A Blind Randomized Trial Comparing Different Doses of Oral Melatonin with Placebo as Premedication in Pediatrics to Alleviate Preoperative Anxiety

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Abstract

Background and objectives: In children, preoperative anxiety in is known to be associated with different postoperative issues, such as regressive behavioral changes, prolonged recovery distress, eating disorders, and bedwetting. Administering pre-anesthetics and sedatives orally is a reliable method for children. This study aimed to evaluate the effectiveness of two different doses of melatonin premedication in reducing preoperative anxiety in children. **Methods**: A double-blind randomized study, carried out after ethical committee approving, and involved 120 children aged 4–10 years, classified as American Society of Anesthesiologists physical status I or II, undergoing elective surgery under general anesthesia in the pediatric surgery department in Bent-Alhuda Teaching Hospital in Al Nasiriya city from July 2023 to the end of January 2024. Participants were randomly assigned into three groups of 40 patients (Groups M04, M02, and Placebo) to receive either oral melatonin 0.4 mg/kg, 0.2 mg/kg, or identical placebo premedication 60 minutes before induction. Anxiety levels were assessed 15 minutes before premedication, 45 minutes after premedication, and during parental separation, while sedation levels were evaluated at three-time points, all after the premedication was administered. **Results:** The three study groups were comparable in terms of mean age, weight, sex, and duration of anesthesia. Following premedication, the M04 group showed a significant reduction in anxiety levels compared to levels in both M02 and placebo groups, with a statistically significant difference ($p > 0.05$). In all time points of assessment, the sedation levels in the M04 group were significantly higher than those in both the M02 and placebo groups. In contrast, the difference between the M02 and placebo groups was insignificant ($p > 0.05$). regarding the hemodynamics; we found the measured hemodynamics were closer to the normal levels in the M04 group while in the other two groups, they were not. **Conclusion:** Administering oral melatonin at a dose of 0.4 mg/kg appears to be more effective than a dose of 0.2 mg/kg or placebo premedication for reducing preoperative anxiety in children during separation from their parents in the preoperative area.
Keywords: General Anesthesia, Oral Melatonin, Pediatrics, Placebo, Premedication, Preoperative Anxiety, Sedation.

1. Introduction

Preoperative anxiety in children is frequently linked to negative postoperative outcomes, including the onset of delirium during recovery and regressive behavioral disorders like nightmares, bedwetting, separation anxiety from parents, and eating disorders(**Perry et al., 2012**). Eliminating of fear and anxiety is crucial for inducing a pleasant anesthesia technique and preventing further adverse effects on the child behaviors with good psychological status(**Kain et al., 2007; Hussein et al., 2024**).. Benzodiazepines, particularly midazolam, along with chloral hydrate and triclofos, are the most commonly

prescribed medications for reducing anxiety (**Gupta et al., 2019**). Melatonin, scientifically known as N-acetyl-5-methoxytryptamine, is a hormone naturally produced in the brain and released by the pineal gland. Its receptors are distributed throughout the central nervous system and various body tissues. Melatonin is renowned for its effectiveness in managing sleep disorders, anxiety, and pain. Additionally, it exhibits anti-inflammatory and antioxidant properties. This hormone is frequently used as a premedication (**Amaral & Cipolla-Neto, 2018**). Melatonin works by interacting with various receptors, such as opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α1- and α2-adrenergic, and melatonergic receptors, which are located in the central nervous system and spinal cord. Melatonin as a premedication has been demonstrated to reduce the requirement for anesthetic induction agents during surgical procedures(**Mellor et al., 2022; Alkhfaji et al., 2024**) .Melatonin is a vital hormone naturally produced by the pineal gland in humans during the night (**Amaral & Cipolla-Neto, 2018**).. Melatonin has been suggested as a substitute for midazolam for premedication prior to anesthesia induction (**Mpellizzeri et al., 2017**). Literature reviews have shown that melatonin premedication has a role in reducing anxiety and pain in infants and children during painful surgical and interventional procedures (**Kettle et al., 2021**). Additionally, premedication with melatonin significantly reduces the induction dose of propofol required for anesthesia in children compared to midazolam (**Norouzi et al., 2019**). This study aimed to evaluate the effectiveness of two different oral doses of melatonin as premedication to reducing preoperative anxiety by comparing them with placebo premedication in children undergoing major surgery with general anesthesia.

2. Patients and Methods

In the pediatric surgery department at Bent-Alhuda Teaching Hospital in Al Nasiriya City from July 2023 to the end of January 2024
This double-randomized comparative investigation was conducted at the Department of Pediatric Surgery in Bent-Alhuda Teaching Hospital, which is located in Bent-Alhuda Teaching Hospital in the south of Iraq. The study involved children within 4 to 10 years old, of both sexes, classified as class I or II ASA, and scheduled for elective major surgery under general anesthesia. The data collection period spanned approximately 6 months, from July 2023 to the end of January 2024, following ethical approval from the Research Committee in Dhi-Qar Health Province in 2023. The total sample size comprised 120 participants.

2.1 The inclusion criteria

Comprised children aged 4 to 10 years, classified with ASA physical status I or II, scheduled for elective major surgery, and whose parents provided informed consent and expressed satisfaction with the study.

2.2 Exclusion criteria

Included ASA greater than II, drug allergy, contraindications for the study drug, lack of awareness or response from the child's parents to questions raised about the child's situation, preoperative vomiting, gastrointestinal disorders, mental and neurological diseases, disapproval or dissatisfaction of the child's parents, inability to obtain the consent of one or both parents, liver disease, children who had sedation medication, and those undergoing emergency surgery. The criteria for discontinuation of patient participation included withdrawal of parents from the study and hospital stay shorter than 12 hours after the intervention.

2.3 Preparation procedures

The children participating in the study were randomly assigned to three groups by using the closed envelope method (40 patients in each group). The premedication for each group was as follows:
IN the 1st group (M02 group); the individuals received oral melatonin solution (3 mg/mL melatonin dissolved in water, with a sugar cube added to mask the bitter taste) at a dose of 0.2 mg/kg. is the 2nd group; (M04 group); the children premedicated with oral melatonin solution (3 mg/mL melatonin dissolved in water, with a sugar cube added to mask the bitter taste) at a dose of 0.4 mg/kg. the 3rd group was the placebo group and the children in this group were premedicated by a combination of 5 mL dextrose and normal saline in equal proportion, administered orally.

In all groups; the premedication was administrated in the morning of the surgery, 60 minutes before the induction of anesthesia, with a maximum dose of melatonin set at 10 mg.

This study was double-blind, and the study drugs were administered by a trained anesthesia technician (who was not involved in the study team). Neither the researchers nor the parents were informed about the type of drug given to the child. Thirty minutes after drug administration, the patient was transferred to the operating room.

2.4 Study Procedure

Before the intervention, a pre-anesthetic assessment was conducted, which included a review of the patient's medical and surgical history, previous anesthesia experiences, drug allergies, clinical examination, airway assessment, and baseline investigations such as complete blood count and blood sugar levels. These details were documented on a predefined form. The parents of the child were provided with information about the study in their native language, and their signatures were obtained on the Informed Consent Form. The child adhered to fasting guidelines as per pediatric recommendations before the procedure.

Children received the premedication drugs orally from the trained anesthesia technician approximately 60 minutes before the induction of general anesthesia. The child's anxiety level was assessed and recorded three times which are before premedication, 45 minutes after the administration of premedication drugs, and at separation from parents by using a four-point scale: 1 = Crying, 2 = Anxious, 3 = Calm, but not cooperative, and 4 = Calm, cooperative or asleepز (**McMillan et al., 1992; Hussein et al., 2024**) . The sedation level for children was assessed also at three times and all of them were after the premedication depending on a four-point scale: 1 = Alert, 2 = Awake, 3 = Drowsy, and 4 = Asleep (**McMillan et al., 1992;Sindhupriya, 2015; Faghihian et al., 2018**).. The hemodynamics were collected after premedication and during surgery by the anesthesia technician at regular intervals.

The current study involved 120 children undergoing elective major surgery under general anesthesia, with 40 patients in each group. The data is presented in Table 1. There

2.5 Preparation of the operation room and anesthesia procedure

The anesthesia procedure commenced with the insertion of an intravenous line. General anesthesia was induced by face mask with 2% sevoflurane in 100% oxygen mixture. Intravenous anesthetic agents, including Ketamine (2 mg/kg via slow intravenous injection), propofol (2.5 mg/kg), and rocuronium (1 mg/kg), were then administered to induce neuromuscular blockade and to facilitate intubation. During operation, patients were mechanically ventilated using pressure-controlled mode with a 75% oxygen concentration. Anesthesia levels were adjusted to maintain stable blood pressure and heart rate within 20% of their baseline values. Standard monitoring, such as continuous electrocardiography, non-invasive blood pressure measurement, and pulse oximetry, was employed. Upon completion of the procedure, the administration of anesthetic gases was gradually reduced to 0% and replaced with 100% oxygen at a flow rate of at least 4 L/min. Once consciousness was regained, extubation was done, and the child was carefully transferred to recovery room and monitored under the supervision of an anesthesia staff. The vital signs were monitored in the PACU until the patient was deemed stable and ready for discharge to the ward.

2.6 Statistical analysis

The data collected underwent thorough revision, coding, and tabulation utilizing the Statistical Package for the Social Sciences (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Analysis was conducted based on the type of data obtained for each parameter. In analytical statistics, the Chi-Square test was employed to examine the relationship between two qualitative variables, while the student's t-test was utilized to assess the statistical significance of the difference between the means of the two study groups.

3. Results

was no notable distinction observed in demographic data, including age, gender, body weight, ASA classification, and duration of anesthesia between the studied groups (p-

value > 0.05 for all demographics) (Table 1).

. Comparison between studied groups regarding the demographic data.1Table

	MT2 Group N = 40		MT4 Group N = 40		Placebo Group N = 40		P value
Age (years)							
Mean ± SD.	7.78 ± 3.18		8.59 ± 2.89		7.18 ± 2.22		0.201
Sex	*No.*	*%*	*No.*	*%*	*No.*	*%*	
Male	28	70.0	22	55.0	24	60.0	0.176
Female	12	30.0	18	45.0	16	40.0	
Weight (kg)							
Mean ± SD.	28.24 ± 11.06		26.32 ± 11.96		27.44 ± 9.12		0.571
ASA Classification	*No.*	*%*	*No.*	*%*	*No.*	*%*	
I	32	80.0	33	82.5	31	77.5	0.341
II	8	20.0	7	17.5	9	22.5	
Duration of anesthesia (min)	52.8±14.5		55.3±13.0		57.7±10.8		0.792

SD: standard deviation.

Table 2. Comparison between studied groups regarding the anxiety level.

Level of anxiety	M02 group N = 40		M02 group N = 40		Pl group N = 40		P value
	No.	%	No.	%	No.	%	
15 min precede premedication							
Crying	11	27.5	14	35.0	15	37.5	M04 & M02 = 0.608
Anxious	26	65.0	25	62.5	23	57.5	
Calm, but not cooperative	3	7.5	1	2.5	2	5.0	M04 & Pl = 0.880
Calm or a sleep	0	0.0	0	0.0	0	0.0	M02 & Pl = 0.678
45 min after premedication							
Crying	0	0.0	10	25.0	12	30.0	M04 & M02 = < 0.001*
Anxious	6	15.0	16	40.0	20	50.0	
Calm, but not cooperative	15	37.5	10	25.0	8	20.0	M04 & Pl = < 0.001*
Calm or a sleep	19	47.5	4	10.0	0	0.0	M02 & Pl = 0.067
At separation from parents							
Crying	3	7.5	8	20.0	3	7.5	M04 & M02 = < 0.001*
Anxious	8	20.0	11	27.5	26	65.0	
Calm, but not cooperative	22	55.0	17	42.5	11	27.5	M04 & Pl = 0.025*
Calm or a sleep	7	17.5	4	10.0	0	0.0	M02 & Pl = 0.067

The comparison of patients' anxiety levels among the three groups is presented in Table 2. Preceding the premedication, the anxiety levels in all groups were comparable (P value > 0.05). 45 minutes after receiving premedication, the anxiety levels in the M04 group were significantly less than which appeared in both the M02 and placebo groups, Table 3 shows the comparison of sedation levels among the three studied groups. Sedation levels were measured at three-time points: 45 minutes after premedication, at separation time, and in the operating room before the induction of anesthesia. After 45 minutes of premedication, the sedation levels in the M04 group were significantly higher whereas the difference between the M02 and placebo groups was not significant regarding anxiety levels. At the time of separation, our results showed that the level of anxiety in M04 group stilled significantly less than which seen in the other groups, while the levels were comparable between the M02 and placebo groups (Table 2).

than those in both the M02 and placebo groups, whereas the difference between the M02 and placebo groups was not significant. At the time of separation, the sedation levels in the M04 group remained significantly higher than those in the other groups, while the levels were comparable between the M02 and placebo groups. Similar results were found when the sedation levels were evaluated in the operating room before the start of general anesthesia (Table 3).

Table 3. Comparison between studied groups regarding the sedation level.

Sedation level	M02 group N = 40		M02 group N = 40		Pl group N = 40		P value
	No.	%	No.	%	No.	%	
After 45 min of premedication							
Alert	1	2.5	19	47.5	21	52.5	M04 & M02 = < 0.001*
Awake	5	12.5	16	40.0	14	35.0	
Drowsy	24	60.0	4	10.0	5	12.5	M04 & Pl = < 0.001*
Asleep	10	25.0	1	2.5	0	0.0	M02 & Pl = 0.803
At separation from parents							
Alert	4	10.	10	25.0	11	27.5	M04 & M02 = < 0.001*
Awake	9	22.5	24	60.0	27	67.5	
Drowsy	22	55.0	4	10.0	2	5.0	M04 & Pl = < 0.001*
Asleep	5	12.5	2	5.0	0	0.0	M02 & Pl = 0.097
Before induction in OR							
Alert	3	7.5	18	45.0	20	50.0	M04 & M02 = < 0.001*
Awake	3	7.5	16	40.0	18	45.0	
Drowsy	23	57.5	4	10.0	2	5.0	M04 & Pl = < 0.001*
Asleep	11	27.5	2	5.0	0	0.0	M02 & Pl = 0.081

***OR**: operation room, *: significant P value.*

Table 4. Comparison between melatonin and placebo regarding vital signs

	M04 group n = 40	M02 group n = 40	Placebo n = 40
HR(beat/min)			
Basal	109.6 ± 32.7	113.76 ± 33.6	112.11 ± 29.16
20 min after premedication	88.41 ± 17.5*	103.54 ± 32.2	107.44 ± 36.8
15 min before induction	84.53 ± 20.1*	115.55 ± 19.9	112.85 ± 29.9
15 min after surgery	80.29 ± 21.6*	109.27 ± 30.9	111.36 ± 44.5
RR (time/min)			
Basal	18.82 ± 4.34	19.53 ± 3.57	17.23 ± 4.04
20 min after premedication	16.83 ± 4.68*	19.88 ± 5.11	17.92 ± 6.17
15 min before induction	17.48 ± 2.23*	19.70 ± 4.20	20.70 ± 5.43
15 min after surgery	16.53 ± 4.76*	19.0 ± 6.17	19.88 ± 6.89
SpO2(%)			
Basal	94.6 ± 2.00	93.80 ± 3.26	93.80 ± 2.76
20 min after premedication	98.30 ± 1.40*	96.20 ± 2.71*	95.60 ± 3.11*
15 min before induction	97.40 ± 2.20*	95.73 ± 2.86*	96.13 ± 2.93*
15 min after surgery	97.83 ± 1.88*	96.78 ± 2.81*	95.48 ± 2.11*

*Data were expressed as mean ± SD. *P < 0.05 is highly significant. SD: Standard Deviation. SpO2: Oxygen Saturation level.*

No significant difference was observed in readings of main hemodynamic variables (HR, RR, and SpO2) at baseline records in the patient ward. However, the data indicated a significant decrease in HR, RR and SpO2 at 20 minutes after giving premedication, 15 minutes pre-induction, and 15 minutes after surgery in the M04 group, while the comparison between M02 and placebo group was comparable for the hemodynamics changes (Table 4). This significant reduction was found in the readings of HR, RR, and oxygen saturation levels after the administration of premedication when compared to baseline readings in the M04 group.

4. Discussion

The objective of using pharmacological substances for premedication is to help patients with amnesia and anxiety reduction, as well as to enhance the hypnotic effects of general anesthesia. Often, children struggle to cooperate and remain still during simple surgical or diagnostic procedures unless they are asleep. Although commonly recommended anesthetic drugs for premedication or sedatives are effective, they come with risks of side effects, and minor mortality, and require considerable human resources. Using natural sleep as an alternative is appealing, provided it can be reliably anticipated. Currently, this approach is mainly feasible for small infants who usually sleep after feeding(**Sury & Fairweather, 2006**). In certain pediatric trials, melatonin has been recommended for its premedication properties in pediatrics needing sedation or general anesthesia for therapeutic or diagnostic procedures, yielding satisfactory outcomes (**Hussein et al., 2024;Wassmer et al., 2001; Bajaj, 2009**) .

Melatonin, a hormone produced by the pineal gland, acts as a natural hypnotic via activating the MT1 and MT2 receptors (**Kurdi & Patel, 2013**). It has been observed to alleviate preoperative anxiety and increase sedation levels without loss of consciousness (**Patel & Kurdi, 2015; Alkhfaji et al., 2023**). Studies on preoperative oral melatonin (0.2–0.5 mg/kg) are few in literature. One such study, conducted by Berrin and colleagues, found that oral melatonin at a dose of 0.5 mg/kg was ineffective as a premedication agent in children. However, these results do not align with the findings of our study. Upon reviewing other trials, we found that some studies evaluating the use of 0.25–0.5 mg/kg of melatonin as premedication in paediatrics produced results consistent with our findings regarding the sedative and anxiolytic properties of oral melatonin at these doses **(Hussein et al., 2024;Isik et al., 2008; Alhamaidah & Kahloul, 2024**) .

We selected children aged 4 to 10 years to ensure they could understand and complete the necessary tests and goals of our study. In a related study, we administered oral melatonin at doses of 0.2 or 0.4 mg/kg. In a previous paediatric trial involving children undergoing neuro-procedures, a maximum dose of 20 mg of oral melatonin was used and found to be safe (**Schmidt et al., 2007**) .

Previously, in their study, Patel and Kurdi found that the peak effect of exogenous melatonin as an oral premedication ranges from 60 to 150 minutes in paediatric patients(**Patel & Kurdi , 2015)** . Therefore, we administered the premedication in both groups within 60 minutes before the induction of anesthesia.

The primary goals in our study were directed to evaluate the effectiveness of oral melatonin at two doses (0.2 and 0.4 mg/kg) in reducing preoperative anxiety and inducing sedative effects to facilitate both the separation of the child from their parents and the induction of anesthesia.

Our study indicated that the use of 0.4 mg/kg of oral melatonin can produce equivalent sedative and anxiolytic effects better than low dose of melatonin (0.2 mg/kg) or placebo. However, the effectiveness of 0.4 mg/kg was significantly observed in our results, and this finding was consistent with the results reported by some previous researchers **(Samarkandi et al. 2005)**. On the other hand, this finding contrasts with some studies where researchers used oral melatonin at higher doses (3 mg, 6 mg), while another study reported the use of melatonin dose 0.4 mg/kg which showed no significant anxiolytic effect of when compared to either midazolam or placebo (**Sury & Fairweather, 2006; Kain et al., 1992**). Sedative premedication aims to decrease preoperative anxiety, thereby facilitating the separation of children from their parents, reducing emotional distress, promoting acceptance of the anesthesia mask, and aiding in the induction of anesthesia **Sheta etal .(2014).**

Other previous studies depended on different scores to evaluate the ease of child separation (**Samarkandi et al., 2005; Kain et al., 1992; Kurdi & Muthukalai (2016).**). Among these scores (25), comparing of oral melatonin group to placebo group, it was observed that children who received oral dose > 0.25 mg/kg or midazolam (0.25 or 0.5 mg/kg) explained less anxiety, which was lower than our results.

In this study, several limitations need to be acknowledged before drawing definitive conclusions. Firstly, the drugs being available in syrup form led to challenges in accurately measuring and administering the drug based on body weight. Secondly, the intraoperative effects of melatonin were solely assessed on

hemodynamic status, without considering anesthetic requirements. Additionally, the study did not evaluate the analgesic effects of melatonin. Finally, the relatively short duration of postoperative follow-up limited the assessment of certain relevant aspects, such as melatonin's effects on postoperative sleep quality.

Conclusion

Premedication with oral melatonin at a dose of 0.4 mg/kg appears to be more effective than premedication with 0.2 mg/kg or placebo for alleviating preoperative anxiety in children undergoing separation from parents in the preoperative area. However, our findings indicate that 0.4 mg/kg of oral melatonin can provide a significant sedative effect if compared with a low dose of melatonin (0.2 mg/kg).

Conflict of Interest

Authors decline no conflict of interest

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