Randomized Controlled Trial

A Placebo-Controlled Randomized Trial Comparing Oral Midazolam, Dexmedetomidine, and Gabapentin on Prophylaxis of Emergence Agitation After Sevoflurane Anesthesia in Adenotonsillectomy

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Background: Sevoflurane causes emergence agitation (EA) in up to 80% of pediatric patients.

Objectives: Using midazolam, dexmedetomidine (DEX), and gabapentin, this work aimed to assess the prophylactic effect of oral premedication on EA incidence experienced by pediatric patients during recovery from sevoflurane anesthesia.

Study Design: Randomized controlled trial.

Setting: Kafrelsheikh University, Kafrelsheikh, Egypt.

Methods: This study was performed on 240 men and women aged 3 to 10 years who were scheduled for adenotonsillectomy. Patients were randomized into 4 equal-sized groups. Thirty minutes before general anesthesia, oral premedication was applied in the form an apple-flavored sugary fluid plus 0.5 mg/kg of midazolam in Group M, 4 µg/kg of DEX in Group D, 10 mg/kg of gabapentin in Group G, or no drugs whatsoever in Group P (placebo).

Results: The incidence of EA was reduced more greatly in the M, D, and G groups than in the P group, and the D group's incidence of EA was lower than that of the M or G groups. The severity of EA exhibited a more significant reduction in the M, D, and G groups than in Group P. Similarly, the time until extubation was more prolonged in the M, D, and G groups than it was in the P group. Hemodynamics measurements were significantly lower in Groups M, D, and G than in Group P, and the D group had a lower hemodynamics measurement than did the M or G groups. Sedation scores were greater in the D and G groups than in the P group, and the D group had a higher sedation score than did Group M.

Limitations: This study used a small sample, took place at a single center, and had a short follow-up period.

Conclusion: Premedication using oral midazolam, DEX, or gabapentin reduced the incidence of EA, and DEX provided the best sedation and hemodynamics of all.

Key words: Dexmedetomidine, emergence agitation, gabapentin, midazolam, sevoflurane

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In pediatrics, emergence agitation (EA) refers to a disturbed awareness, a confusion in the attention paid to the surrounding environment, and perceptive changes such as hypersensitivity to any stimulus and hyperactive motor behavior that a child experiences immediately after a period of anesthesia (1). Applying inhalational anesthetic agents to children subjected to surgery under general anesthesia can frequently cause EA, which occurs at a rate ranging from 18 to 80% (2). Perioperative anxiety commonly manifests in pediatric patients and may result in difficulty in anesthesia induction, exaggerated postoperative pain, and EA. Sedative premedication is thus usually utilized to promote children's cooperation and therefore induce anesthesia smoothly (3,4).

Proper premedication may alleviate EA or prevent its development. The oral route is a widely accepted, cost-effective, and proper method for giving medications in pediatrics. Additionally, the oral route is generally more comfortable and accepted than the other routes for administering premedication (5).

Midazolam, a benzodiazepine, exerts its antidepressant and anxiolytic effects by targeting gamma-aminobutyric acid (GABA) receptors within the brain (6). This interaction enhances the inhibitory effects of GABA. Qualities of midazolam include amnesiac properties, which can be advantageous in diminishing the recollection of potentially distressing perioperative events, and efficacy in reducing preoperative anxiety (7).

Dexmedetomidine (DEX) is an alpha 2-adrenoceptor agonist that exhibits remarkable selectivity and possesses sympatholytic, sedative, anxiolytic, and analgesic-sparing properties while also causing minimal respiratory function impairment (8).

Gabapentin is a GABA analog known as one of the anticonvulsant drugs. This substance is well-tolerated and has known impacts on pain and anxiety (9).

This work aimed to compare the prophylactic effects of oral midazolam, DEX, and gabapentin premedication on the incidence of postoperative EA after inducing sevoflurane general anesthesia for adenotonsillectomy.

Methods

This randomized, placebo-controlled, triple-blind prospective study was performed on 240 boys and girls aged 3 to 10 years who met the status of I or II according to the American Society of Anesthesiologists (ASA) and were scheduled for adenotonsillectomy. The study was carried out from July 2023 to March 2024 following approval from the Ethical Committee Kafrelsheikh University Hospitals, Egypt (approval code: KFSIRB200-21) and registration at Clinicaltrials.gov (ID: PACTR202308758655839). Written informed consent was obtained from the patients' relatives.

Exclusion criteria were congenital anomalies, history of allergy to the medication included in the study, and cardiac or respiratory diseases.

Randomization and Blinding

Parallel randomization was done using a computer-generated randomization table in closed, sealed, opaque envelopes. Patients were randomly sorted into 4 groups of equal size. Each group received a different oral premedication 30 minutes before the induction of general anesthesia. Group P, the placebo group, received a plain, apple-flavored sugary fluid free of drugs. Group M received the sugary fluid containing 0.5 mg/kg of dissolved midazolam. Group D received the sugary fluid containing 4 μg/kg of dissolved DEX, and Group G received the sugary fluid that contained 10 mg/kg of dissolved gabapentin.

Caregivers, outcome assessors, and patients were blinded to the group allocation.

All patients underwent history taking, clinical assessments, and routine laboratory investigations.

Methods of monitoring included electrocardiography, noninvasive blood pressure tests, pulse oximetry, capnography, and temperature probes.

To reiterate, patients received oral premedication according to group allocation before the operation.

Anesthesia was induced by using an anesthesia breathing circuit (Mapleson F) with assisted spontaneous respiration through sevoflurane (8%) and O_2 at a flow of 6 L/minute. After adequate anesthesia depth was reached, the IV cannula was inserted. Sevoflurane was reduced to 2%, fentanyl (1 μg/kg) and atracurium (0.5 mg/kg) were administered, and then the endotracheal tube was inserted. Anesthesia maintenance was achieved by using 2% sevoflurane. Then, the pressure-controlled mode was applied to maintain ET_{CO2} at 35-40 mmHg and O_2 flow at 2 L/minute.

Sevoflurane was discontinued at the end of the surgery. Atropine (0.01 mg/kg) and neostigmine (0.04 mg/kg) were given to counteract the residual neuromuscular blockade. Assisted spontaneous breathing with 8 L per minute of O_2 was provided. The patient was extubated after the coughing reflex and normal breathing had returned.

Afterward, patients were transferred to the post-anesthesia care unit (PACU), where O_2 saturation was monitored with pulse oximetry. O_2 (6 L/minute) was given, with a face mask used when needed. The patient was discharged from the PACU after receiving a score greater than 8 on the Aldrete recovery scale.

Intraoperative and PACU monitoring was performed by an anesthetic assistant who was blinded to the type of premedication received and was asked to adhere to a fixed protocol of PACU care.

The incidence and degree of EA after 15 minutes (T15) and then 30 minutes (T30) following PACU admission were evaluated on the Pediatric Anesthesia Emergence Delirium (PAED) scale (10), which was composed of 5 behavioral items. Each item was scored from 0 (extremely) to 4 (not at all). The total score was the sum of the values for all 5 items. EA was defined as a PAED score of 10 or greater; if the score ranged from 10 to 12, it denoted moderate EA, and a score of 13 or higher denoted severe EA. Fentanyl (1 µg/kg) was given as a rescue medication for extreme EA; if EA did not decrease within 5 minutes, propofol (0.5-1 mg/kg) was administered, with O_2 saturation monitored by pulse oximetry. O_2 (6 L/minutes) was also applied, with a face mask used if necessary.

Sedation level after emergence was estimated by the Ramsay Sedation Score (RSS) (11). On this scale, a score of one denotes an anxious and delirious or restless patient or both; 2 denotes a cooperative, oriented, and calm patient; 3 denotes a patient responsive to orders only; 4 denotes a patient who responds quickly to a slight glabellar tapping or loud sound; 5 denotes a patient who gives a weak response to a slight glabellar tapping or loud sound, and 6 denotes an unresponsive patient.

Postoperative pain was assessed via a score on the Children and Infants' Postoperative Pain Scale (CHIPPS) (12). If the CHIPPS score was less than 5, ketorolac (1 mg/kg) diluted in 10 mL of normal saline was administered through IV, and if the score was greater than 5, fentanyl (1 µg/kg) was given as a rescue medication in the PACU, with O_2 saturation monitored via pulse oximetry.

Time until extubation (the duration between the closure of inhalational anesthesia and the event of extubation), duration of anesthesia (the time from the induction of anesthesia to the closure of the inhalational anesthetic), time until the emergence of anesthesia (the duration from extubation to the recording of the patient's response in the form of purposeful movement or eye-opening in the PACU), and the length of the PACU stay were recorded.

The primary outcome was the incidence and degree of EA in the PACU by PAED. The secondary outcomes were the duration of anesthesia, time until extubation, time until the emergence of anesthesia, level of sedation after emergence, and postoperative pain.

Sample Size Calculation

The sample size calculation was done in G*Power 3.1.9.2 (Universitat Kiel). We performed a pilot study (using 10 patients in each group). We found that the incidence of agitation at T15 (the primary outcome) was 60% in Group P and 30% in Group D. The sample size was based on a 95% confidence limit, a study power of 90%, and a group ratio of 1:1:1:1, and 4 patients were added to each group to overcome dropout. Therefore, we recruited 60 patients in each group.

Statistical Analysis

IBM SPSS Statistics Version 27 (IBM©) was utilized to analyze results statistically. The Shapiro-Wilks test and histograms were utilized to evaluate the normality of the data distribution. The Chi-square test was used to analyze qualitative variables, expressed as frequencies and percentages. ANOVA (F) with post hoc analysis was expressed to analyze quantitative parametric data presented as means and standard deviations. The Kruskal-Wallis test analyzed nonparametric variables, expressed as the median and interquartile range (IQR). A 2-tailed *P*-value < 0.05 was considered statistically significant.

Results

In this work, we evaluated 253 patients for eligibility. Ten patients did not meet the criteria (6 due to active infection, 3 due to obstructive sleep apnea syndrome, one because of a cleft palate), and 3 did not agree to share in the study. The remaining patients were randomized into 4 groups (60 patients/group). All allocated patients were followed up and analyzed statistically (Fig. 1). The 4 groups showed insignificant differences in demographic data and duration of surgery (Table 1).

Among the 4 groups, the heart rate (HR) and mean arterial pressure (MAP) measurements also showed insignificant differences at the baseline and 5-minute marks. More significant reductions in these measurements occurred at the 10-, 15-, 20-, 25-, 30-, and 35-minute marks as well as at the end of surgery in the M, D, and G groups than in the P group. Compared to the

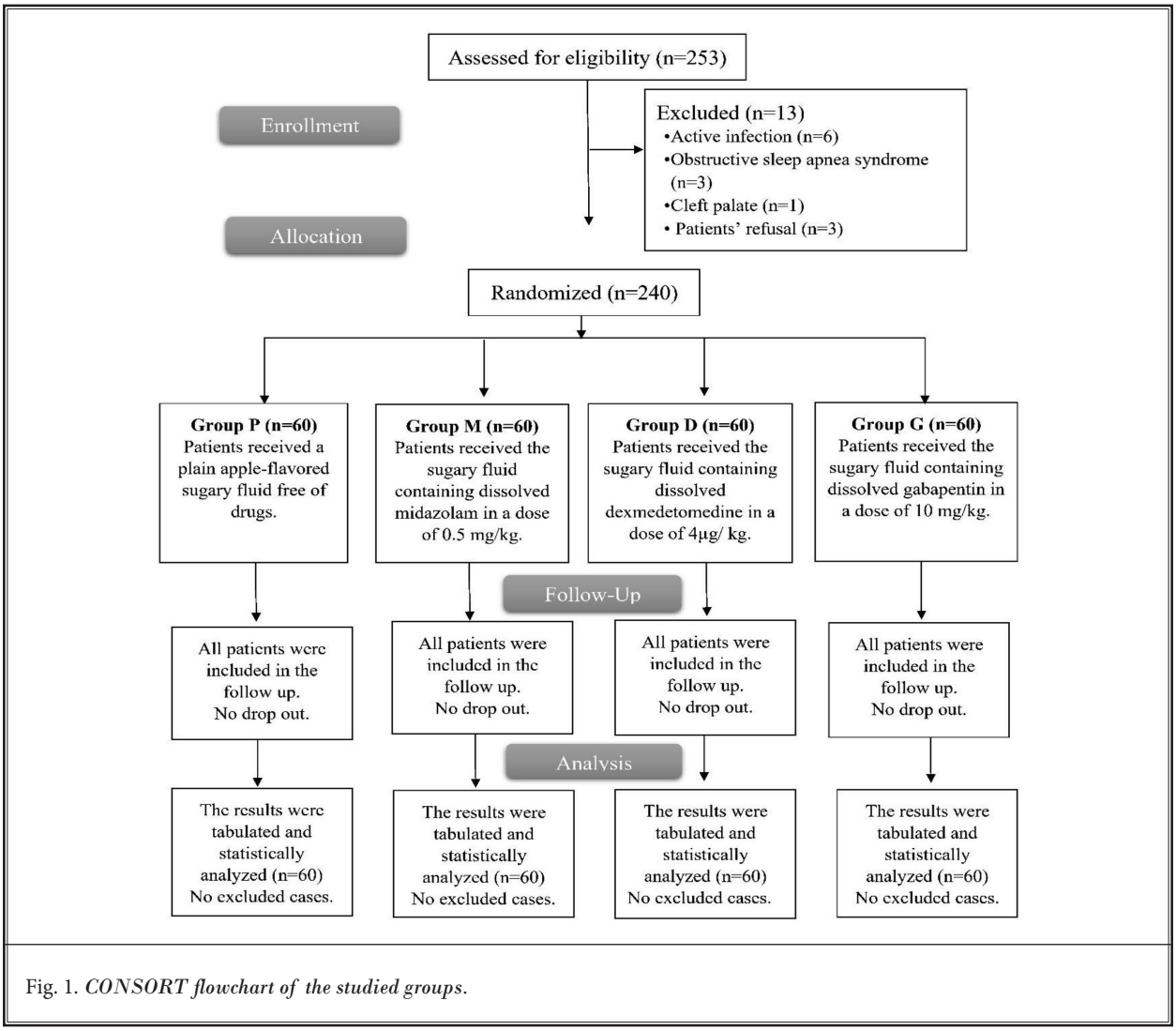

Fig. 1. *CONSORT flowchart of the studied groups.*

Table 1. *Demographic data and duration of surgery of the studied groups.*

		Group P (n = 60)	Group M (n = 60)	Group D (n = 60)	Group G (n = 60)	*P* value
Age (years)		6.3 ± 2.57	7.1 ± 2.05	6.4 ± 2.08	6.1 ± 1.83	0.090
Gender	Male	34 (56.67%)	29 (48.33%)	38 (63.33%)	35 (58.33%)	0.415
	Female	26 (43.33%)	31 (51.67%)	22 (36.67%)	25 (41.67%)	
Weight (kg)		26.8 ± 8.79	28.9 ± 8.13	26.6 ± 7.45	25.7 ± 7.04	0.142
Height (cm)		117.9 ± 16.58	122.5 ± 13.39	118.2 ± 13.58	116.5 ± 11.74	0.107
Duration of surgery (min)		32.3 ± 5.16	33.8 ± 7.39	31.4 ± 8.29	34.3 ± 9.13	0.131

Data are presented as mean ± SD or frequency (%).

M and G groups, the D group showed more significant reductions in the HR and MAP measurements. Groups M and G showed insignificant differences between them (Fig. 2).

Differences in duration of anesthesia, time until emergence, and PACU stay were insignificant among the 4 groups. Time until extubation was significantly more prolonged in Groups M, D, and G than in Group P ($P < 0.05$), while the differences in this measurement among the D, G, and M groups were insignificant (Table 2).

The incidence of EA at T15 and T30 was significantly lower in Group M, Group D, and Group G than in Group P ($P < 0.05$). This incidence was lower in Group D than in Group M or Group G ($P < 0.05$), between which the

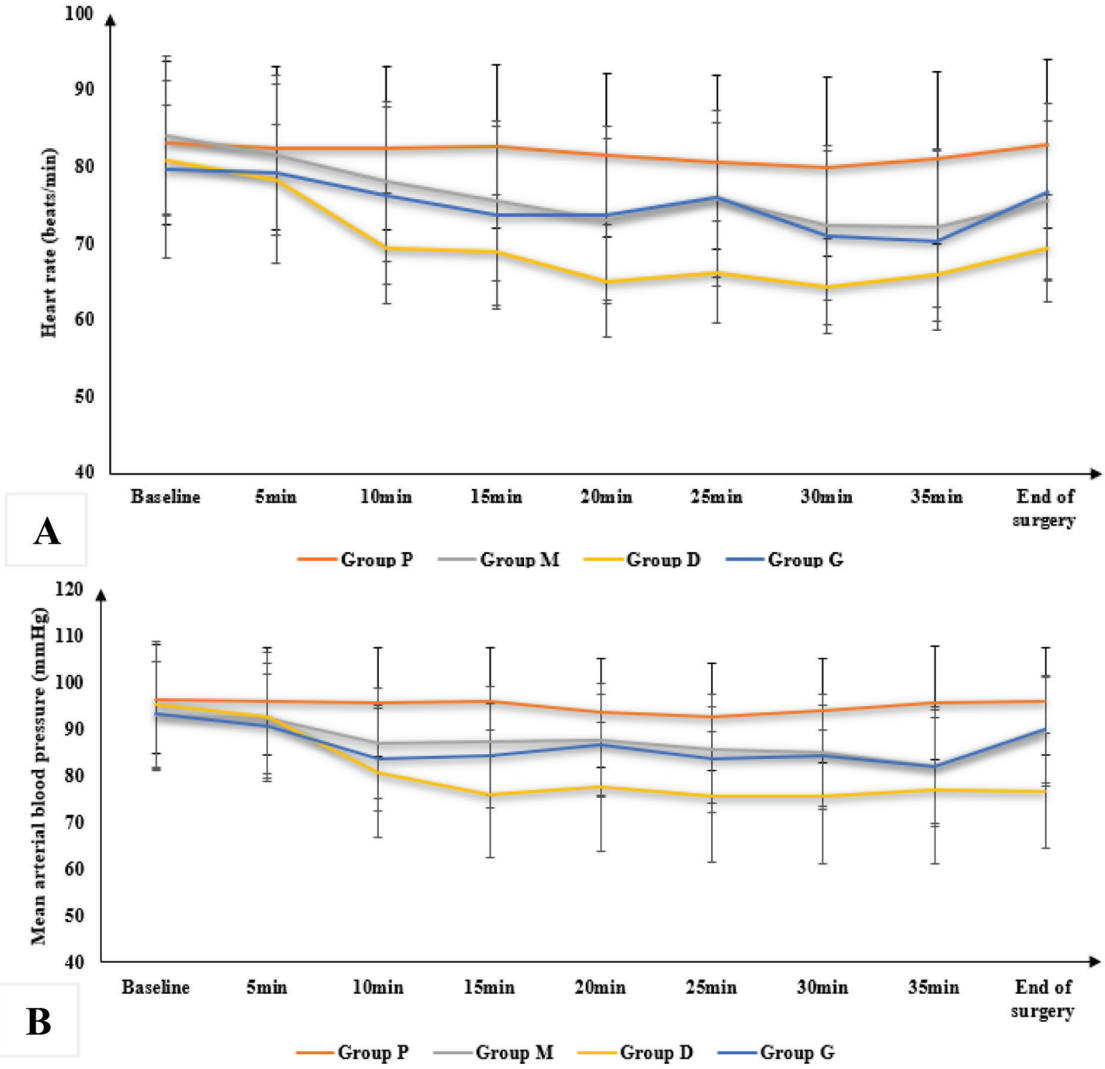

Fig. 2. *Changes in the heart rate (A) and mean arterial blood pressure (B) of the studied groups.*

difference in EA incidence was insignificant. The severity of EA at T15 and T30 was also significantly lower in Groups M, D, and G than in Group P ($P < 0.05$) (Table 3).

The RSS was significantly greater in Groups D and G than in Group P ($P < 0.05$) and was also higher in Group D than in Group M ($P < 0.05$), while Group G was comparable to Groups D and M in that regard. CHIPPS

Table 2. *Duration of anesthesia, time until extubation, time until emergence, and PACU stays of the studied groups.*

	Group P (n = 60)	Group M (n = 60)	Group D (n = 60)	Group G (n = 60)	*P* value
Duration of anesthesia (min)	49.1 ± 6.42	50.7 ± 8.12	51.1 ± 7.95	52.6 ± 9.16	0.122
Time until extubation (min)	4.9 ± 1.41	5.8 ± 1.16	6.3 ± 1.66	6.1 ± 1.43	< 0.001
	P1	0.01	< 0.001	< 0.001	
	P2		0.133	0.496	
	P3			0.869	
Time until emergence (min)	7.1 ± 1.6	7.3 ± 1.12	7.7 ± 1.69	7.6 ± 1.51	0.106
PACU stay (min)	34.9 ± 5.88	33.4 ± 6.11	33.9 ± 4.43	32.3 ± 4.79	0.065

Data are presented as mean ± SD. P1: *P* value compared to Group P, P2: *P* value compared to Group M, P3: *P* value compared to Group D.

scores were much lower in Groups D and G than in Groups P and M ($P < 0.05$). However, the CHIPPS scores between Groups M and P were comparable and were significantly lower in Group D than in Group G ($P < 0.05$) (Table 4).

Neither hypotension nor bradycardia occurred in any of the patients.

Discussion

The newest inhalational anesthetic drugs, such as desflurane and sevoflurane, are known for their fast recovery profile and washout. These drugs are also known for their accompanying approximate 80% increase in the incidence of EA if any of them is utilized as a single anesthetic agent (13).

EA may lead to injuries in patients and medical staff and is accompanied by other postoperative adverse events (14). The precise mechanism of EA following inhalational anesthetics is unclear (15). This phenomenon could possibly be explained by such anesthetics' fast wash period, which may contribute to patients' inability to adapt to their surroundings and the experience of parental separation, as well as postoperative pain (16).

In the present study, EA was significantly less common in patients who received midazolam, DEX, or gabapentin than in patients who were placed in the placebo group. Patients who received DEX endured significantly fewer incidences of EA than did those who received midazolam or gabapentin. The midazolam, DEX, and gabapentin groups had significantly less severe EA than did the placebo group while also experiencing similar durations of anesthesia, times until emergence, and PACU stays. However, the midazolam, DEX, and gabapentin groups took a significantly longer time to extubate than did the placebo group, with no significant differences between the DEX and gabapentin groups or the DEX and midazolam groups. The DEX and gabapentin groups showed significantly higher levels of sedation than the placebo group, but sedation levels between the DEX and midazolam groups were comparable.

As for postoperative pain, the DEX and gabapentin groups had significantly lower degrees thereof than did the placebo and midazolam groups. The latter 2 groups showed no significant difference in postoperative pain between them, but the DEX group

Table 3. *Incidence and degree of emergence agitation in the studied groups.*

		Group P (n = 60)	Group M (n = 60)	Group D (n = 60)	Group G (n = 60)	*P* value
At T15						
Incidence		35 (58.33%)	24 (40%)	10 (16.67%)	21 (35%)	< 0.001
		P1	0.044	<0.001	0.010	
		P2		0.004	0.571	
		P3			0.021	
Degree	Moderate	29 (48.33%)	21 (35%)	9 (15%)	18 (30%)	< 0.001
	Severe	6 (10%)	3 (5%)	1 (1.67%)	3 (5%)	
At T30						
Incidence		30 (50%)	19 (31.67%)	6 (10%)	16 (26.67%)	< 0.001
		P1	0.041	<0.001	0.008	
		P2		0.003	0.546	
		P3			0.018	
Degree	Mild	12 (20%)	13 (21.67%)	6 (10%)	14 (23.33%)	< 0.001
	Moderate	17 (28.33%)	5 (8.33%)	0 (0%)	2 (3.33%)	
	Severe	1 (1.67%)	1 (1.67%)	0 (0%)	0 (0%)	

Data are presented as frequency (%). T15: 15 minutes. T30: after 30 minutes. P1: *P* value compared to Group P. P2: *P* value compared to Group M. P3: *P* value compared to Group D.

Table 4. *RSS and CHIPPS of the studied groups.*

		Group P (n = 60)	Group M (n = 60)	Group D (n = 60)	Group G (n = 60)	*P* value
RSS		2 (2 - 4)	3 (2 - 4)	4 (3 - 4.25)	3.5 (2 - 5)	0.002*
		P1	0.570	<0.001*	0.032*	
		P2		0.004*	0.114	
		P3			0.183	
CHIPPS	Score <5	30 (50%)	33 (55%)	53 (88.33%)	44 (73.33%)	< 0.001*
	Score ≥5	30 (50%)	27 (45%)	7 (11.67%)	16 (26.67%)	
		P1	0.583	<0.001*	0.008*	
		P2		<0.001*	0.036*	
		P3			0.036*	

Data are presented as median (IQR) or frequency (%). RSS: Ramsey sedation score. CHIPPS: Children and Infant Postoperative Pain Scale. P1: *P* value compared to Group P. P2: *P* value compared to Group M. P3: *P* value compared to Group D.

experienced a greater reduction in pain than did the gabapentin group.

In a result consistent with our findings, Badawy et al (17) reported that after strabismus surgery, the incidence and severity of EA following the administration of desflurane anesthesia were lower in a group of patients who received preoperative gabapentin than in the control group. Also, the duration of emergence showed statistically greater prolongation in the gabapentin group than in the control group. Furthermore, Keles and Kocaturk (18) illustrated that after dental procedures performed under general anesthesia, the duration of anesthesia and sedation score were comparable between a group of patients who received DEX and a group of patients who received midazolam. However, the DEX group exhibited a significantly lower EA score than did the midazolam group. Additionally, Prabhu and Mehandale (19) demonstrated that among patients who received elective surgeries lasting less than 2 hours, those who were given DEX experienced significantly fewer incidences of EA than did those who were given midazolam. Moreover, Peng et al (20) demonstrated that whether patients received DEX or midazolam made no difference in their recovery time or length of PACU stay. Also, DEX was a superior premedication to midazolam, since the former promoted sedation preoperatively and reduced postoperative pain. In agreement with the present findings, Salman et al (21) found that EA scores were significantly lower in the gabapentin group than the control group. Conversely, Feng et al (22) performed a meta-analysis of 12 RCTs that sorted 422 patients who had received DEX into one group and 448 patients who had received midazolam into another. Feng et al stated that the DEX and midazolam groups endured a similar EA incidence. This result may be attributed to the large sample size.

According to the results of our research, the superiority of DEX may be related to its capability to induce sedation and analgesia without causing considerable respiratory depression, its minimal influence on hemodynamics, and its efficiency in minimizing an incidence of EA.

The economic burden of emergence agitation (EA) is substantial, with potential consequences including treatment costs for injuries, such as airway or vocal cord damage, which can lead to long-term harm (23). Furthermore, EA often results in increased demands on staff, which can be a significant outcome in itself (13). Prolonged amounts of time spent in operating rooms or recovery rooms are also common consequences of EA, leading to additional costs (15). Although the exact financial burden of EA has not been quantified, the cost of operating rooms has been estimated to be approximately $36-37 per minute, while recovery rooms cost around $9 per minute (24,25). Moreover, the costs of treating injuries, increased staff demands, and potential need for additional sedative medications may further contribute to the economic impact of EA (26). Additionally, the risk of EA poses a threat to health care staff, who may be at risk of workplace injuries that require facility-funded treatment (13).

This study revealed that DEX may be the most cost-effective option among pediatric sedative premedications due to its superior efficacy in reducing EA, which could lead to savings on the costs of additional medications and interventions. While the study did not compare costs directly, the similar durations of anesthesia, emergence, and PACU stays shared by the DEX, midazolam, and gabapentin groups suggest similar costs in these areas. DEX is effective in reducing EA in pediatric patients. While DEX is more expensive than midazolam, the former medication imposes a shorter recovery time and less respiratory depression, which can lead to long-term cost savings (27). Gabapentin, despite being efficacious, may not be a cost-effective option due to its similar efficacy to the less expensive midazolam. However, although gabapentin is used for EA and is effective in reducing both EA and postoperative pain, gabapentin is more expensive than midazolam (28).

Midazolam, which has been used commonly to reduce EA, has been shown to be cost-effective due to its low cost and availability. However, midazolam can cause respiratory depression and prolonged sedation, which can lead to increased recovery time and higher health care costs (29).

Limitations

The small sample, single-center setting, and short follow-up period limited our study. Further studies that compare different doses of other medications at different ages and operations.

Conclusions

Premedication using oral midazolam, DEX, or gabapentin reduces EA incidence in pediatric patients and provides better sedation and hemodynamics than does a placebo. Among all the substances tested, DEX is superior.

Author Contributions

Study concept and design: AMA and MFA; analysis and interpretation of data: AAE and SKA; drafting of the manuscript: MFA; critical revision of the manuscript for important intellectual content: AAE and SKA; statistical analysis: AAE.

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