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A Randomized Placebo Study on Premedication with Oral Melatonin for Children Undergoing Elective Therapeutic Cardiac Catheterization

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ABSTRACT

Background: The occurrence of preoperative anxiety in children is linked to various postoperative consequences, including regressive behavioral disturbances, prolonged distress during recovery, eating disorders, and bedwetting.

Objectives: This study aimed to assess the effectiveness of oral melatonin premedication in alleviating preoperative anxiety in children and its sedative effects.

Methods: A randomized comparative study involved children aged 2 to 12 years scheduled for elective cardiac catheterization under general anesthesia. The sample comprised 80 patients, randomly assigned to two groups of 40 each. Group A received 0.5mg/kg oral melatonin as a premedication agent, while Group B received an identical placebo.

Results: in regarding demographics; Both groups were comparable. There was a notable contrast in the average anxiety scores following 30 minutes of premedication, during separation from parents, and 5 minutes before induction ($P < 0.001$, $P = 0.003$, and $P = 0.020$, respectively). Similarly, a considerable disparity was evident in the sedation levels across all assessment points ($P < 0.001$).

Conclusion: Administering of oral melatonin as a premedication might mitigate preoperative anxiety levels in pediatric patients undergoing therapeutic cardiac catheterization, with no notable adverse effects.

Keywords: Melatonin, Premedication, Pediatrics, Interventional Catheterization, General Anesthesia, Placebo Study, Anxiety.

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INTRODUCTION

Congenital heart disease (CHD) is the most prevalent and potentially life-threatening among all birth defects, impacting nearly 1 in every 100 newborns. The progress in surgical techniques and, more recently, interventional catheterization procedures has facilitated the correction of an expanding range of congenital heart defects through surgery. As a result, a growing number of patients, including those with complex defects, now have the chance to transition into adolescence and adulthood[1, 2].

Anxiety poses a genuine concern in pediatric anesthesia, primarily arising from the fear of surgery, the distress associated with separation from parents, and underlying conditions such as congenital cardiac disease. In this specific context, it can have significant consequences, particularly on the hemodynamic status, underscoring the necessity for preventive measures[3]. Anesthesiologists, especially when dealing with pediatric patients with congenital heart disease scheduled for therapeutic cardiac intervention, must carefully consider the consequences. These include reflex responses to painful stimuli, ensuring the child remains immobile, and the potential depression of cardiovascular and respiratory functions[4]. Approximately 65% of children undergoing surgery and anesthesia experience significant anxiety and stress, particularly in the preoperative holding area. This situation often extends to the parents, further exacerbating the child's response before surgery. The level of anxiety in children has been identified as a strong predictor for the occurrence of hallucinations during the recovery period and the onset of unfavorable behavioral changes, such as nightmares and enuresis[5, 6]. Children undergoing diagnostic and interventional cardiac catheterization frequently require deep sedation or general anesthesia. Although there are valid arguments for both approaches, in practical terms, the level of sedation necessary for these procedures in children is nearly equivalent to that achieved with general anesthesia (GA). This level of sedation is essential to suppress reflexes triggered by painful stimuli and to ensure the child remains immobile during the procedure[4]. To furnish cardiologists with the most relevant hemodynamic data, it is crucial to prevent the depression of cardiovascular and respiratory functions. Although these goals are usually attainable through tracheal intubation and mechanical ventilation, the depth of anesthesia required to accommodate a tracheal tube may unavoidably lead to some reduction in myocardial contractility and alterations in respiratory mechanics[7].

In general, if patients' preoperative anxiety is not adequately managed through premedication, it can impact surgical outcomes, including postoperative pain, analgesic requirements, and the length of hospital stay[8, 9]. Naturally, N-acetyl-5-methoxy-tryptamine, commonly known as melatonin, is a biogenic amine that was initially discovered in the mid-20th century (1958) by Aaron B. Lerner at Yale University[10, 11]. Over time, melatonin has been found to be synthesized not only in humans but also in animals, plants, and even unicellular organisms such as bacteria. In humans, melatonin is primarily produced by the pineal gland, a small pine-cone-shaped structure situated on the roof of the third ventricle deep within the brain[12]. Recently, attention has been drawn to the benefits of utilizing oral melatonin in pediatric patients, as it has been recognized for its anesthetic properties[13]. Melatonin belongs to the endogenous indolamines group and can be employed as an oncostatic agent, recognized for its antioxidant, anti-inflammatory, and anticonvulsant properties, among others. The common routes of administration include oral and sublingual, with no significant side effects reported in association with melatonin administration[14]. Research exploring the anesthetic effects of melatonin in adult subjects has demonstrated a comparable effectiveness in reducing pre-operative anxiety when compared to midazolam, which is considered the gold standard[15, 16]. Additionally, melatonin seems to be linked with a lower incidence of postoperative anxiety, sleep disturbances, and manifestations of confusion or delirium[17]. However, some other studies have suggested that melatonin may not be as efficient as midazolam in achieving these outcomes[18].

Recently, melatonin has been proposed as an effective agent for reducing preoperative anxiety levels, and its premedication has been suggested to be comparable to midazolam[17,19-22].

The objective of our trial was to evaluate the anxiolytic and sedative effects of oral melatonin in pediatric subjects diagnosed with simple congenital heart diseases undergoing therapeutic cardiac catheterization under general anesthesia.

METHODS

This study is a randomized double-blinded controlled trial conducted at Al-Nasiriya Heart Center in Iraq, involving 80 patients of both sexes aged 4 to 12 years with simple congenital heart diseases (atrial septal defect (ASD), ventricular septal defect (VSD)) undergoing cardiac catheterization over a 14-month period. Parents of participating children received comprehensive information about the study's objectives before signing informed consent forms. The children were categorized into two groups, melatonin and placebo, following written informed consent from their parents and approval from the local ethical committee of Thi-Qar Health Provenance.

Inclusion criteria encompassed individuals with American Society of Anesthesiologists status (ASA) II–III, aged

4 to 12 years, scheduled for non-emergency cardiac catheterization to address ASD or VSD, regardless of gender. Exclusion criteria involved parent refusal or uncooperative patients, allergy to the study drug, any oral disorder hindering drug administration, and mental retardation.

On the day preceding surgery, anesthetic plan details were discussed with the parents, covering fasting hours, current medication, and obtaining written consent. All patients underwent comprehensive evaluations, including a full medical history, clinical examination with age, body weight, height, and airway assessment. Laboratory investigations included complete blood count, arterial blood gas analysis, liver function tests, coagulation profile, serum electrolytes (Na+, K+), and blood sugar levels.

The patients were randomly allocated using the closed envelope method into two groups: The 1st group is the Melatonin Group (N=40): Patients received licensed oral melatonin (Colonis Pharma) at a dose of 0.5 mg/kg. The first dose was administered at midnight before the day of the intervention, and the second dose was given in the morning of the intervention (90 minutes before the induction of anesthesia), with a maximum allowable dose of 20 mg. It is worth noting that the utilization of two sequential doses of melatonin before surgical interventions has not been extensively studied in children, but it has been employed in some clinical studies involving adults[23-26].

The 2nd group (Placebo Group, N=40): Patients in this group received an identical-looking placebo. The placebo was administered at midnight before the day of the intervention and in the morning of the intervention (90 minutes before the induction of anesthesia).

All study drugs were prepared by the investigating anesthesiologist and were administered by another observer. Attending anesthesiologists, responsible for further assessment and management of the patient, were blinded to the given drug. The drugs were administered to children in the presence of their parents after obtaining baseline measurements of Heart Rate (HR), Oxygen Saturation (SpO2), and Mean Arterial Pressure (MAP) in the patient ward. Measurements were taken 30 minutes after premedication, 5 minutes before induction, and 10 minutes after induction.

The study drug was orally administered to the child in a sitting position using a 5-mL syringe. HR, Mean Blood Pressure (MBP), and SpO2 were measured every 30 minutes after drug administration until transfer to the Operating Room (OR) and continued during the procedure and in the recovery room.

Child anxiety levels were assessed by a blinded observer at various points: 15 minutes before morning premedication, 30 minutes after premedication, at the time of separation from parents, and 5 minutes before induction of anesthesia in the OR. The assessment used a four-point scale: 1 = Crying, 2 = Anxious, 3 = Calm but not cooperative, and 4 = Calm, cooperative, or asleep.

Sedation levels were evaluated at 30 minutes after drug administration, at the time of separation from parents, and 5 minutes before starting general anesthesia, using a four-point scale: 1 = Alert, 2 = Awake, 3 = Drowsy, and 4 = Asleep[27-29].

The initiation of general anesthesia involved the administration of sevoflurane (8%) through a face mask with a 100% oxygen mixture. The intravenous line was placed after the loss of consciousness, followed by the administration of intravenous anesthetic agents: fentanyl (1–2 μg/kg slow IV), propofol (1–2.5 mg/kg), and rocuronium (0.9 mg/kg) to provide neuromuscular blockade and facilitate the intubation procedure. Patients were mechanically ventilated using pressure-controlled ventilation mode with a 50% oxygen mixture, and end-tidal CO2 was monitored by mainstream capnography, maintained between 30 and 35 mmHg. The anesthetic level was adjusted to maintain stable blood pressure, heart rate, and respiratory rate (baseline ± 20%).

Standard monitoring included electrocardiogram, noninvasive blood pressure, pulse oximetry, and capnography. After the surgery, anesthetic gases were discontinued to 0%, replaced with 100% oxygen at a flow rate of ≥4 L/min. Once the child was awake, the endotracheal tube was removed, and the patient was transported to the post-anesthetic care unit (PACU) under the supervision of an anesthesiologist for monitoring vital signs until discharge to the ward.

Sample size calculation was conducted using G-power analysis, considering an 80% statistical power, a significance level of 0.05, and aiming to detect a 30% difference in anxiety and sedation states at parent separation between groups. This yielded a total sample size of 68 cases, with an anticipated dropout rate of 10%, resulting in a total of 80 cases (40 in each group).

Statistical analysis involved revising, coding, and tabulating the collected data using IBM SPSS Statistics. Descriptive statistics (mean, standard deviation) were employed for numerical data, and the Student T-test was used to assess significant differences between the means of the two study groups. The Chi-Square test examined relationships between qualitative variables.

RESULTS

Both groups exhibited comparability in terms of baseline demographics **(Table 1)**.

Table 1: Comparison between melatonin and placebo regarding to personal data.

	Melatonin N = 40		Placebo N = 40		Test	P
Age (years)						
Mean ± SD	6.68 ± 2.12		6.95 ± 2.06		t = 0.588	0.558
Min. – Max.	4.0 – 11.0		4.0 – 12.0			
Sex	**No.**	**%**	**No.**	**%**		
Male	30	75	30	75	$\chi^2 = 0$	1.000
Female	10	25	10	25		
Weight (kg)						
Mean ± SD.	22.85 ± 5.70		23.63 ± 6.46		t = 0.569	0.571
Min. – Max.	12.0 – 33.0		12.0 – 37.0			

SD.: Standard deviation, Min.: Minimum, Max.: maximum, t: Student t test, χ^2: Chi–Square, P value comparing between melatonin and placebo.

Table 2: Comparison between melatonin and placebo regarding to anxiety level.

Anxiety level	Melatonin N = 40		Placebo N = 40		Test	P
	No.	**%**	**No.**	**%**		
Before 15 min before premedication						
Crying	11	27.5	15	37.5	$\chi^2 = 1.063$	MC=0.661
Anxious	26	65	23	57.5		
Calm, but not cooperative	3	7.5	2	5		
Calm, cooperative or a sleep	0	0	0	0		
After 30 min of premedication						
Crying	0	0	12	30	$\chi^2 = 38$	
Anxious	6	15	18	45		<0.001*
Calm, but not cooperative	15	37.5	10	25		
Calm, cooperative or a sleep	19	47.5	0	0		
At separation time						
Crying	8	20	3	7.5	$\chi^2 = 13.254$	MC=0.003*
Anxious	11	27.5	26	65		
Calm, but not cooperative	17	42.5	11	27.5		
Calm, cooperative or a sleep	4	10	0	0		
At 5 min before induction						
Crying	7	17.5	9	22.5	$\chi^2 = 12.172$	MC= 0.025*
Anxious	9	22.5	18	45		
Calm, but not cooperative	19	47.5	13	32.5		
Calm, cooperative or a sleep	5	12.5	0	0		

χ^2: Chi–Square, MC: Monte Carlo, P value comparing between melatonin and placebo.

*: Significant when p value <0.05.

Before the children received the second dose of premedication, anxiety levels in both the melatonin and placebo groups were similar. However, after 60 minutes of taking melatonin, anxiety levels in the melatonin group were significantly lower compared to the placebo group. This trend continued at the time of separation, where anxiety levels in the melatonin group remained significantly lower than those in the placebo group. Five minutes before induction, when the children were about to be put to sleep, the anxiety level in the melatonin group was lower than that in the placebo group. Notably, about 47% of children in the treatment group were calm but not cooperative, while in the placebo group, more than 50% of children were either crying or in an anxious state **(Table 2)**.

Thirty minutes after taking the second dose of premedication, sedation levels in the melatonin group were significantly higher than those in the placebo group. This indicates that melatonin was effective in inducing sedative effects in children before surgery. The elevated sedation levels persisted at separation time, with the melatonin group showing significantly higher sedation levels compared to the placebo group. Additionally, a statistically significant difference in sedation levels between the two groups was observed at 5 minutes before induction. This suggests that children who received melatonin were significantly more likely to be asleep at 5 minutes before induction than children who received the placebo **(Table 3)**.

Table 3: Comparison between melatonin and placebo regarding to sedation level.

Sedation	Melatonin N = 40		Placebo N = 40		Test	P
	No.	%	No.	%		
After 30 min of premedication						
Alert	2	5	22	55	χ^2=45.507	MC<0.001*
Awake	6	15	14	35		
Drowsy	23	57.5	4	10		
Asleep	9	22.5	0	0		
At separation time						
Alert	2	5	1	2.5	χ^2=25.993	MC<0.001*
Awake	6	15	26	65		
Drowsy	23	57.5	13	32.5		
Asleep	9	22.5	0	0		
At 5 min before induction						
Alert	4	10	21	52.5	χ^2=41.949	MC<0.001*
Awake	9	22.5	18	45		
Drowsy	22	55	1	2.5		
Asleep	5	12.5	0	0		

$\chi2$: Chi–Square, MC: Monte Carlo, P value comparing between melatonin and placebo.

*: Significant when p value <0.05.

DISCUSSION

Melatonin is considered a biomarker, utilized for early identification of certain disorders and their follow-up. Its use has also been supported in clinical preventive and therapeutic applications in newborns, children, and adults, relying on its physiological regulatory effects[30, 31]. In the field of anesthesia, melatonin has been regarded as effective in reducing anxiety in adults. However, in children, the results still remain inconclusive or disparate [17, 26, 32-34].

This study was conducted to evaluate melatonin efficacy in reducing the anxiety level in pediatric undergoing therapeutic cardiac catheterization and its sedative effects preoperatively. The results indicated that the anxiety level was significantly reduced in the melatonin group. Before administration the 2nd dose of premedication the anxiety level was similar in both groups. However, it was noticed that melatonin has an effective role in reducing the level of anxiety in children, especially in the first hour after giving the second dose of it. We also had positive results for melatonin, at the expense of the placebo, in providing a stellar level of sedation at a rate of more than 50% in the group of children who received melatonin, it had a very high significant value in the various evaluation periods for the sedation level.

Results varied between different published RCTs, as well as the doses that were evaluated and used. In a pilot study conducted by Gitto et al in 2016, they illustrated that melatonin boosts the effectiveness of propofol in pediatric patients as well. Furthermore, when it comes to sedation levels appropriate for children, melatonin proves to be just as efficient as midazolam. These findings provide justification for employing melatonin as a premedication option for pediatric surgical cases[19]. According to the findings of meta-analysis study which conducted by Wang et al. the melatonin can decrease postoperative pain scores in minor degree, reduce postoperative opioid consumption and decreases the number of patients with analgesic requirements[35]. These results supported by Tunay et al. when they compared the postoperative analgesic effects of melatonin and vitamin C and the found that 6 mg of melatonin can reduce the pain score in the early postoperative period[36]. While in 2015, Kirksey and his colleagues had not been proven that melatonin has pain-reducing properties adult patients[37]. The melatonin can reduce pain during the perioperative time and also has effectiveness in reducing of the additional fentanyl use[38]. Premedication with oral melatonin can be decreased pain scores and tramadol consumption and enhanced sleep quality after elective prostatectomy sedation scores and subjective analgesic efficacy during the postoperative period[23]. The premedication with oral melatonin in adults showed a positive effect in reducing postoperative pain, in addition to many benefits especially in the early postoperative period[39-41]. Melatonin was found to be effective in many of animal models of pain as an analgesic agent, and this led to indicate its clinical application[42]. The pain level after dental procedures had been reduced with oral melatonin premedication[15]. There are some studies that gave preference to midazolam over melatonin in use as a premedication agent to provide an acceptable level of sedation[29, 43]. Melatonin and its analogs have been proposed as potential alternatives to midazolam for pediatric premedication in children[44, 45]. In contrast, another study demonstrated that midazolam was more effective than melatonin in reducing anxiety during anesthesia induction in children. However, participants who received melatonin experienced less severe delirium upon emergence compared to those who received midazolam[5, 18, 46]. Melatonin showed a low sedative effects than midazolam and dexmedetomidine when used preoperatively as a premedication in paediatric anaesthesia[47]. In a comparative study which conducted to

evaluate the effect of oral melatonin and oral midazolam as premedication in paediatric dental patients, the results were that the premedication with oral midazolam in paediatric patients is superior to that with melatonin with a higher parents' and operator's satisfaction[48]. In paediatrics, orally administration of melatonin offers several advantages such as: improving the initiation and quality of sleep, regulating circadian rhythms and reducing preoperative anxiety[49, 50]. Both melatonin and the non-selective MT1/MT2 receptor agonist agomelatine exhibit anxiolytic-like properties in animal models of anxiety[51, 52]. Additionally, it has been assured that melatonin's anxiolytic effect is linked to the activation of the GABAergic system[53]. Melatonin demonstrates a notable dose-dependent increase in GABA concentrations within the central nervous system[33]. This characteristic of melatonin likely arises from the reciprocal interaction between the GABA and MT2 receptor systems[53]. In adults, numerous studies have shown that preoperative administration of 5 mg of oral melatonin has a clinically significant impact on reducing anxiety and enhancing post-operative pain management[41, 54-57].

CONCLUSION

Oral melatonin emerges as a favorable option for pre-anesthetic medication compared to the placebo. The study suggests that melatonin at a dosage of 0.5mg/kg effectively serves as an alternative premedicant for children in mitigating preoperative anxiety. Additionally, oral melatonin premedication demonstrates superior analgesic properties compared to placebo premedication.

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