0 (0)	1 (33.3)	

*P from the ANOVA, ***P < 0.001 vs. midazolam group; ###P < 0.001 vs. S-ketamine group Tukey post-hoc test; [a]P from Chi-square test (χ2-test)*

S-ketamin and dexmedetomidine groups, respectively, had experienced significant resistance, crying and mask refusing. Again, it should be stated that these percentages were not statistically significant (Table 2).

Hemodynamic and respiratory parameters

Hemodynamic parameters (systolic and diastolic blood pressure, heart rate) were assessed at four time points: before induction, after induction, intraoperatively, and at the end of surgery. Systolic pressure after induction was significantly higher in the S-ketamine group compared with the other

Table 2. Comparison of the parental separation anxiety and mask acceptance scale in premedication therapy subgroups

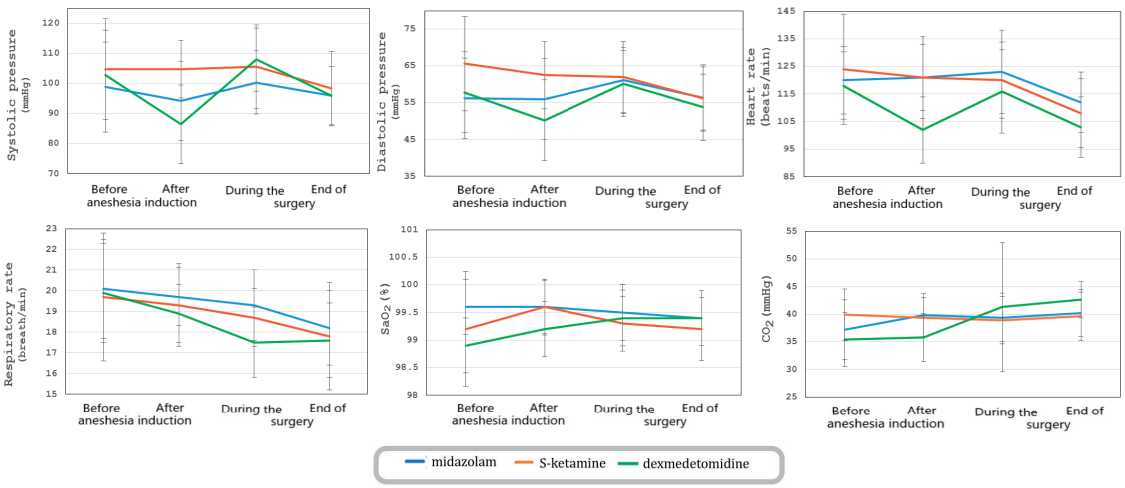
Variable	Midazolam (n = 30)	S-ketamine (n = 30)	Dexmedetomidin (n = 30)	P
Parental separation anxiety scale, n (%)				
Excellent	16 (53.3)	15 (50.0)	11 (36.7)	0.627
Good	5 (16.7)	7 (23.3)	12 (40.0)	
Fair (acceptance with struggle)	2 (6.7)	4 (13.3)	5 (16.7)	
Poor	7 (23.3)	4 (13.3)	2 (6.7)	
Mask Acceptance Scale – children behaviour				
Calm, cooperative	15 (50.0)	16 (53.3)	8 (26.7)	0.532
Cooperative with reassurance	3 (10.0)	5 (16.7)	9 (30.0)	
Moderate fear of mask, not easily calmed	4 (13.3)	2 (6.7)	7 (23.3)	
Significant resistance, crying, severe fear of the mask	4 (13.3)	5 (16.7)	5 (16.7)	
Significant agitation, combative, crying, refusing mask	4 (13.3)	2 (6.7)	1 (3.3)	

P from the Chi-square test (χ^2-test)

groups. All groups showed significant intraoperative changes in systolic pressure, with the largest increase observed in the dexmedetomidine group. Diastolic pressure before and after induction was also significantly higher in the S-ketamine group, while intragroup analysis demonstrated a significant intraoperative decrease in diastolic pressure in the S-ketamine and dexmedetomidine groups. Heart rate was lowest in the dexmedetomidine group after induction and at the end of surgery, with significant decreases observed in both the S-ketamine and dexmedetomidine groups over time. These changes reflect physiological responses to surgical stress.

Respiratory parameters (respiratory rate, oxygen saturation (SaO_2), and $PetCO_2$) were evaluated at the same time points. The dexmedetomidine group exhibited the lowest respiratory rate intraoperatively, with a significant decrease throughout the procedure. SaO_2 was lowest in the dexmedetomidine

Figure 2. Hemodynamic and respiratory parameters during the preoperative, operative and post-operative procedure in children according to premedication subgroups



group before and after induction, and lowest in the S-ketamine group at the end of surgery. Dexmedetomidine was associated with a progressive increase in SaO_2 intraoperatively. CO_2 levels were initially lowest in the dexmedetomidine group but highest at the end of surgery, with the greatest intraoperative increase. All observed changes remained within physiological limits.

Results of haemodynamic and respiratory data are presented at the Figure 2 (Figure 2).

Level of sedation and postoperative excitation at the end of surgery

Level of sedation was estimated by using Ramsey scale. Analysis confirmed that there was no significant difference in the sedation level between three different intranasal premedication therapeutic subgrups. The group premedicated with S-ketamine (47% of children) and dexmedetomidine (40% of children) exhibited Ramsey scale scores 2 i.e. they were alert, cooperative, oriented and calm. The same percentage of children in the dexmedetomidine group (40%) were awake, anxious or restless, or both (Ramsey scale 1), while this level of sedation had 23% of S-ketamin group of children. Children with that level of sedation (Ramsey scale 1) were the most represented in the control group (premedication with midazolam) i.e. 53% of them. Results are presented at the Table 3 (Table 3).

Level of postoperative excitation in this current study was assessed by using the Postoperative Excitation Scale (PAED scale). Our results confirmed the absence of significant difference between the values of the PAED score, neither the distribution of PAED values according to cut-off values categories, in children with different nasal premedication: midazolam, S-ketamine, dexmedetomidine. Mild or no agitation (< 10 points of the PAED scale) had 83% children in midazolam group, 100% in

Table 3. Sedation level (Ramsey scale) and postoperative excitation level (PAED scale) in premedication therapy subgroups

Sedation level – Ramsey scale	Midazolam (n = 30)	S-ketamine (n = 30)	Dexmedetomidin (n = 30)	P
Patient is awake, anxious and agitated or restless, or both	16 (53.3)	7 (23.3)	12 (40.0)	0.436
Patient is awake, cooperative, oriented and tranquil	9 (30.0)	14 (46.7)	12 (40.0)	
Patient response to commands only	5 (16.7)	6 (20.0)	4 (13.3)	
Patient exibits brisk response to light physical stimulus, i.e. touch	0 (0)	2 (6.7)	1 (3.3)	
Patient exibits slow response to stronger physical stimulus, i.e. sternum pressure	0 (0)	1 (3.3)	1 (3.3)	
Patient exibits no response	0 (0)	0 (0)	0 (0)	
PAED scale	4.0 (1.0–7.0)	2.0 (0.0–5.0)	4.0 (2.0–6.0)	0.108a
PAED scale – categorical values (cut-off values)				
< 10 points mild or without agitation	25 (83.3)	30 (100)	26 (86.7)	0.192
10–15 moderate agitation	2 (6.7)	0 (0)	3 (10.0)	
> 15 severe post-surgery agitation	3 (10.0)	0 (0)	1 (3.3)	

P from the Chi-square ($\chi 2$)-test; [a]Kruskal-Wallis test

S-ketamine group and almost 87% of children in dexmedetomidine group. Those high percentages of children with low level of postoperative excitation speaks in favor of premedication's, so as general anesthesia adequacy.

Pain scales in children according to implemented intranasal premedication therapy

Results presented at the Table 4 showed statistically significant difference in postoperative pain level according to FACES pain scale for the children between 3 and 7 years (there were 76 children in this group). The weakest pain was observed in the S-ketamine group. It is worth-mentioning that the highest level of pain was detected in midazolam group, while pain level positioned between other two groups was noticed in dexmedetomidine group of children. It is important to report that minimal pain was experienced by 61% in midazolam, 100% in S-ketamine and in 70% of dexmedetomidine group. Severe pain was noticed in 18% of midazolam group, while 20% in dexmedetomidine group. Results of this analysis confirmed S-ketamine's superiority in pain suppression over the other two intranasal premedication therapies (Table 4).

Using the FLACC pain scale in children under 3 years of age (there were 12 children younger than 3 years) confirmed no difference in pain scale points, so as in distribution according the cut--off values according to the numbers of points of this scale (describing the pain level from no pain to severe pain). In midazolame and S-ketamin groups 50% of children had no pain (0 points), while 62.5% of children in dexmedetomidine group. Mild pain had other 50% in midazolame group and 37.5 % in dexmedetomidine group. The result about S-ketamin group according to which 50% of children had severe pain, but the total number of children under the 3 years in this group is small (n = 2), so this results should be analysed with caution because just one child had in fact severe pain.

Discussion

Results of this current study confirmed that the intranasal route of drug administration is a reliable and effective, minimally traumatic route, with a quick effect due to the rich vascularization of the drug administration site. Along with this intranasal administration of midazolam, S-ketamine and dexmedetomidine has been shown to be a safe and effective premedication in children undergoing tonsillectomy. This study revealed that intranasal aplication of S-ketamine significantly lower intraoperatively opioids' usage, as do the analgesics postoperatively. For the three tested intranasal premedication drugs we could not confirm an absolute advantage, which opens a space for further investigation in this area of surgery-related pharmacology in pediatric population.

Table 4. Pain scales (FACES or FLACC) in a group of older (3-7 y.) and younger (below 3 y.) children according to type of premedication therapy

Variable	Midazolam (n = 30)	S-ketamine (n = 30)	Dexmedetomidin (n = 30)	P
FACES pain scale (children 3-7 y.)				
Points	2.0 (0–5)	0 (0–0)***	1.0 (0–3.5)##	0.001
Interval values (cut-off values), n(%)				
Minimal pain (0–2 points)	17 (60.7)	28 (100)	14 (70)	0.006a
Moderate pain (4–6 points), analgetic therapy is needed	6 (21.4)	0 (0)	2 (10.0)	
Severe pain (8–10 points) urgent intervention is needed	5 (17.9)	0 (0)	4 (20)	
FLACC pain scale (children < 3 y.)				
Points	1.5 (0–3)	2.0 (0–4)	0 (0–2)	0.609
Interval values (cut-off values), n(%)				
Without pain (0 points)	1 (50.0)	1 (50.0)	5 (62.5)	0.203a
Mild pain (1–3 points)	1 (50.0)	0 (0)	3 (37.5)	
Moderate pain (4–6 points)	0 (0)	1 (50.0)	0 (0)	
Severe pain (7–10 points)	0 (0)	0 (0)	0 (0)	

*P from Kruskal Wallisov test, ***P<0.001 vs. midazolam group; ##P<0.01 vs. S-ketamine group ; [a]Chi-square χ2-test*

Children divided in three intranasal premedication groups were matched according to age and gender, so their demographic and antropometric characteristics (gender, age, BMI) were similar which allowed for correct conclusions to be drawn. According to data from other studies, the male gender more often requires adenotonsillar surgery, which correlates with our research; a higher percentage of boys were distributed across all three groups (precisely from 57% to 70%).[23]

Analyzing the preoperative level of separation anxiety according to the parental scale, as well as the MAS scale, no significant difference was observed between the groups of children who received intranasal premedication with midazolam, S-ketamine or dexmedetomidine. The majority of children in all three groups rated "excellent" or "good" in terms of acceptance of separation from their parents, indicating the effectiveness of all three drugs in controlling separation anxiety before induction of anesthesia.

A more detailed analysis of the parental scale shows that in the midazolam group more than half of the children (53.3%) were rated as "great", while in the dexmedetomidine group this percentage was slightly lower (36.7%). On the other hand, a higher percentage of children in the dexmedetomidine group was rated as "good" (40%), which indicates that most children in this group reacted positively, although to a slightly lesser extent than with midazolam or S-ketamine. In the S-ketamine group, the distribution was more even between the "great" and "good" categories. The percentage of children who accepted separation from their parents with resistance or poorly was the lowest in the dexmedetomidine group, which may indicate a slight additional reduction in separation anxiety in this group, although it is not statistically significant. Using the MAS scale, we showed that the majority of children in all groups calmly accepted the mask or were scared, but without active resistance. The largest number of children who completely calmly accepted the mask was in the S-ketamine group (53.3%) and midazolam (50%), while in the dexmedetomidine group this percentage was slightly lower (26.7%). The increased percentage of children in the dexmedetomidine group who are fearful but accept the mask, as well as those who show mild resistance, may be due to the lower initial dose of the drug or individual characteristics of anxiety. The results of our study are partially consistent with a study published in 2023 by Alam and associates, where 60 patients aged 3 to 6 years, ASA I physical status, were divided into two groups according to intranasal premedication type. One group was intranasally premedicated with midazolam 0.2 mg/kg, and the other group with dexmedetomidine 1 μg/kg, 50 min before anesthesia induction. The results showed that intranasally applied dexmedetomidine is an effective and safe alternative for premedication in children, provides better hemodynamic stability, a better level of sedation during induction of anesthesia, enables more successful separation from parents compared to intranasally applied midazolam with minimal side effects and postoperative complications.[24]

Also, in a study published in 2021 by Diwan et al., the superiority of intranasal dexmedetomidine compared to intranasal midazolam was confirmed in providing significantly better sedation, lower levels of anxiety and easier separation from parents, which is not in accordance with our research where there was a similar effectiveness of both drugs.[25]

Regarding the duration of the operation, intranasal premedication with different types of drugs (midazolam, S-ketamine or dexmedetomidine) didn't differ according to the operation's duration. This indicates that the choice of premedication does not directly affect the operative time course in elective tonsillectomies and similar procedures. Similar findings have been reported in previous studies where intranasal sedatives did not significantly alter the duration of surgery in pediatric patients.[26]

Analysis of the amount of bolus propofol given during surgery also showed no significant differences between groups. All three groups received an average dose of about 3 mg/kg, which is in line with standard protocols for the induction of general anesthesia in children. The slight increase in propofol in the dexmedetomidine group probably reflects individual differences in the sedative effect and did not have statistical significance, that is, a clinically significant value.

A significant difference was observed in the amount of fentanyl given during surgery. Children premedicated with S-ketamine received a lower amount of opioid (fentanyl) compared to the midazolam and dexmedetomidine groups. This finding may be explained by the additional analgesic

and sedative effect of S-ketamine that reduces the need for intraoperative opioids, which is consistent with research published in by Qi and colleagues.[27] These findings support the role of S-ketamine in enabling a safer anesthetic strategy by reducing opioid requirements, which is particularly important in pediatric patients due to the risk of opioid--related adverse effects, such as respiratory depression and nausea.[26]

The amount of muscle relaxant (Rocuronium bromide) administered was similar in all three groups, indicating that the type of nasal premedication does not affect the amount of muscle relaxant consumed during surgery.

In this study, changes in hemodynamic parameters were analyzed in children premedicated with three different intranasal drugs during tonsillectomy. The results show that premedication with S-ketamine leads to significantly higher values of systolic and diastolic pressure immediately after induction compared to midazolam and dexmedetomidine, while the values during the operation itself and at the end of the operation were not statistically significantly different between the groups. Post-induction heart rate was significantly lower in the dexmedetomidine group compared to the midazolam or S-ketamine groups, consistent with the known sympatholytic effect of alpha 2 agonists. The result of this part of the study is in accordance with the study of Yuen and associates.[28]

The increased blood pressure values after induction in the S-ketamine group can be explained by its sympathomimetic effect, which includes parasympathetic inhibition and sympathetic stimulation, which was previously described in studies in the pediatric population.[29] In contrast, dexmedetomidine reduces the activity of the sympathetic system and can cause mild bradycardia and a drop in blood pressure, which is reflected in the lower values after induction in our study as well as in the study published by Diwan and coworkers.[25] Midazolam, as a benzodiazepine, shows a minimal effect on blood pressure and heart rate, which was also confirmed in earlier research such as one of the papers by Vasakova et al.[30]

During the surgery itself, the blood pressure and heart rate values did not differ significantly between the groups, which indicates that all three premedication strategies provide hemodynamic stability, without the need for additional intervention. These results are consistent with the reports of other study that intranasal S-ketamine and dexmedetomidine provide safe hemodynamic control during short-term surgical procedures in children.[25,26]

It is important to point out that, although the observed hemodynamic changes are statistically significant, they were not clinically significant, *i.e.* did not require additional therapeutic interventions. This confirms that intranasal premedication in children can be administered without the risk of serious hemodynamic complications. Respiratory parameters were also monitored. The results showed that before the introduction and immediately after the introduction of general anesthesia there is similar respiratory frequency in the 3 premedication subgroups, which indicates that all three drugs in the applied doses do not cause clinically significant ventilation disorders. During the operation, a significantly lower respiratory frequency was registered in the dexmedetomidine group compared to the groups that received midazolam and S-ketamine, while at the end of the operation, respiratory frequency values were equal between the groups. Our data are in accordance with data from the literature, which state that dexmedetomidine, as a highly selective alpha 2 adrenergic agonist, can lead to a transient decrease in respiratory frequency.[31] In the work of Yuen et al.[28], intranasally applied dexmedetomidine in children did not cause significant changes in saturation or apnea, but a slight decrease in respiratory frequency was also observed. Also, research by Behrle and associates [32] indicates that intranasally applied dexmedetomidine causes minimal negative effects on respiratory functions and that patients are mostly hemodynamically stable. On the other hand, midazolam and S-ketamine did not significantly affect respiratory frequency in our study.

The values of blood oxygen saturation in our research remained within physiological limits in all groups, although some differences were statistically significant, they had no clinical significance. The analysis of PetCO2 values showed that they were the lowest in the group with dexmedetomidine immediately after the introduction, while at the end of the operation the values were higher compared to the other groups. This oscillation can be explained by changes in the anesthesia depth and the slight effect of dexmedetomidine on the respiratory center,

which is also described in the literature, in a paper published in 2006 by Sikich et al.[33]

Intranasal premedication with midazolam, S-ketamine and dexmedetomidine provided stable respiratory function, with a minimal decrease in respiratory frequency in the group with dexmedetomidine, without clinically significant disturbances of ventilation and oxygenation.

Regarding postoperative sedation, assessed by the Ramsey scale, there was no significant difference between children premedicated with different types of nasal premedication implemented in this current study. Most of the children in the groups premedicated with S-ketamine and dexmedetomidine were awake, cooperative and calm (Ramsey scale 2), while in the midazolam group they were awake but anxious or restless (Ramsey scale 1). All this indicates that all three drugs provide a satisfactory level of sedation. The previously mentioned Yuen et al confirm the results of our research that dexmedetomidine in children induces sedation that allows easy cooperation and reduced anxiety.[28] While Lethin[34] stated in their research that midazolam provides adequate anxiolysis, but in some cases children may remain awake and anxious, which is the result of our control group.

The occurrence of postoperative apnea was not significantly different between the groups. In the groups with S-ketamine and dexmedetomidine, three children each (10%) had postoperative apnea, while not a single apnea was recorded in the group with midazolam. There was a difference in the occurrence of postoperative apnea between the groups in terms of the number of subjects and according to the time of occurrence after surgery, which did not have statistical significance. Children in the S-ketamine group developed apnea immediately after discharge, while in the dexmedetomidine group two children had apnea immediately after discharge and one child later, in the ward. Apnea may be a result of drug pharmacokinetics and pharmacodynamics, whereby dexmedetomidine may cause longer but mild sedative effects, which is consistent with research by Behrle and Simonini.[32,35]

Using the PAED scale, no significant difference was shown in postoperative excitation in children premedicated with different types of nasal premedication. In all groups, most children had mild or no postoperative agitation. Ykeizumi et al.[36] has already showed in their study that intranasal dexmedetomidine and S-ketamine reduce postoperative agitation in children, while midazolam can cause slightly more pronounced agitation, but without statistically significant differences. Analysis of pain in children aged 3 to 7 years showed the lowest pain intensity in S-ketamine group, while children premedicated with midazolam and dexmedetomidine had moderately expressed pain. The results indicate an analgesic advantage of S-ketamine in the pediatric population, which is consistent with a studies published by Liu et al.[37] and Qian et al.[38], who highlight the analgesic potential of S-ketamine and its ability to reduce intraoperative opioid use and postoperative need for additional analgesics. Adverse reactions were rare and did not show a significant difference between the groups, which confirms the safety of all three types of intranasal premedication in pediatric patients, which is in accordance with data from the literature.[39-41]

This study has several limitations that should be considered when interpreting the results. The relatively small sample size may limit the statistical power and generalizability of the findings. This was a single-center study performed in a tertiary pediatric institution, which may reduce the external validity of the results and their applicability to other clinical settings. Also, the study design did not include complete blinding of investigators and caregivers, which may have introduced observer and performance bias, particularly in the assessment of subjective outcomes such as sedation quality, separation anxiety, and postoperative behaviour. Therefore, larger multicentre, randomized studies with blinded outcome assessment are needed to confirm the present findings and thus improve comparative efficacy and safety evaluation of intranasal premedication protocols in pediatric tonsil surgery.

Conclusion

In conclusion, according to theoretical considerations, other authors' experiences and our own results, we can conclude that the intranasal route of drug administration is a reliable and effective, nontraumatic route, fast-acting medicine due to the rich vascularization of the drug administration site. Intranasal administration of midazolam, S-ketamine and dexmedetomidine has been shown to be a safe and effective premedication in children

undergoing tonsillectomy. The most convincing results of this current study is regarding intranasally administered S-ketamine which leads to a reduction in the use of opioids intraoperatively and the analgesics postoperatively, which is an advantage compared to intranasal administration of midazolam and dexmedetomidine.

None of the intranasal premedication agents demonstrated a clear overall advantage; therefore, drug selection should be individualized based on the patient's clinical condition, the desired effect (anxiolysis, sedation, or analgesia), and the potential for adverse effects.

References

1. Yeshuroon-Koffler K, Shemer-Avni Y, Keren-Naus A, Goldbart AD. Detection of common respiratory viruses in tonsillar tissue of children with obstructive sleep apnea. Pediatr Pulmonol. 2015;50(2):187-95.

2. Jadhav U, Bhanushali J, Sindhu A, Reddy BSK, Toshniwal A, Rashmika M. A comprehensive review of pediatric obstructive sleep apneja: from assessment to intervention. Cureus. 2025;17(1):e78051.

3. Azamar A, De la Torre-González C, Juárez-Villegas L, Sadowinski-Pine S, Álvarez-Neri H. Asymmetric palatine tonsil in a pediatric patient: is it always a malignant neoplasm? Bol Med Hosp Infant Mex. 2021;78(5):461-6.

4. Han CJ, Bergman M, Harley RJ, Harley EH. The pediatric indications for tonsillectomy and adenotonsillectomy: race/ethnicity, age, and gender. Laryngoscope Investig Otolaryngol. 2023;8(2):577-83.

5. Zhang G, Xin L, Yin Q. Intranasal dexmedetomidine vs oral midazolam for premedication in children: a systematic review and meta-analysis. Front Pediatr. 2023;11:1264081.

6. Deshmukh PV, Kulkarni SS, Parchandekar MK, Sikchi SP. Comparison of preanesthetic sedation in pediatric patients with oral and intranasal midazolam. J Anaesthesiol Clin Pharmacol. 2016;32(3):353-8.

7. Dave NM. Premedication and Induction of Anaesthesia in paediatric patients. Indian J Anaesth. 2019;63(9):713-20.

8. Strunk CL, Nichols ML. A comparison of the KTP/532-laser tonsillectomy vs traditional dissection/snare tonsillectomy. Otolaryngol Head Neck Surg. 1990;103(6):966–71.

9. Morgenstein SA, Jacobs HK, Brusca PA, et al. A comparison of tonsillectomy with the harmonic scalpel versus electrocautery. Otolaryngol Head Neck Surg. 2002;127(4):333-8.

10. Dickerson SC. Perioperative guidelines in anesthesia. Otolaryngol Clin North Am. 2019;52(6):981-93.

11. McGuire SR, Doyle NM. Update on the safety of anesthesia in young children presenting for adenotonsillectomy. World J Otorhinolaryngol Head Neck Surg. 2021;7(3):179-85.

12. Wexler DB. Recovery after tonsillectomy: sharp dissection techniques. In: Bluestone CD, Stool SE, eds. Pediatric Otolaryngology. 3rd ed. Philadelphia: Saunders; 1996. p. 1324-7

13. De Cassai A, Boscolo A, Tonetti T, Ban I, Ori C. Assignment of ASA-physical status relates to anesthesiologists' experience: a survey-based national study. Korean J Anesthesiol. 2019;72(1):53-9.

14. Saubermann AJ, Lagasse RS. Prediction of rate and severity of adverse perioperative outcomes: "Normal accidents" revisited. Mt Sinai J Med. 2012;79(1):46-55.

15. Rosenbaum A, Kain ZN, Larsson P, Lönnqvist PA, Wolf AR. The place of premedication in pediatric practice. Paediatr Anaesth. 2009;19(9):817-28.

16. Janse van Rensburg E, Indiveri L, Mogane P. The perioperative use of dexmedetomidine in paediatric patients. Children (Basel). 2025;12(6):812

17. Ramsay MAE, Newman KB, Jacobson RM, et al. Sedation levels during propofol administration for outpatient colonoscopies. Proc (Bayl Univ Med Cent). 2014;27(1):12-5.

18. Singla D, Chaudhary G, Dureja J, Mangla M. Comparison of dexmedetomidine versus midazolam for intranasal premedication in children posted for elective surgery: a double-blind, randomised study. South Afr J Anaesth Analg. 2015;21(6):12-5.

19. Singariya G, Malhotra N, Kamal M, Jaju R, Aggarwal S, Bihani P. Comparison of nebulized dexmedetomidine and ketamine for premedication in pediatric patients undergoing hernia repair surgery: a randomized comparative trial. Anesth Pain Med (Seoul). 2022;17(2):173-81.

20. Crellin DJ, Harrison D, Santamaria N, Huque H, Babl FE. The psychometric properties of

the FLACC scale used to assess procedural pain. J Pain. 2018;19(8):862-72.

21. Walimbe H, Muchandi S, Bijle MNA, et al. Comparative evaluation of the efficacy of topical anesthetics in reducing pain during administration of injectable local anesthesia in children. World J Dent. 2014;5(2):129-33.

22. Simić D. Pedijatrijska anesteziologija. In: Simić D, ed. Pedijatrijska anesteziologija. Beograd: Akademska misao; 2020. p. 107-11.

23. Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: tonsillectomy in children (update). Otolaryngol Head Neck Surg. 2019;160:S1-42.

24. Alam MF, Kumar A, Zea O. Comparative evaluation of intranasal dexmedetomidine and intranasal midazolam for premedication in children: a randomised double blind study. Int J Acad Med Pharm. 2023;5(5):219-24.

25. Diwan G, Bharti A, Rastogi K, Gupta P. Comparison of intranasal dexmedetomidine and midazolam as premedication in pediatric surgical patients: a prospective, randomized double-blind study. Anesth Essays Res. 2020;14(3):384-9.

26. Zhang K, Zhang G, Zhang Y, et al. Efficacy of intranasal dexmedetomidine-esketamine sedation for pediatric acceptance of facemask: single-center, double-blind, randomized controlled trial. BMC Anesthesiol. 2025;25(1):67.

27. Qi JW, Li C, Qiu XY, et al. Effects of intranasal dexmedetomidine and esketamine for premedication on postoperative pain after tonsillectomy and adenoidectomy in children: a randomized clinical trial. BMC Anesthesiol. 2025;25(1):84.

28. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. Anesth Analg. 2008;106(6):1715-21.

29. Loomba RS, Gray SB, Flores S. Hemodynamic effects of ketamine in children with congenital heart disease and/or pulmonary hypertension. Congenit Heart Dis. 2018;13(5):646-54.

30. Vasakova J, Duskova J, Lunackova J, et al. Midazolam and its effect on vital signs and behavior in children under conscious sedation in dentistry. Physiol Res. 2020;69(Suppl 3):S305-14.

31. Shen F, Zhang Q, Xu Y, et al. Effect of intranasal dexmedetomidine or midazolam for premedication on the occurrence of respiratory adverse events in children undergoing tonsillectomy and adenoidectomy: a randomized clinical trial. JAMA Netw Open. 2022;5(8):e2225473.

32. Behrle N, Birisci E, Anderson J, Schroeder S, Dalabih A. Intranasal dexmedetomidine as sedative for pediatric procedural sedation. J Pediatr Pharmacol Ther. 2017;22(1):4-8.

33. Sikich N, Lerman J. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. Anesthesiology. 2007;105(6):1098-110.

34. Lethin M, Paluska MR, Petersen TR, Falcon R, Soneru C. Midazolam for anesthetic premedication in children: considerations and alternatives. Cureus. 2023;15(12):e50309.

35. Simonini A, Brogi E, Cascella M, Vittori A. Advantages of ketamine in pediatric anesthesia. Open Med (Wars). 2022;17(1):1134-47.

36. Ykeizumi LS, Correia Da Silva R, Villar G, et al. Combined dexmedetomidine and ketamine in pediatric anesthesia: a brief review. J Anesth Crit Care. 2021;5(2):46-52.

37. Liu F, Kong F, Zhong L, Wang Y, Xia Z, Wu J. Preoperative esketamine alleviates postoperative pain after endoscopic plasma adenotonsillectomy in children. Clin Med Res. 2023;21(2):79-86.

38. Qian Q, Liu HX, Li YQ. Effect of esketamine nasal drops on pain in children after tonsillectomy using low temperature plasma ablation. Front Pediatr. 2023;11:1110632.

39. Gómez-Manzano FJ, Laredo-Aguilera JA, Cobo-Cuenca AI, et al. Evaluation of intranasal midazolam for pediatric sedation during the suturing of traumatic lacerations: a systematic review. Children (Basel). 2022;9(5):640.

40. Liao Y, Xie S, Zhuo Y, et al. Intranasal dexmedetomidine vs oral midazolam for premedication in children: a systematic review and meta-analysis. Paediatr Anaesth. 2022;32(9):1107-19.

41. Singh C, Pandey RK, Saksena AK, Chandra G. A comparative evaluation of intranasal midazolam and dexmedetomidine for their sedative and anxiolytic effects in children. J Clin Pediatr Dent. 2014;39(2):135-42.