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Effect of nebulized dexmedetomidine on gag reflex suppression and sedation quality in pediatric patients undergoing gastrointestinal endoscopy: a randomized controlled trial

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Abstract

Background Pediatric patients undergoing upper gastrointestinal (GI) interventions frequently require sedation and analgesia due to the challenges associated with endoscopic probe placement, particularly the gag reflex. This study investigates the effects of nebulized dexmedetomidine as a premedication on the gag reflex in pediatric patients undergoing gastrointestinal endoscopy.

Methods We conducted a single-center, prospective, randomized controlled trial at the Pediatric Gastroenterology Clinic of Ondokuz Mayis University School of Medicine from January to April 2024. Participants aged 2–17 years scheduled for upper GI endoscopy were randomized to receive nebulized dexmedetomidine (2 µg /kg) or no premedication. The primary outcome measured was the severity of the gag reflex during the procedure. Secondary outcomes included cough incidence, separation anxiety, postoperative agitation, and endoscopist satisfaction. Statistical analyses were performed with significance set at $p < 0.050$.

Results A total of 120 patients were analyzed. The dexmedetomidine group demonstrated a significantly lower incidence of gag reflex (88.3% with no gag reflex vs. 30% in the control group, $p < 0.001$) and coughing (95% vs. 55%, $p < 0.001$). Separation anxiety scores were also significantly lower in the dexmedetomidine group ($p < 0.005$). Additionally, the need for additional anesthetics was reduced, and endoscopist satisfaction was significantly higher. No significant differences in complications were observed between the two groups ($p = 0.600$).

Conclusions Nebulized dexmedetomidine is a safe and effective premedication for pediatric patients undergoing endoscopic procedures, significantly reducing gag and cough reflexes, decreasing anesthetic requirements, and enhancing endoscopist satisfaction. This approach improves the comfort and safety of pediatric endoscopy procedures.

Trials registration ClinicalTrials.gov: NCT06218797, date of registration 27/12/2023.

Keywords Nebulized dexmedetomidine, Pediatric anesthesia, Endoscopy, Gag reflex, Sedation

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Introduction

Pediatric patients undergoing upper gastrointestinal interventions often require sedation and analgesia because they cannot tolerate the endoscopic placement of the probe. One of the most significant challenges encountered during endoscopic probe placement is the development of the gag reflex. In these patients, discomfort can lead to increased secretion, laryngospasms, pain, and undesirable hemodynamic changes. Severe complications, such as esophageal rupture, occur rarely [1]. Effective premedication can reduce preprocedural anxiety, making the intervention less traumatic for the child and more comfortable for the practitioner [2]. Premedication can be administered via alternative routes such as oral, buccal, intranasal, and sublingual, in addition to the intravenous route [3].

Dexmedetomidine provides sedation, analgesia, sympatholysis, and hemodynamic stability without causing respiratory depression [4, 5]. The nebulized form is a noninvasive option for pediatric patients. The effect of nebulized dexmedetomidine in different doses on parental separation and mask acceptance scores has been studied [6]. Evidence suggests that the combination of nebulized dexmedetomidine and ketamine reduces the gag reflex in patients undergoing dental treatment [7] and suppresses the cough reflex during awake fiberoptic intubation in adult patients [8].

Application of topical lidocaine can suppress the gag reflex in adults but may increase airway-related side effects in pediatric patients [9]. Whether the administration of nebulized dexmedetomidine prevents the gag reflex in upper gastrointestinal endoscopy in pediatric patients remains explored.

This study aimed to investigate the potential benefits of nebulized dexmedetomidine as a premedication to suppress the gag reflex in pediatric patients undergoing gastrointestinal endoscopy. We hypothesized that administration of nebulized dexmedetomidine during premedication can significantly reduce gagging in pediatric patients.

Methods

Study design

This single-center, prospective, randomized controlled study was conducted between January and April 2024 at the Pediatric Gastroenterology Clinic of Ondokuz Mayis University School of Medicine. Approval was obtained from the Local Ethics Committee (OMU KAEK; approval number: 2022/185). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and registered in ClinicalTrials.gov (NCT06218797) before enrolling the first patient. No changes were made to the study protocol after the study was initiated. Written informed consent was obtained from the parents of all participants, and informed assent was obtained from all children aged older than 7.

Participant selection

The study enrolled patients aged 2–17 years, weighing ≥ 10 kg, and classified with physical status I or II using the system by the American Society of Anesthesiologists (ASA), who were scheduled for diagnostic upper gastrointestinal endoscopy. The exclusion criteria were pediatric patients with known allergies to the study drugs; those with an ASA class ≥ III; those with psychiatric or psychological disorders, neurological conditions or intellectual disability, asthma, a history of upper respiratory tract infection in the past 4 weeks, heart conditions, or obesity (body mass index ≥ 35 kg/m^2); and those weighing < 10 kg.

Randomization

A block randomization list was generated by a researcher not involved in the study using a web-based program (www.randomizer.org), and the patients were randomly assigned in a 1:1 ratio to either the nebulized dexmedetomidine or control groups. Opaque envelopes were prepared by the same researcher. The envelope containing the patient group assignment was handed to the anesthesiologist 30 min before the procedure by an assistant who was not involved in the study. The anesthesiologist who performed the procedure, the endoscopist, nurses in the procedure and recovery rooms, and the researchers who analyzed the study results were blinded to patient allocation. A single study investigator (ET) had access to the randomization code to prepare the study drugs in case of an emergency during the procedure.

Administration of nebulized dexmedetomidine

After a 6-h fasting period, the patients were brought to the preoperative waiting room, and standard ASA monitoring was applied (electrocardiography [ECG], noninvasive blood pressure, and peripheral oxygen saturation [SpO_2]). The intravenous line was inserted prior to the start of any procedure. Dexmedetomidine hydrochloride (Precedex 100 µg/mL) was administered using an electric compressor nebulizer (Eco Smart; Saify Healthcare, Medi Devices, India) at a dose of 2 µg/kg (maximum 100 µg), diluted with isotonic solution to a volume of 5 mL. The drugs were administered by the anesthesiologist at least 20 min before anesthesia induction in an area where assessments related to the study were not performed. No premedication was administered to the control group.

Endoscopic procedure

In the procedure room, the patients underwent standard ASA monitoring (ECG, SpO_2, and noninvasive blood pressure monitoring). The anesthetic technique was standardized for all patients. Before the endoscope was inserted into the posterior pharynx, each patient received three applications of 10% lidocaine spray. Infusion of lactated ringer's solution at 10 mL/kg/h was initiated. All patients breathed spontaneously and received supplemental oxygen through a nasal cannula at a rate of 3–4 L/min during the procedure. After monitoring, the patients were administered intravenous midazolam 0.05 mg/kg, propofol (1 mg/kg)–ketamine (0.5 mg/kg). The endoscopy was initiated once the patients reached an adequate sedation level (Ramsay sedation scale score ≥ 5—asleep; sluggish response to light glabellar tap or loud auditory stimulus) [10]. Endoscopy was initiated once the patients reached an adequate sedation level, defined as a Ramsay Sedation Scale (RSS) score > 5 (asleep; sluggish response to light glabellar tap or loud auditory stimulus), and the sedation protocol was planned to maintain this level throughout the procedure [10]. RSS was assessed every 5 min until the end of the procedure. If the target sedation level was not reached within 2 min before the start of the endoscopy, or if the RSS dropped below 5 at any time during the procedure, additional doses of propofol (0.5 mg/kg) were administered in bolus form until the appropriate sedation level was achieved. The endoscopist was allowed to proceed once the patient reached a RSS of > 5. The requirement for additional doses was recorded as specified. At the end of the procedure, the patients were transferred to the post-anesthesia care unit (PACU) within the same unit once they achieved a Steward recovery score > 6 [11]. All study participants were observed in PACU for 3 h according to routine practice. The children were discharged once they were awake, hemodynamically stable, had a patent airway, did not experience nausea or vomiting, and had well-controlled pain, according to standard clinical protocols.

Changes in the mean arterial pressure and heart rate > 20% from baseline; oxygen desaturation (SpO_2 < 92%) lasting longer than 15 s; need for jaw thrust or manual ventilation; laryngospasm (wheezing, stridor, and respiratory distress); increased secretions (saliva production and tracheobronchial secretions requiring aspiration); vomiting (at least once); shivering (muscle activity involving the entire body); hiccups (characterized by involuntary and sudden rhythmic inhalation sounds); and agitation were defined and recorded as adverse events.

The gag reflex can be triggered by the insertion of the endoscope into the oropharynx; severity was recorded as follows: 0 = no gagging, 1 = minimal (1–2 episodes) gagging, 2 = moderate (3–4 episodes) gagging, and 3 = severe (> 5 attacks) gagging. The incidence and severity of coughing episodes within the first 5 min of the procedure were recorded as follows: 0 = no coughing, 1 = minimal (single episode) coughing, 2 = moderate (coughing lasting ≤ 5 s), and 3 = severe (coughing lasting > 5 s, accompanied by bucking). Limb movements were assessed as either absent or obvious.

Postoperative delirium (severity and frequency) was assessed using the Pediatric Anesthesia Emergence Delirium (PAED) scale [12]. At the end of the preoperative phase, parental separation was assessed using the four-point Parental Separation Anxiety Scale (PSAS) as follows: 1 = easy separation; 2 = whimpers but is easily reassured with no clinging; 3 = crying with an inability to be easily reassured, but not clinging to parents; and 4 = crying and clinging to parents. PSAS scores of 1 and 2 indicated acceptable separation, whereas scores of 3 and 4 indicated difficult separation.

The duration of the procedure (time from endoscope insertion to removal) and recovery (time from procedure completion to achieving a Steward recovery score of 6) were recorded. All endoscopies were performed by two pediatric gastroenterologists, with the patient in the left lateral position. At the end of the procedure, the endoscopist rated patient satisfaction on a 4-point scale (1 = excellent, 2 = good, 3 = fair, and 4 = poor).

Outcomes

The primary outcome of our study was the severity of the gag reflex during the procedure after the insertion of the endoscope. Secondary outcomes included the incidence of cough during the procedure, number of patients with limb movements, PAED scores, parental separation anxiety scores, incidence of unexpected events, need for additional anesthetics, endoscopist satisfaction, duration of the endoscopic procedure, and recovery time.

Statistical analysis

Sample size

The sample size was calculated using G*Power software (Düsseldorf, Germany). Based on a prior study that examined the effect of intravenous dexmedetomidine on the gag reflex, we assumed a 70% reduction in the incidence of the gag reflex for the nebulized dexmedetomidine group [13]. Using Fisher's exact test for two independent proportions, with a power of 0.80 and an alpha error of 0.05, the calculation revealed that the required number of patients was 51 per group. Considering an approximate 20% dropout rate, we decided to include 60 patients in each group.

Statistical methods

The data were analyzed using IBM SPSS V23. The normality of the distribution was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Categorical variables were compared between groups using the Chi-square test, Fisher's exact test, Yates correction, and the Fisher–Freeman–Halton test. Multiple comparisons of proportions were performed using the Bonferroni-adjusted Z test. For the comparison of normally distributed variables between the two groups, an independent-samples t-test was used, whereas the Mann–Whitney U test was used for non-normally distributed data. Repeated-measures analysis of variance was used to compare normally distributed data across three or more time points, with Bonferroni adjustment for multiple comparisons. For non-normally distributed data across three or more time points, the Friedman test was used, with post-hoc analysis using the Dunn test. Statistical significance was set at $p < 0.050$.

Results

Of the 129 patients who were assessed for eligibility, nine were excluded; four patients or their guardians refused to sign the informed consent form, and five patients did not meet the inclusion criteria. Consequently, data from 120 patients were analyzed (Fig. 1).

There were no significant differences between the two groups regarding demographics or procedural factors (Table 1). The incidence of the gag reflex was significantly different between the groups ($p < 0.001$). In the dexmedetomidine group, the reflex was lost in 53 children (88.3%) and was mild in seven (11.7%), while moderate reflexes were not recorded. In contrast, in the control

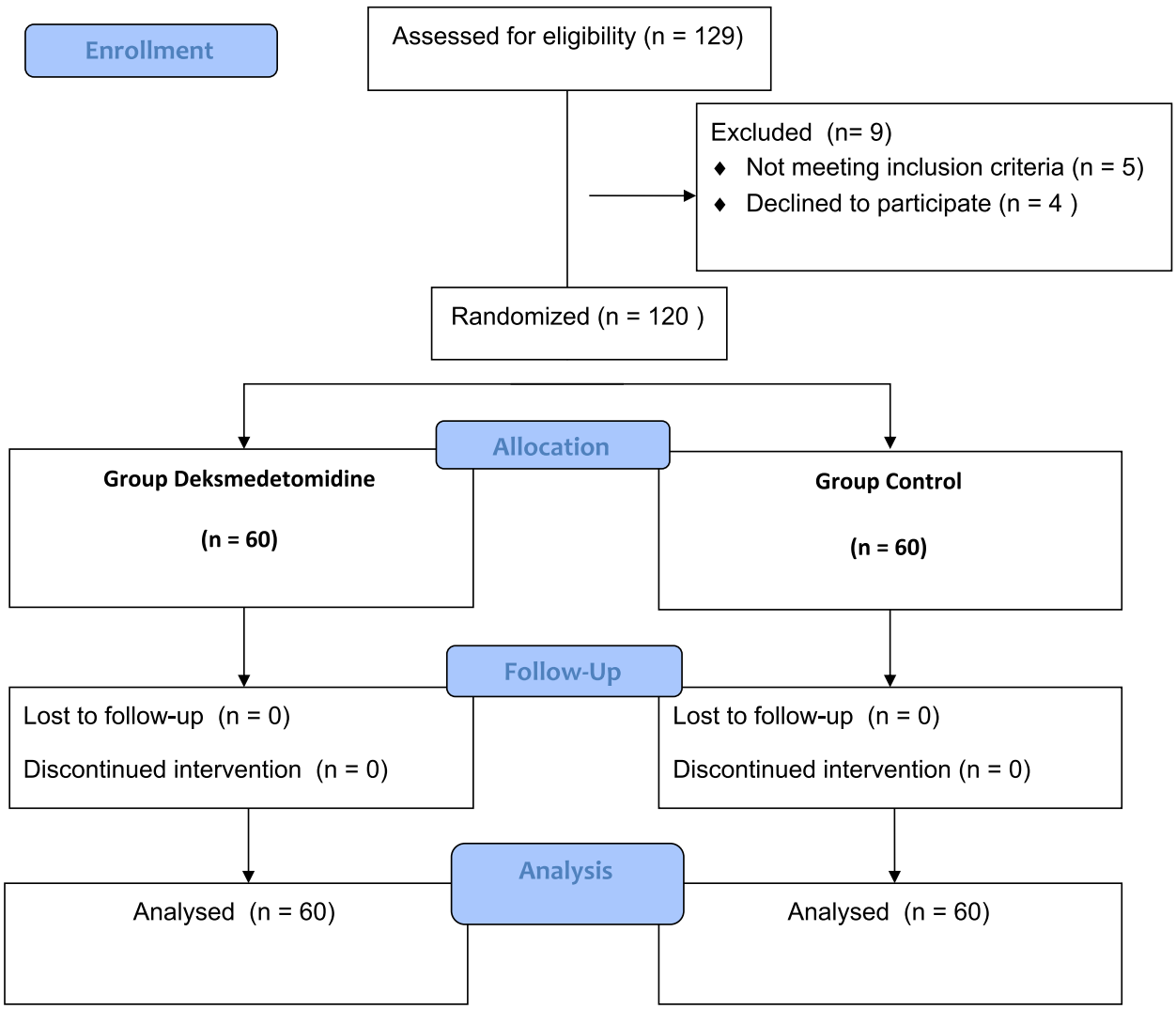

Fig. 1 CONSORT flow diagram of the study

Table 1 Patient demographics and clinical outcomes

	Group Deksmedetomidine ($n=60$)	Group Control ($n=60$)	*p*
Sex. female/male *n (%)*	33 (55) / 27 (45)	36 (60) / 24 (40)	0.580
ASA (I/ II) *n (%)*	45 (75) / 15 (25)	46 (76.7) / 14 (23.3)	1.00
	mean ± SD (95% CI) / median [Q1-Q3]	mean ± SD (95% CI) / median [Q1-Q3]	
Age, years	12 [2-17]	11 [2-17]	0.058
Weight, kg	39.5 ± 15.22	38.3 ± 19.15	0.705
Duration of procedure (min)	15 [5-20]	12 [5—50]	0.100
Duration of recovery (min)	2 [1-5]	2 [1-5]	**0.001**

Continuous variables are presented as median [Q1-Q3] or mean ± standard deviation (95% CI) and categorical variables are presented as counts (%). Statistically significant difference is highlighted in bold

Abbreviations: ASA American Society of Anesthesiologists

group, the gag reflex was depressed in 18 children (30%), was mild in 34 (56.7%), and moderate in 8 (13.3%).

The incidence of coughing was significantly lower in the dexmedetomidine group than in the control group ($p<0.001$). Furthermore, episodes of coughing were absent in 57 (95%) and 33 (55%) children in the dexmedetomidine and control groups, respectively. Mild coughing was observed in 3 children (5%) in the dexmedetomidine group and in 22 (36.7%) in the control group. Moderate coughing was observed only in the control group ($n=5$; 8.3%).

Movements of the extremities against the placement of the endoscopy probe were significantly less common in the dexmedetomidine group than in the control group ($p<0.001$) (Table 2).

Parental Separation anxiety was significantly lower in the dexmedetomidine group ($p<0.005$) than in the control group (Table 1). In the dexmedetomidine group, 49 children (81.7%) did not show separation anxiety when their parents left, compared to 33 (55%) in the control group. The PAED scores and need for additional anesthetics were lower in the dexmedetomidine group than in the control group (median, 25 vs. 50 mg, $p<0.001$). Additionally, endoscopist satisfaction was higher in the dexmedetomidine group. No significant differences were observed between the groups in terms of complications ($p=0.600$) (Table 3).

Table 2 Comparison of gag reflex, cough incidence, and limb movements between nebulized dexmedetomidine and control groups in pediatric endoscopy

	Group Deksmedetomidine ($n=60$)	**Group Control ($n=60$)**	***p***
Gagging events *n (%)*			
no gagging	53 (88.3)	18 (30)	**<0.001**†
minimal	7 (11.7)	34 (56.7)	
moderate	0 (0)	8 (13.3)	
Cough *n (%)*			
no cough	57 (95)	33 (55)	**<0.001**‡
minimal	3 (5)	22 (36.7)	
moderate	0 (0)	5 (8.3)	
Limb movements *n (%)*			
None	43 (71.7)	14 (23.3)	**<0.001**§
Obvious	17 (28.3)	46 (76.7)	

†Fisher-Freeman- Halton test

§ Ki-kare testi; categorical variables are presented as counts (%). Statistically significant difference is highlighted in bold

Discussion

Our study demonstrated that the premedication of pediatric patients undergoing endoscopic procedures with nebulized dexmedetomidine significantly reduced the incidence of the gag reflex, coughing, and movements of the extremities compared with absence of premedication. Additionally, the total dose of sedative agents required during the procedure was lower in the nebulized dexmedetomidine group than in the control group, with a corresponding increase in endoscopist satisfaction.

Nebulized dexmedetomidine offers distinct advantages over the intranasal and oral routes owing to its rapid and effective absorption. Its bioavailability through the nasal and buccal mucosa is approximately 65% and 82%, respectively, supporting its efficacy as a sedative agent [14]. The primary reason for preferring nebulization over intranasal administration is a lower likelihood of causing adverse effects, such as nasal irritation, coughing, vocal cord irritation, and laryngospasm. Additionally, although oral administration can pose challenges in uncooperative

Table 3 Outcomes of pediatric endoscopy: a comparative analysis of nebulized dexmedetomidine and control groups

	Group Deksmedetomidine (*n* = 60)	Group Control (*n* = 60)	*p*
Parental seperation anxiety *n (%)*			
Child separates easily	49 (81.7)	33 (55)	**0.005**
Child whimpers, but is easily assured (not clinging to parents)	10 (16.7)	23 (38.3)	
Cries and cannot or is difficult to be assured (not clinging to parents)	1 (1.7)	4 (6.7)	
Complication *(n%)*			
None	55 (91.7)	57 (95)	0.600‡
Hypoxia	3 (5)	3 (5)	
Bradycardia	2 (3,3)	0 (0)	
PAED	4.5 (0—11)	8 (3—15)	**< 0.001**†
Propofol consumption (mg)	25 (0—80)	50 (0—140)	**< 0.001**†
Endoscopist satisfaction			
Excellent	47 (78.3)	8 (13.3)	**< 0.001**‡
Good	13 (21.7)	29 (48.3)	
Fair	0 (0)	22 (36.7)	
Poor	0 (0)	1 (1.7)	

† Mann Whitney U Test; Independent two sample t test, mean ± s. deviation, median (minimum – maximum). Statistically significant difference is highlighted in bold

Abbreviations: *PAED,* Pediatric Anesthesia Emergence Delirium

children, the nebulized form, applied as an atomized spray, minimizes drug loss by effectively covering the mucosal surface, thereby enhancing clinical efficacy [15]. Nebulized dexmedetomidine acts on the locus coeruleus of the central nervous system, and induces brain activity similar to that during natural sleep, potentially reducing the risk of disorientation; it is thus considered an effective and well-tolerated premedication method in pediatric patients [16].

The incidence of gag reflex during upper gastrointestinal endoscopy is approximately 29% [17]. In children, gagging tends to be more pronounced and challenging to control during endoscopic procedures, leading to discomfort and difficulties that may prolong the procedure and distract the endoscopist [18]. In our study, gagging, the primary outcome, was significantly reduced from 70 to 11% in the nebulized dexmedetomidine group compared to the occurrences in the control group. Similarly, the incidence of cough was significantly lower in the dexmedetomidine group, consistent with the observations of Antony et al., who found that nebulized dexmedetomidine significantly reduces moderate-to-severe cough compared to intravenous administration in patients undergoing fiberoptic bronchoscopy [19]. Despite using fewer sedative agents during the procedure, these findings suggest that application of topical dexmedetomidine effectively suppresses airway reflexes, which is consistent with the results from other studies [20] and leads to greater endoscopist satisfaction.

Separation anxiety remains a challenge in pediatric procedures. In terms of nebulized dexmedetomidine, Jin et al. found a dose of 2 μg/kg effective to manage separation anxiety in children aged 3–6 years [21]. Similarly, Anupriya et al. reported that doses of 2–3 μg/kg were safe and effective for children aged 1–8 years, with higher doses improving parental separation anxiety among younger children [6]. In our study, although the mean age of the patients was 11–12 years, higher than that in similar studies, we observed that children in the younger age group who received nebulized dexmedetomidine separated from their parents more easily, despite the lower dose. However, the optimal dose for children remains undetermined, and further studies are needed to evaluate the age-specific dosing of nebulized dexmedetomidine across different pediatric groups.

Postoperative agitation is common in pediatric patients, with reported incidences ranging from 10–66% due to factors such as incomplete cognitive development, environmental fear, and high pain sensitivity [22]. Recent literature suggests that nebulized dexmedetomidine is a safe and effective premedication for pediatric patients, with high success rates and minimal side effects. Compared to other premedication regimens, it significantly reduces postoperative agitation and separation anxiety, likely owing to its analgesic properties and ability to induce a natural sleep state [23]. In a study conducted by Abdel-Ghaffar et al., premedication of preschool children with nebulized dexmedetomidine was associated with more satisfactory sedation, shorter recovery times, and reduced postoperative agitation compared to nebulized ketamine or midazolam; these observations suggest that this agent may offer a potential advantage for premedication in pediatric patients [24]. Furthermore, a large cohort study involving 17,948 pediatric patients found that a combination of intranasal dexmedetomidine (2 μg/kg) and ketamine (1 mg/kg) achieved a 93% sedation success rate, underscoring the efficacy of nebulized dexmedetomidine in minimally invasive procedures such as pediatric endoscopy [25]. Similarly, in our study, the PAED scores were lower in the dexmedetomidine group.

Longer recovery times can be problematic in outpatient settings, as they may necessitate extended monitoring, impacting resource utilization and patient safety. Ryu et al. found that administration of dexmedetomidine was associated with prolonged recovery times [26]. In contrast, in our study, the recovery times in the nebulized

dexmedetomidine and control groups were significantly shorter than those in the intravenous dexmedetomidine group. We attribute this finding to the sedative effects of the nebulized dexmedetomidine, which reduced the need for additional anesthetic agents during the procedure.

This study had several limitations. First, this was a single-center study, which may limit the generalizability of our findings. Second, owing to the nature of the nebulized administration, the patients could not be blinded to the treatment. Third, due to the limited patient volume in the pediatric endoscopy unit, we had to broaden the age range and did not stratify patients by age, which could have influenced the sedation scores, as the sedation response may vary with age. Lastly, the plasma concentrations of dexmedetomidine were not measured. The pharmacokinetics of nebulized dexmedetomidine remain understudied, and further large-scale multicenter studies are needed to determine the optimal inhaled concentration.

Conclusions

In conclusion, nebulized dexmedetomidine is a safe and effective premedication agent for pediatric patients undergoing endoscopic procedures. The method significantly reduces gagging and coughing, lowers the need for anesthetic agents, and enhances endoscopist satisfaction. This approach reflects a comfortable and safe procedure and contributes to improved patient and provider outcomes in pediatric endoscopy.

Abbreviations

ASA	American Society of Anesthesiologists
ECG	Electrocardiography
SpO2	Peripheral oxygen saturation
PONV	Postoperative nausea and vomiting
PACU	Post-anesthesia care unit
PAED	Pediatric Anesthesia Emergence Delirium scale
PSAS	Parental Separation Anxiety Scale

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None.

Authors' contributions

ET and BD: Conceptualization, Methodology, Investigation, Software, Writing-Original draft preparation, Funding acquisition; YBU, EK, CK, SB: Methodology, Validation, Software, Reviewing and Editing; SB, BD and YBU: Visualization, Investigation, Reviewing and Editing. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study available from thr corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ondokuz Mayis University Clinical Research Ethics Committee (approval no: 2022/185). The study was conducted in accordance with the Declaration of Helsinki. The trial was registered prior to patient enrollment in the clinical trial database using the ClinicalTrials.gov (Identifier: NCT06218797). Written informed consent was obtained from all participants and/or their legal guardians on the day before surgery. The study was performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) checklist guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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