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Original article

Oral Pregabalin versus Oral Midazolam as Sedative Premedication for Pediatric Tonsillectomy: A Randomized Controlled Trial

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Abstract:

Background: Premedication in pediatric cases plays a critical role in achieving anxiolysis, which facilitates a smoother separation from parents and simplifies the induction of anesthesia. This research assessed the efficacy of pregabalin as a premedication agent in pediatric anesthesia relative to the commonly used midazolam. **Methods:** This randomized, double-blind controlled study involved 90 children aged 1 to 7 years undergoing tonsillectomy. Participants were randomly allocated into three equal groups receiving pregabalin syrup at 3.5 mg/kg (Group P), midazolam at 0.5 mg/kg (Group M), or a placebo solution (Group C). The primary outcome was assessed using the postoperative pediatric agitation scale (Watcha), while secondary outcomes included parental separation anxiety, acceptance of the anesthesia mask, FLACC (Face, Legs, Activity, Cry, Consolability) pain scores, and extubating time. **Results:** Postoperative Watcha scale were significantly reduced in Groups P and M in comparison with the controls ($p<0.05$), with scores in the two intervention groups being similar. Groups P and M demonstrated significantly improved parental separation anxiety and mask acceptance relative to controls. The intervention groups exhibited significantly diminished FLACC scores at the Post-Anesthesia Care Unit (PACU) and at 2, 4, and 6h postoperatively. Extubation time following cessation of general anesthesia was significantly prolonged in group M as opposed to both P and control groups ($p<0.001$). **Conclusions:** Pregabalin and midazolam showed similar effects on emergency agitation, parental separation anxiety, mask acceptance, and time of first analgesia requirements. However, pregabalin demonstrated greater efficacy in postoperative pain reduction and didn't prolong the extubating time in comparison to midazolam.

Keywords: Oral Pregabalin, Midazolam, Pediatric sedation, Tonsillectomy, premedication.

Introduction

Tonsillectomy, with or without concurrent adenoidectomy, represents one of the most prevalent surgical interventions implemented in the pediatric population, aiming to completely remove the tonsils by dissecting the peritonsillar space. While this procedure is routine, it presents significant emotional challenges for pediatric cases [1]. Hospitalization and surgery can provoke considerable anxiety, with anesthesia induction being one of the most distressing experiences for children. To manage this, anesthetic plans must be carefully tailored to the child's age and temperament, incorporating both pharmacological and nonpharmacological techniques [2].

Anxiety management in pediatric cases is crucial for ensuring smooth separation from caregivers and successful anesthesia induction. Children who exhibit high levels of anxiety often face greater difficulty during these transitions and are more likely to display postoperative maladaptive behaviors [3]. Ideally, premedication should achieve effective anxiolysis with minimal adverse effects (AEs), offering a predictable onset and ease of administration. Agents like midazolam are widely used for their sedative and anxiolytic properties, helping to prevent the physiological stress that can arise from perioperative anxiety [4].

Gabapentanoids, such as pregabalin, have gained attention in recent years for their potential benefits in pediatric anesthesia, particularly in managing postoperative pain and anxiety [5]. Pregabalin's high binding affinity for specific calcium channels enhances its anxiolytic and analgesic effects, making it a promising premedication agent. Despite these advantages, clinical experience with pregabalin in pediatric anesthesia remains limited, and its AEs, such as dizziness and somnolence, warrant further investigation, particularly in young patients [6].

While increasing attention is being directed toward as a premedication for pediatric anesthesia, most evidence comes from studies on its use in adults or for neuropathic pain and seizures in children. There remains a gap in high-quality literature specifically addressing pregabalin's efficacy and safety in pediatric anesthesia, highlighting the demand for more focused investigation to gain comprehensive insight into its role in this context [4].

This work aimed to assess pregabalin role as premedication in pediatrics anesthesia in comparison to traditionally used midazolam regarding (emergence agitation (EA), separation from mother, cannulation, mask ventilation, and postoperative pain) in tonsillectomy operations.

Patients and methods

This randomized, double-blind, controlled study enrolled 90 pediatric cases, aged between 1 and 7 years, of both genders, classified as ASA physical status I or II, who were scheduled to undergo tonsillectomy. The investigation was carried out from September 2023 through August 2024 at Benha University Hospitals, subsequent to approval by the Ethical Committee of Benha University Hospitals, Qalyubia, Egypt (approval reference: Ms 6-9-2023). Written informed consent was acquired from the parents or guardians following a detailed briefing on the study's aims, and participants were assigned unique confidential identification codes to ensure privacy.

Exclusion criteria included cases with intellectual disabilities or developmental delays, hypersensitivity or contraindications to the interventions drugs, current administration of psychiatric agents, history of seizure disorders, presence of any severe or uncontrolled systemic illnesses (e.g., asthma, renal insufficiency), recent (within 2 weeks) administration of central nervous system-active agents, hyperactivity disorders, or gastrointestinal dysfunction.

Randomization and blindness

Eligible subjects were randomized in a parallel-group design into three equal arms utilizing computer-generated random allocation sequences. Allocation concealment was ensured by placing assignment codes into sequentially numbered, sealed, opaque envelopes, prepared by a research assistant independent of the study investigators. The envelopes were opened by an anesthesia resident who was not involved in case care or outcome assessment. The study was carried out in a double-blind manner, with both the cases and the investigators blinded to the identity of the pre-anesthetic test medications. Syrups were prepared by a pharmacist in similar 5 ml volumes, matched for color and taste.

Participants were categorized into three groups: Group P received pregabalin syrup [3.5 mg/kg (Lyribalin 100 mg/5 ml)]; Group M was administered midazolam [0.5 mg/kg (Mediathetic® 5 mg/ml)] mixed in apple juice; and Group C received a placebo solution identical in taste, appearance, and color to the active medications.

Study procedure

Preoperative:

Eligible children underwent thorough clinical evaluation, including detailed history taking, physical examination, and laboratory investigations comprising complete blood count, coagulation studies, and renal and hepatic function tests. Premedication with either pregabalin or midazolam was administered oneh prior to the surgical procedure, prior to separation from the parents. The child's anxiety level during parental separation was documented and quantified using the Parental Separation Anxiety Scale (PSAS) [7].

Intraoperative:

Eligible children were separated from their mothers and upon arrival in the operating room, standard monitoring was established, including electrocardiography, non-invasive blood pressure, pulse oximetry, and capnography. Heart rate (HR) and mean arterial pressure (MAP) were recorded prior to general anesthesia (GA) induction and subsequently at 10-minute intervals throughout the surgical procedure. An intravenous cannula, either 22- or 24-gauge, was inserted into the dorsum of the hand. The case's response to intravenous cannulation was assessed by an independent observer, blinded to the administered premedication, utilizing the Groningen Distress Rating Scale (GDRS) [8].

GA was induced with fentanyl at a dose of 1 μg/kg and propofol at 2–3 mg/kg. Once an adequate depth of anesthesia was achieved, endotracheal intubation was performed using an appropriately sized tube, which was then securely fixed in place. Assisted spontaneous ventilation was subsequently initiated. The child's response to induction was evaluated using the Mask Acceptance Scale.

The maintenance phase of general anesthesia was carried out utilizing sevoflurane administered at concentrations between 2% and 4%, delivered in a balanced mixture comprising 50% air and 50% oxygen. Throughout the surgical procedure, continuous monitoring of the case's hemodynamic parameters was performed. Specifically, any elevation exceeding 20% above baseline values in HR or MAP, whether induced by surgical stimuli or occurring spontaneously at any intraoperative time point, prompted an increase in the sevoflurane concentration to ensure adequate anesthetic depth and hemodynamic stability. All operative interventions were carried out by a consistent surgical team employing standardized and uniform techniques to minimize variability. Upon completion of the surgical procedure, cases were carefully awakened from anesthesia, promptly extubated, and subsequently transferred to the Post Anesthesia Care Unit (PACU) for close postoperative monitoring. The duration elapsed from cessation of anesthetic agents to extubation was documented.

Postoperative

Postoperative EA was evaluated using the Watcha scale at 10, 20, and 30 m following surgery. The Faces, Legs, Activity, Cry, Consolability (FLACC) scale [9] , a behavioral scoring tool commonly used in pediatric anesthesia recovery. The scale ranges from 1 to 5, where 1 indicates an obtunded state with no response to stimulation; 2 represents a sleeping child responsive to movement or stimulation; 3 denotes an awake and calm child; 4 indicates prolonged crying; and 5 reflects severe agitation with thrashing behavior requiring restraint. Secondary outcomes included assessment of PSAS, GDRS, mask acceptance scale, and hemodynamic parameters—HR and MAP—measured pre-procedure and every 10 m until the end of surgery. Other secondary outcomes were time to extubation following discontinuation of GA, postoperative pain evaluated by the pediatric FLACC pain scale, timing of first rescue analgesia, total doses of diclofenac sodium administered, and parental satisfaction.

Study measurements

The Primary outcome was EA was assessed using a modified 5-point Watcha Scale [10], a behavioral scoring tool commonly used in pediatric anesthesia recovery. The scale ranges from 1 to 5, where 1 indicates an obtunded state with no response to stimulation, 2 represents a sleeping child responsive to movement or stimulation, 3 denotes an awake and calm child, 4 indicates prolonged crying, and 5 reflects severe agitation with thrashing behavior requiring restraint. The secondary outcomes were assessment of PSAS, GDRS, mask acceptance scale, hemodynamic parameters (HR and MAP) which was measured pre-procedure and every 10 m till the end of surgery, time to extubation, time to extubation after discontinuation of GA. Postoperative pain assessed by pediatric FLACC pain scale, time of first rescue analgesia need, doses required of diclofenac sodium, and parents satisfaction.

Statistical analysis

Statistical analyses were carried out utilizing SPSS software, version 27 (IBM©, Chicago, IL, USA). The normality of distribution for continuous variables was evaluated using the Shapiro-Wilks test in conjunction with visual inspection of histograms. Parametric variables were stated as mean ± standard deviation (SD) and compared across groups employing one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test. For non-parametric variables, data were expressed as median and interquartile range (IQR) and analyzed using the Kruskal-Wallis test, with subsequent pairwise comparisons adjusted using the Bonferroni correction method. Categorical variables were summarized as frequencies and percentages, with group comparisons performed via the Chi-square test. A two-tailed p-value of less than 0.05 was considered indicative of statistical significance.

Sample size estimation was performed utilizing G*Power software (version 3.1.9.6). Setting the alpha level at 0.05 and statistical power at 90%, it was determined that a minimum of 30 subjects per group would be required to detect an effect size (Cohen's d) of 0.957 concerning the primary outcome measure, namely emergence agitation score, as established in prior study [11]. This calculation accounted for an anticipated dropout rate of 20%.

Results:

Among 109 cases assessed for eligibility, 12 were deemed ineligible based on predefined criteria, while 7 declined to enroll in the study. Consequently, 90 participants were randomly distributed evenly into three groups, each comprising 30 individuals. All randomized subjects completed the follow-up protocol and were incorporated into the comprehensive statistical analysiss. (**Figure 1)**

Demographics and duration of surgery were insignificantly different between the studied patients. **(Table 1)**

The PSAS, mask acceptance scale, and GDRS scores were similar between Groups P and M but were significantly elevated in Group C as opposed to both Groups P and M (p<0.05). Watcha scale scores at 10, 20, and 30 m postoperatively were significantly diminished in Groups P and M as opposed to Group C (p<0.05), with scores between Groups P and M being similar (**Table 2)**

FLACC scores were significantly diminished in Groups P and M as opposed to Group C upon arrival at PACU and at 2, 4, 6, and 8h postoperatively (p<0.05), while scores at 10 and 12h were similar among the three groups. Additionally, FLACC scores at PACU, and 2 and 8h were significantly diminished in Group P as opposed to Group M (p<0.05). **(Figure 2)**

HR values at baseline and at the end of surgery were similar across groups, but significant differences were observed at 10, 20, and 30 m intraoperatively (p<0.05). HR remained similar between Groups P and M at all measured time points. MAPs were similar at baseline and at surgery completion but were significantly diminished at 20 and 30 m in Groups P and M as opposed to Group C (p<0.05). At 10 m, MAP was significantly diminished in Group M as opposed to Group C (p= 0.030) and similar to Group P. (**Figure 3)**

Time to extubation after GA discontinuation was significantly longer in Group M in contrast with Groups P and C (p<0.001). Time to first rescue analgesia request exhibited diminished difference between Groups P and M but was significantly shorter in Group in contrast with to both Groups P and M (p<0.001). Rectal diclofenac consumption exhibited diminished variation among the three groups. Parental satisfaction exhibited diminished differences between Groups P and M but was significantly diminished in Group C (p= 0.001). (**Table 3)**

Table 1: Demographics and duration of surgery of the enrolled patients

		Group P (n=30)	Group M (n=30)	Group C (n=30)	P
Age (years)		4.5±1.22	4±1.5	4.3±1.76	0.352
Sex	**Male**	18(60.0%)	19(63.33%)	17(56.67%)	0.870
	Female	12(40.0%)	11(36.67%)	13(43.33%)	
Weight (kg)		18±4.29	16.8±4	18.1±5.39	0.494
ASA physical status	**I**	20(66.67%)	23(76.67%)	23(76.67%)	0.600
	II	10(33.33%)	7(23.33%)	7(23.33%)	
Duration of surgery (min)		36.1±11.58	37.8±10.47	35.9±9.9	0.742

Data are presented as mean ± SD or frequency (%). ASA: American society of anesthesiologists.

Table 2: Parents separation anxiety scale, GDRS and mask acceptance scale of the enrolled patients

		Group P (n=30)	Group M (n=30)	Group C (n=30)	P
Parents separation anxiety scale	**Mild**	12(40.0%)	11(36.67%)	1(3.33%)	**<0.001***
	Moderate	16(53.33%)	15(50.0%)	2(6.67%)	
	Sever	2(6.67%)	3(10.0%)	12(40.0%)	
	Extreme	0(0.0%)	1(3.33%)	15(50.0%)	
		P1= 0.734, **P2<0.001*, P3<0.001***			
GDRS	**Calm**	11(36.67%)	10(33.33%)	2(6.67%)	**<0.001***
	Mild distress	8(26.67%)	9(30.0%)	3(10.0%)	
	Serious distress	9(30.0%)	9(30.0%)	10(33.33%)	
	Severe distress	1(3.33%)	1(3.33%)	6(20.0%)	
	Panic	1(3.33%)	1(3.33%)	9(30.0%)	
		P1=0.998, **P2=0.001*, P3=0.001***			
Mask acceptance scale	**Combative**	2(6.67%)	3(10.0%)	13(43.33%)	**<0.001***
	Moderate fear of mask	9(30.0%)	11(36.67%)	15(50.0%)	
	Cooperative with reassurance	11(36.67%)	7(23.33%)	1(3.33%)	
	Calm	8(26.67%)	9(30.0%)	1(3.33%)	
		P1=0.717, **P2<0.001*, P3<0.001***			
Watcha scale	**10min**	2(2-3)	2(1-2)	4(3-5)	**<0.001***
		P1=0.555, **P2<0.001*, P3=0.002***			
	20min	2(2-3)	2(2-3)	4(3-5)	**<0.001***
		P1=1, **P2<0.001*, P3<0.001***			
	30min	2(2-3)	2(2-3)	4(3-4)	**<0.001***
		P1=1, **P2<0.001*, P3<0.001***			

Data are presented as frequency (%) or median (IQR). * Significant P<0.05. P1: compared between groups P and M, P2: compared between groups P and C, P2: compared between groups M and C. GDRS: Groningen distress rating scale.

Table 3: Time to extubation post- general anethesia discontinuation , time of first analgesia, rectal diclofenac consumption and parent satisfaction of the enrolled patients

		Group P (n=30)	Group M (n=30)	Group C (n=30)	P
Time to extubation post- general anethesia discontinuation (min)		9±0.91	12±1.13	7.3±0.45	**<0.001***
		P1<0.001*, P2<0.001*, P3<0.001*			
Time of first analgesia (hr)		5.1±0.99	4.8±1.03	3.3±0.99	**<0.001***
		P1=0.811, **P2<0.001*, P3=0.001***			
Rectal diclofenac consumption		10(33.33%)	12(40.0%)	14(46.67%)	0.573
Parent satisfaction	**Very satisfied**	8(26.67%)	9(30.0%)	3(10.0%)	**0.021***
	Satisfied	10(33.33%)	11(36.67%)	7(23.33%)	
	Fair	8(26.67%)	7(23.33%)	6(20.0%)	
		P1=0.957, **P2=0.034*, P3=0.011***			

Data are presented as mean ± SD or frequency (%). * Significant P<0.05.

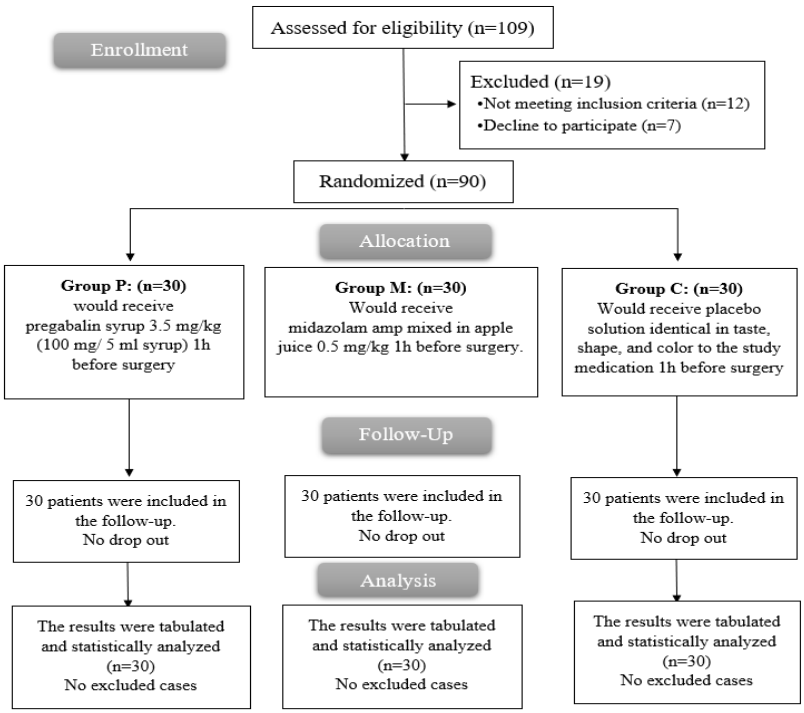

Figure 1: CONSORT flowchart of the enrolled patients

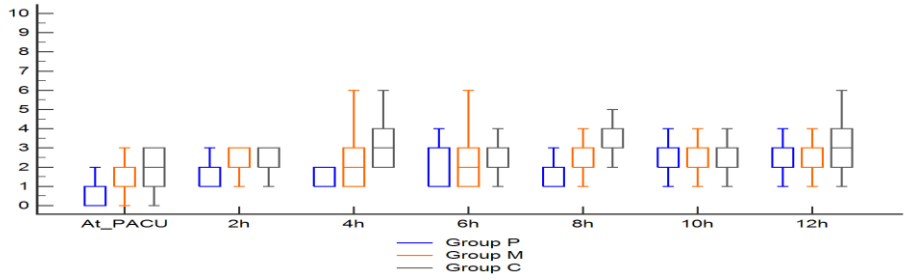

Figure 2: Faces, legs, activity, cry, consolability of the enrolled patients

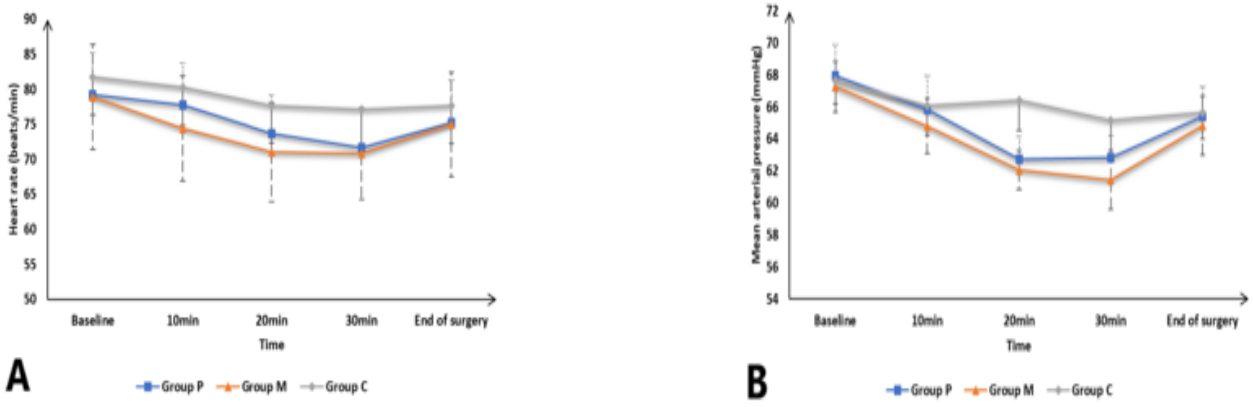

Figure 3: (A) Heart rate and (B) Mean arterial pressure of the enrolled patients

Discussion

Premedication has been extensively utilized in anesthetic practice to attenuate case anxiety, enhance case cooperation, and potentiate the overall anesthetic effect. The benzodiazepine midazolam, an anxiolytic drug, is the most used premedication, however it holds several AEs [12]. So, the need for safe and effective alternatives for pediatric sedation is still inconclusive. As far as current literature reveals, this research represents the pioneering study to compare between pregabalin versus midazolam as oral premedication drugs in terms of its sedating and anti-anexity effect in pediatric tonsillectomy operation under inhalational anaesthesia.

The study results revealed that Watcha scale for pediatric agitation assessment was significantly diminished at 10, 20 and 30min in premedication groups than controls with scores being similar between M and P groups. Parents separation anxiety, mask acceptance scale and GDRS were similar between groups P and M but were significantly elevated in controls. FLACC was significantly diminished in P and M groups as opposed to control groups at most time-points, however FLACC at early postoperative period, pregabaline exhibited superior effect than midazolam. Also, time of extubation after discontinuation of GA was significantly prolonged in group M in contrast with groups P and C. finally, parents satisfaction was elevated in premedicated groups.

According to our findings, Watcha scale for emergence agitation assessment was significantly diminished at 10, 20, and 30min in the premedicated groups than Controls. In agreement with our findings, Talaat and El Gendy. [13] demonstrated that postoperative PAED scores measured at 10, 20, and 30 m were similar between Groups P and M. Similarly, Marouf's study [11], on pregabalin premedication for EA in pediatric cases stated that the pregabalin cohort exhibited diminished EA scores and reduced analgesic demands relative to controls.

In the present study, PSAS, GDRS, and mask acceptance scores were similar between Groups P and M but significantly elevated in the control group, indicating that both pregabalin and midazolam effectively improved these parameters. These findings align with those of Mahdy and associates [14], who demonstrated that pregabalin premedication significantly decreased preoperative anxiety, as evidenced by diminished VAS-A as opposed to controls.

In the current study, FLACC scores were significantly diminished in the premedication groups at PACU, 2, 4, 6, and 8h postoperatively across the three groups. Notably, FLACC scores at PACU and 2h were significantly diminished in Group P as opposed to both Groups M and C. Consistent with these results, Talaat and El Gendy [13] stated significantly reduced postoperative FLACC scores at PACU arrival and discharge in Group P versus Group M. Moreover, Marouf study [11] observed that cases receiving pregabalin after tonsillectomy required fewer doses of paracetamol. Feng and associates [15] in a meta-analysis of 18 studies, stated that preoperative pregabalin administration was associated with decreased postoperative pain, opioid consumption, and incidence of nausea and vomiting, though the effects varied according to dosage and surgical procedure.

Contrary to our findings, White and associates [16] stated that preoperative administration of pregabalin (75–300 mg) enhanced perioperative sedation but did not yield significant improvements in preoperative anxiety, postoperative pain, or overall recovery following minor surgical procedures.

Regarding time of extubation after the discontinuation of GA, it was significantly prolonged in group M than (groups P and C). In agreement with our results, Talaat and El Gendy. [13] stated that group P

exhibited a significantly diminished duration of stay in time to extubate after the discontinuation of GA as opposed to midazolam.

In this research, the time of first analgesia was insignificant different between group P and group M, but was significantly elevated than control group. However, Rectal diclofenac consumption was insignificantly different among the three groups. These findings were in discordance with Salman and associates [17] exhibited that the total analgesic requirement in postoperative 24h was significantly diminished in cases received gabapentin group as opposed to the controls.

According to our study, HR and MAP at baseline and at end of surgery were similar across the three groups. However, significant differences in HR and MAP were observed at 10, 20, and 30 m intraoperatively among the groups. Contrasting with our results, Talaat and El Gendy [13] noticed that HR measurements following anesthesia induction were significantly elevated in cases receiving midazolam at 10, 20, 30, 40, 50, and 60 m as opposed to those receiving pregabalin. They documented significantly elevated MAPs at 30 and 40 m post-induction in Group M in contrast with Group P.

In our study, parent satisfaction was insignificantly different between groups P and M, however it was significantly better in premedication groups as opposed to controls. In agreement with us, Elrashidy and associates [18] exhibited that the pregabalin cohort had significantly better satisfaction as opposed to the placebo group and exhibited diminished anxiety levels .

Our findings indicated that AEs within the first 24h postoperatively were similar across all three groups. Consistent with these results, Park and associates [19] stated similar incidence of postoperative AEs between the control and pregabalin groups during the initial 24-hour postoperative period. Conversely, Marouf .[11] observed a significantly diminished postoperative vomiting incidence in Group P as opposed to controls. Notably, no cases in either group experienced dizziness.

Study limitations encompassed a relatively small sample size and single-center design. Additionally, case follow-up was limited to a relatively short duration. Furthermore, the most validated PAED scale for assessing emergence delirium was not utilized.

Conclusions:

Pregabalin had the same effect as midazolam on emergency agitation, GDRS, mask acceptance scale, PSAS, time of first analgesia requirements, and parent satisfaction. However, pregabalin demonstrated greater efficacy in postoperative pain and time of extubation after the discontinuation of GA reduction in comparison to midazolam. Further investigations of larger and stratified sample size are recommended for more accurate results with longer duration of follow-up to detect the long-term possible AEs.

No conflict of interest

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