Original Article

A Comparative Study Between Two Doses of Oral Melatonin as Pre-medication in Children Undergoing Surgery: A Double-Blinded Randomised Trial

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Abstract

Background: Pre-medication with sedatives is the cornerstone of pharmacological therapy for kids having surgery. According to some research, melatonin can additionally reduce the symptoms of anxiety. The primary objective of this study was to compare the effectiveness of two doses of oral melatonin as pre-medication on preoperative anxiety levels of children undergoing surgeries. **Methods:** In this double-blinded randomized controlled trial, 126 children, aged 4 to 14, of either sex, with an ASA I or II, scheduled for elective surgery were randomly assigned to get either melatonin 0.4 mg/kg (Group M4) or melatonin 0.2 mg/kg (Group M2), with 63 kids in each group. All children have had the same anesthetic strategy. The primary outcome was Preoperative anxiety and sedation assessed by the Modified Yale Preoperative Anxiety Scale (mYPAS-SF). The secondary outcome was the child-parent separation Score (CPSS). **Results:** Both groups were comparable in terms of demographic characteristics and baseline data. The anxiety score for total patients was 36 ± 7.43 points. Among all age groups, there was no statistically significant difference between the two studied groups according to RR (P=0.234) and HR P= (0.178) Before induction of anesthesia. All patients in both groups had normal SPO2 pre-operatively and before the induction of anesthesia. According to the Modified Yale Preoperative Anxiety Score (mYPAS-SF), The mean anxiety score preoperative in M4 and M2 is 36.53 ± 8.25 and 35.47 ± 6.54, respectively, with no statistically significant (p=0.427). Post medication (prior induction of anaesthesia), the mean anxiety score in M4 and M2 was 33.76 ± 12.08 and 39.54 ± 11.92, respectively, with a statistically significant difference (p=0.008). The group's sedation scores following pre-medication were statistically significant (P = 0.005). However, M 4 group members experienced the greatest minimal sedation (46%) and M 2 group members the least (22.2%). During child-parental separation, 66.7% and 47.6% of the children in groups M4 and M2 were unafraid, cooperative, and asleep. There was a statistically significant variance (P = 0.021). **Conclusion:** M4 acts significantly better on anxiety levels and child-parent separation with comparable effects on hemodynamic and respiratory parameters and without any case of deep sedation.

Keywords: Melatonin, Pediatric Surgery, Children, Sedation, Parental Separation.

Introduction

Preoperative anxiety in children may be more damaging than it is in adults. First, in contrast to adults, children are more likely to suffer greater autonomic nervous activity,

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which increases the time needed to induce, maintain, and recover from anaesthesia.[1,2] Second, a child's inability to adjust to unfamiliar medical surroundings is hampered by fear of the unknown, which may also lead to an increase in unintentional injuries. Additionally, children who are anxious before surgery are three times more likely to have delirium, nightmares, separation anxiety, sleep issues, nighttime sobbing, enuresis, tantrums, apathy, withdrawal, eating disorders, attacks on authority, and undesirable behavioural changes.[3,4] If anxiety is not under control, it can lengthen hospital stays and impede the healing of wounds.[5] Numerous studies have revealed varying anxiety incidence rates ranging from 25% to 80%. Children's less-developed cognitive and communicative abilities suggest that they are more prone to anxiety.[6] This anxiety spikes when they reach the operating room and are separated from their parents, which causes uncooperative actions during anesthesia induction.[7]

Benzodiazepines, H1 antihistaminics, and alpha2 agonists (clonidine or dexmedetomidine) are preoperative medications frequently used as anxiolytics in pediatric settings.[8] Despite being effective, these medications have a longer sedative effect, which could prolong post-anesthesia recovery. Recently, melatonin has been suggested as an efficient medication in anxiety management, with a substantial decrease in preoperative anxiety and postoperative pain.[9] This neurohormone, produced by the pineal gland and naturally promotes sleep, has other physiological benefits, such as anti-oxidant, oncostatic, anti-inflammatory, and anticonvulsant characteristics.[10,11] The anxiolytic effects of melatonin, established mainly in adults, are thought to result from its facilitation of γ-aminobutyric acid (GABA) transmission.[12] Melatonin is usually given to treat sleep abnormalities, seizure disorders, and neonatal sepsis in children and newborns. Despite its reported effectiveness and excellent safety record, its use as an anxiolytic in the pediatric population is still limited.[13] Because of its less sedative impact comparable to other medications, the patient can transit to the operating room on foot rather than in a bed.[14]

Furthermore, melatonin may improve postoperative analgesia, avoid respiratory depression, enhance postoperative recovery, and reduce sleep disturbance.[14] Additionally, some melatonin formulations may give more extraordinary taste acceptability than the traditionally used pre-medications, which have a bitter aftertaste that could increase compliance in a younger population.[15] Despite these advantages, a few modest clinical trials have assessed melatonin pre-medication in pediatric settings with conflicting results regarding its effectiveness and the proper dosage.[15-17] This study aimed to compare the efficacy of two doses of oral Melatonin as Pre-medication on preoperative anxiety levels of children undergoing surgeries.

Patients and Methods

A double-blind, randomized, controlled trial was conducted at Babil Teaching Hospital for Maternity and Children, a tertiary children's hospital in Iraq, from November 2021 to February 2023, with formal ethical approval obtained from the Ministry of Health's ethical committee (Reference No. 59/10/2021) and informed parental consent. One hundred twenty-six children, aged 4 to 14 years old, who were scheduled for elective surgery under general anaesthesia and had an American Society of Anesthesiologists (ASA) physical status classification of either I or II were included in the study.

Exclusion criteria were pediatric patients with physical status of ASA III or more, lung, heart, neurological, CNS disorder, diabetes, psychiatric illness, thyroid storm, drug allergy, liver disease, sleep disorders, intake of antipsychotics, or history of recent surgery. Patients who have already experienced sedation, those who have taken benzodiazepines, opioids, or any other sedatives in the past month, patients undergoing emergency surgery, or who declined to participate were also excluded from the study. Before surgery, each patient got a complete evaluation, including a history review, physical examination, and laboratory tests. Children were randomized into two groups (group M2 and group M4), including 63 patients each. They had oral pre-medication with Melatonin 60 minutes before anesthesia, at 0.2 mg/kg (max 10 mg) and 0.4 mg/kg (max 10 mg) in group M4. One milliliter of the used syrup was equal to 2.5 mg of melatonin.

Sample Size Calculation

The sample size was calculated with a given 95% confidence interval, a 0.5 standard deviation (anticipated variance), and a 5% margin of error, as follows:

$$n = \left(\frac{Z_1 - \mathbf{a}/2^{+\mathbf{z}}1 - 3)}{ES} \right)^2$$

Where α is the selected level of significance, and $Z_{1-\alpha/2}$ is the value from the standard normal distribution holding 1- α/2 below it, 1- β is the selected power, and $Z_{1-\beta}$ is the value from the standard normal distribution holding 1- β below it, and ES is the effect size.

The predicted sample size was raised to take into account any potential expected drop-outs (10%). There were 126 participants in total included in the current study.

Randomization

An envelope method and a computer-generated random array were used to divide the included patients into two groups by simple randomization occurred on a 1:1 ratio of Melatonin 0.2 mg/kg (max 10) to the other melatonin dose 0.4mg/kg (max 10). Both doses of melatonin were taken as syrup in the same quantity and given to the child per kg. Each parent was assigned a private data form coded with the serial number. The surgical team that carried out the procedures comprised three pediatric surgeons. An independent pharmacist was not involved in the direct care of patients but rather in preparing experimental drugs. Delivered to a nurse, she was not involved with the study's research team or gathering of information. Triple-blinding was used for the interventions; in other words, it was blinding for the patient, the caregivers, and

the researchers, who were unaware of who received which drug or was assigned to which group.

All children were kept off oral intake on the day of operation for a minimum of 6 hours for solids and 2 hours for clear fluids. Pre-medication with melatonin was administered 60 minutes before entry to the operating room in both groups. Patients got general anesthesia with preoxygenation for 3 minutes, used ketamine (1-2 mg/kg) and propofol (2-4 mg/kg) for induction, then a laryngeal mask airway was inserted, maintained anesthesia with 2% sevoflurane mixed with 2 L/m of oxygen to control the depth of hypnosis.

The primary outcome was the preoperative anxiety assessed by the Modified Yale Preoperative Anxiety Scale-short form (m-YPAS-SF) before (time 1) and following (time 2) the transition to the operating room (OR).[18] This scale contains 18 items divided into four categories: overall activity (ranging from 1-4), emotional expressivity (ranging from 1-4), degree of arousal (ranging from 1-4), and vocalization (ranging from 1-6). Based on the domain, the severity of children's behaviour can be rated on a scale from 1 to 4 or 1 to 6. Each domain's generated scores are totaled, split by 4, and multiplied by 100. The scale goes from 22.92 to 100, and a score of at least 30 indicates anxiousness. This modified version of the observational scale (mYPAS-SF) applies to younger patients (from the age of 2 years). It is simple to use and complete in a shorter time. The mYPAS-SF has excellent reliability and validity.[19,20]

The secondary outcomes were Sedation levels and Child attitude toward Parent Separation. Before entering the OR, sedation was assessed using the University of Michigan sedation scale (UMSS). The UMSS is an observable scale that rates alertness from 0 (awake) to 4 (unresponsive to deep stimulation) on a 5-point scale.[21,22] Child attitude toward Parent Separation was assessed by the Child-Parent Separation Score (CPSS), which is a 4-point scale. Grade 1 of the CPSS was considered adequate for statistical comparison, whereas Grades 2, 3, and 4 were considered unsatisfactory.[16]

Statistical Package for the Social Sciences version 26.0 software (SPSS Inc., 233 South Wacker Drive, 11th Floor Chicago, IL, USA) was used to analyze the data. Quantitative data has been distributed: mean, standard deviation (mean ± SD), median, and range. Age, gender, and ASA grade were the categorical data analyzed using the Chi-square test. The Kruskal-Wallis estimation of variance assessment, the Mann-Whitney U test, and the Wilcoxon matched pairs test were used to analyze nonparametric data. The Chi-Square test was performed to investigate the connection between two qualitative parameters. When the predicted count is less than 5 in more than 20% of the cells, the Fisher-Exact or Monte Carlo test was employed to assess the association between two qualitative parameters. The statistical significance of the variation between more than two factors was evaluated using an ANOVA with a repeated-measures test. Statistical significance was defined as $P< 0.05$.

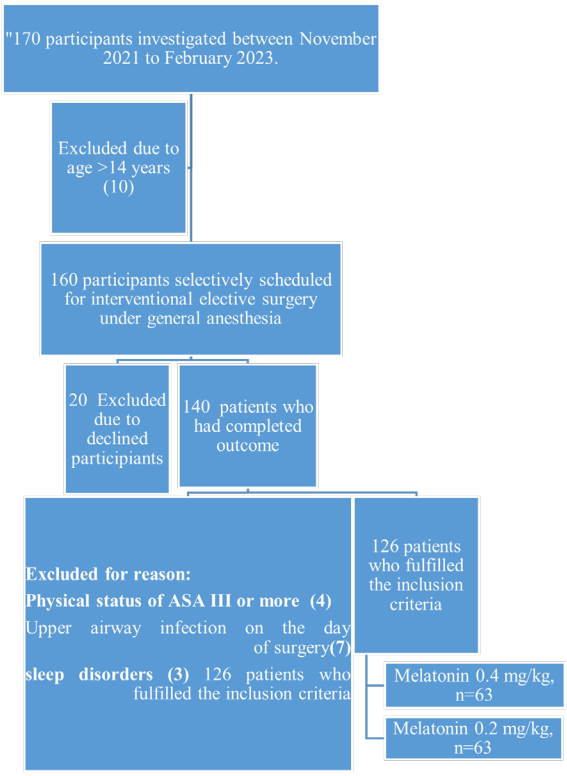

Figure 1: Flowchart of the Included Study Participants.

Results

The mean age of M 4 and M 2 was 8.59 ± 2.89 versus 7.78 ± 3.18, with no significant difference between the two groups (p=0.254). More than half of the patients in groups M4, M2, and total patients were males (69.8, 58.7, and 64.3% respectively). Patients' mean weights in M 4 and M 2 were 28.24 ± 11.06 versus 26.32 ± 11.96 kg, with no statistically significant among groups (p=0.351) (Table 1). The majority of surgical procedures involved hernias and appendectomy. 36.5% and 42.9% of individuals in M4 and M2, respectively, underwent appendectomy surgery. 22.2 % and 17.5% of group M4 and M2 patients, respectively, underwent left inguinal hernias. According to the number of procedures conducted, there was no statistically significant difference between the two groups (p=0.371) (Table 2).

The mean anxiety score preoperative in M4 and M2 is 36.53 ± 8.25 versus 35.47 ± 6.54, respectively, with no statistically significant (p=0.427). Post medication (prior induction of anesthesia), the mean anxiety score in M4 and M2 is 33.76 ± 12.08 versus 39.54 ± 11.92, respectively, with a statistically significant difference (p=0.008) (Table 3). During child-parental separation, 66.7% of the children in group M4 were unafraid, cooperative, and asleep. There was a statistically significant difference when scores were compared with that of M 2 groups (P =0.021) (Table 4). All groups' post-medication sedation scores were statistically significant (P = 0.005). However, the minimal sedation was highest in the M 4 group (46%) and lowest in the M 2 group (22.2%). This demonstrates that neither MT dosage sedated kids (Table 5).

Table 1: Demographic Characteristics of the Studied Groups.

Variable	Parameter	M 4 (n=63)	M 2 (n=63)	Test	p-value
Age	Mean ± SD	8.59 ± 2.89	7.78 ± 3.18	χ^2=2.74	0.254
	Range (Min-Max)	4-14	4-14		
	4 to 7 years	26 (41.3%)	33 (52.4%)		
	>7 to 10 years	16 (25.4%)	17 (27%)		
	>10 years	21 (33.3%)	13 (20.6%)		
Sex, n (%)	Male	44 (69.8%)	37 (58.7%)	χ^2=1.69	0.196
	Female	19 (30.2%)	26 (41.3%)		
Weight	Mean ± SD	28.24 ± 11.06	26.32 ± 11.96	χ^2=0.876	0.351
	Range (Min-Max)	14-57	11-55		

p-value: the difference between M 4 and M 2, p non-significant if >0.05, *P significant if <0.05, ** p highly significant if <0.001. SD: standard deviation, Min: minimum, Max: maximum, n: number, %: percentage, χ^2:Chi–Square, t: Student t-test.

Table 2: Surgeries Performed among the Studied Groups.

Variable	Parameter	M 4 (n=63)	M 2 (n=63)	Total (n=126)	Test	P-value
Name of surgery	Left inguinal hernia	14 (22.2%)	11 (17.5%)	25 (19.8%)	χ^2=14.04	0.371
	Appendectomy	23 (36.5%)	27 (42.9%)	50 (39.7%)		
	Right inguinal hernia	14 (22.2%)	11 (17.5%)	25 (19.8%)		
	Left hydrocele	4 (6.3%)	2 (3.2%)	6 (4.8%)		
	Circumcision	1 (1.6%)	0 (0%)	1 (0.8%)		
	Right hydrocele	2 (3.2%)	0 (0%)	2 (1.6%)		
	Bilateral inguinal hernia	1 (1.6%)	0 (0%)	1 (0.8%)		
	Right undescended testis	1 (1.6%)	3 (4.8%)	4 (3.2%)		
	Left undescended testis	1 (1.6%)	0 (0%)	1 (0.8%)		
	Submental cyst	1 (1.6%)	2 (3.2%)	3 (2.4%)		
	Lymph node biopsy axillary	1 (1.6%)	1 (1.6%)	2 (1.6%)		
	Hypospadias	0 (0%)	3 (4.8%)	3 (2.4%)		
	Lymph node biopsy axillary	0 (0%)	2 (3.2%)	2 (1.6%)		
	Meatal stenosis	0 (0%)	1 (1.6%)	1 (0.8%)		

p-value: the difference between M 4 and M 2, p non-significant if >0.05, *P significant if <0.05, ** p highly significant if <0.001, %: percentage, χ^2: Chi–Square

Table 3: Comparison between Two Melatonin Doses According to Pre and Post-medication Anxiety and Sedative.

Variable		Mean	SD	SE	95% Confidence Interval for Mean		Min	Max	Test	p-value
					Lower Bound	Upper Bound				
mYPA-SF PRE	M 4	36.5317	8.25142	1.03958	34.4537	38.6098	22.92	61.50	t=0.797	0.427
	M 2	35.4749	6.53988	.82395	33.8279	37.1220	22.92	49.00		
	Total	36.0033	7.43411	.66228	34.6926	37.3141	22.92	61.50		
mYPA-SF POST medication	M 4	33.7635	12.07710	1.52157	30.7219	36.8051	22.92	74.00	t=2.704	0.008*
	M 2	39.5448	11.92563	1.50249	36.5413	42.5482	22.92	61.50		
	Total	36.6541	12.30077	1.09584	34.4853	38.8229	22.92	74.00		

p-value: the difference between M 4 and M 2 pre and post-medication, p non-significant if >0.05, *P significant if <0.05, ** p highly significant if <0.001. SD: standard deviation, SE: standard error, Min: minimum, Max: maximum, %: percentage, t: Student t-test.

Table 4: Child-parent Separation Scale Score among the Studied Groups.

Variable	M 4 (n=63)	M 2 (n=63)	Total (n=126)	Test	p-value
Patient unafraid, cooperative and asleep	42 (66.7%)	30 (47.6%)	72 (57.1%)	χ^2=9.71	0.021*
Slight fear or crying, quiet with reassurance	15 (23.8%)	20 (31.7%)	35 (27.8%)		
Moderate fear, crying, not quiet with reassurance	0 (0%)	7 (11.1%)	7 (5.6%)		
Crying, need restraint.	6 (9.5%)	6 (9.5%)	12 (9.5%)		

p-value: the difference between M 4 and M 2, p non-significant if >0.05, *P significant if <0.05, ** p highly significant if <0.001, %: percentage, χ^2:Chi–Square.

Table 5: Sedation Scale Score among the Studied Groups.

Variable	M 4 (n=63)	M 2 (n=63)	Total (n=126)	Test	p-value
Awake and alert	34 (54%)	49 (77.8%)	83 (65.9%)	χ^2=7.94	0.005*
Minimally sedated: tired/ sleepy, appropriate response to verbal conversation and/or sound	29 (46%)	14 (22.2%)	43 (34.1%)		
Moderately sedated: somnolent/ sleeping, easily aroused with light tactile stimulation or a simple verbal command	0	0	0		
Deeply sedated: deep sleep, arousable only with significant Physical stimulation	0	0	0		
Unarousable	0	0	0		

P-value: the difference between M 4 and M 2, p non-significant if >0.05, *P significant if <0.05, ** p highly significant if <0.001, %: percentage, χ^2: Chi–Square."

Discussion

Our study indicated that preoperative oral melatonin produces equivalent sedation, anxiolysis, hemodynamic stability, and pain reduction in children undergoing anesthesia-induced surgery. Preoperative stress is common for anybody before surgery, but it is prevalent for pediatric patients. Reduced preoperative anxiety, lessened separation from parents, and lessened emotional stress are all benefits of sedative pre-medication for children undergoing anesthetic induction.[23] When deciding which pre-medication to give a child, it is essential to consider the child's age, weight, method of administration, physiology and psychology relative to their age, and any underlying medical or surgical condition.[24] Melatonin, a hormone produced by the pituitary gland that is naturally hypnotic, works by activating the MT1 and MT2 MT receptors.[25] It has been reported to raise sedation levels without compromising orientation and causing preoperative anxiolysis. Children's preoperative anxiety is linked to various postoperative outcomes, including eating disorders, bedwetting, longer recovery-phase suffering, and postoperative regressive behavioural abnormalities.[26,27] The dose of melatonin is from 0.5 to 10 mg. It is recommended that melatonin be taken between thirty and sixty minutes before going to bed.[28] Several studies[29,30] used a dose of melatonin up to a maximum of 10 mg, and this maximum dose is equal to adult,[9] as other studies[31,32] suggested using 9 mg as a maximum dose for kids. A recent study described the maximum dose as 1–20 mg and iterated prescriptions as 1–25 mg. Overweight and obese people received equal maximum doses as normal-weight people, while children under nine received similar doses as children over nine.[33] A few studies have been conducted on children receiving preoperative oral MT (0.2–0.5 mg/kg). One[34] has shown that oral MT (0.5 mg/kg) is useless for treating children as pre-medications. Impellizzeri *et al*.[13] investigated the efficacy of oral Melatonin 0.5 mg. kg (max 20 mg) and oral midazolam 0.5 mg. kg (max 20 mg) in alleviating anxiety in 80 children aged 8-14 years (40 per group) before elective surgery. The anxiety level of children, as determined by the mYPAS, were no significant differences between the groups in the preoperative (p= 0.430) and during anesthesia induction (p = 0.729). The authors found that both of them did not affect the outcome. Faghihian *et al*.[35] compared the effect of 0.5 mg/kg of melatonin VS midazolam 0.5 mg/kg and placebo as pre-medication. They concluded that oral midazolam and oral melatonin were more effective in sedating patients than placebo. Other studies using various doses of oral MT (0.25 mg/kg and 0.5 mg/kg).[21,36,37] have demonstrated favourable outcomes. A larger dose of melatonin (0.4 mg/kg) reduced preoperative anxiety, made it easier for parents to separate their children, and improved mask induction compliance. A faster onset of drowsiness and a longer time to emerge were linked to the more significant dose of 0.4 mg/kg.

The child's behaviour while separated from their parents, their cooperation during venipuncture, and the development of MT side effects served as our secondary end measures. In the current study,

CPSS was used to evaluate parental separation. During child-parental separation, 42 (66.7%) of the children in M4 and 30(47.6%) in M2 were unafraid, cooperative, and asleep. There was a statistically significant (P= 0.021). Other studies[36,38,39] used different scores that measured the ease of separation. Among these investigations, one study,[36] when compared to the placebo group, it was observed that children in the MT 0.25 mg/kg and 0.5 mg/kg or midazolam 0.25 mg/kg and 0.5 mg/kg groups showed less anxiety, which was in accordance with the results of our study. However, in the other study,[38] It was pointed out that the groups' separation anxiety degrees did not significantly vary when 0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg of oral MT were contrasted to 0.5 mg/kg of oral midazolam; yet, the children's average ages in these studies were 3.5 ± 0.6 and 5.1 ± 2.35 years respectively.[36,38] Another study[39] compared the ease of parent separation between midazolam 0.5 mg/kg (Group A) or Melatonin 0.5 mg/kg MT (Group B) or 0.75 mg/kg MT (Group C) or placebo (Group D) and concluded that 88%, 72%, 80% and 0% of the children in Groups A, B, C and D, respectively, were free of anxiety. However, the most effective anxiolytic was midazolam and two doses of MT. Despite not being statistically significant, but had an anxiolysis effect.

In our investigation, all of the groups' post-prescription sedation scores were significantly different (P = 0.005). However, the minimal sedation was highest in the M 4 group (46%) and lowest in the M 2 group (22.2%). This demonstrates that neither of the MT dosages sedated kids. This was consistent with another trial in which, when comparing midazolam to MT and placebo, midazolam generated the maximum level of sedation. Like the placebo, MT had no sedative effects.[39] This finding was identical to other researchers' investigations.[34,40] According to our research, MT at doses of 0.4 and 0.2 mg/kg did not cause drowsiness. Therefore, we can conclude that patients who receive MT before surgery will need less preoperative monitoring (no sedation). Comparable study results in the midazolam group, as opposed to MT and placebo, showed a substantial increase in the time in seconds needed for CCT after pre-medication.[39] These agreed with a comparable study conducted on children[41] using the Trieger dot test. Whereas more children in the melatonin and midazolam groups reported greater mYPAS scores in the operating room than in the preoperative room compared to the placebo group, the current study confirmed an earlier study that revealed that neither the statistical significance nor the clinical significance of this difference was reached.[42] There are two possible explanations for this: either melatonin and midazolam's hypnotic and anxiolytic effects are dose-dependent, or[36,38,39] it is possible that the study's mild doses did not have the intended effect. However, higher doses of residual sedation are not preferred because they lengthen the PACU stay for pediatric ambulatory procedures.[35,43] Our results concur with those of Sury and Fairweather,

who found that oral melatonin was inefficient as a sedative for children undergoing magnetic resonance imaging.[44] Investigators found no additive benefit of melatonin on the length required for profound drowsiness in children who were given 3 or 6 mg of the supplement, a placebo, or chloral hydrate.

Limitations

This research had limitations, including the lack of a placebo-controlled group and effects on postoperative parameters and the total outcome was not assessed. Additional research is required to examine these features of observations.

Conclusion

M4 acts significantly better on anxiety levels and child-parent separation with comparable effects on hemodynamic and respiratory parameters and without any case of deep sedation.

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