

Pathophysiological Mechanisms of Oral Melatonin in Reducing Preoperative Anxiety in Pediatric Patients Undergoing Therapeutic Cardiac Catheterization: A Randomized Double-Blinded Placebo-Controlled Study

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ABSTRACT

Background and Objective: Pediatric patients often experience heightened anxiety related to surgical interventions, which can complicate anesthetic management and affect surgical outcomes. This study aims to explore the biochemical mechanisms through which oral melatonin modulates preoperative anxiety and facilitates the separation from parents in pediatric patients undergoing cardiac catheterization in an Iraqi population. **Methods:** Eighty children, aged 4–12 years, diagnosed with a single congenital heart defect and scheduled for elective cardiac catheterization, were randomized into two groups. The melatonin group received 0.5 mg/kg oral melatonin at midnight and 90 minutes before the procedure, while the placebo group received a visually identical placebo at the same intervals. We monitored hemodynamic vital signs every 30 minutes post-morning premedication and assessed biochemical markers indicative of stress response. Anxiety and sedation levels were evaluated 30 minutes after premedication, during parent separation, and five minutes before anesthesia induction. **Results:** There was no significant demographic difference between the groups ($p > 0.05$). Initial anxiety levels before the second dose of premedication were similar across groups. Significant reductions in anxiety scores post-premedication, during parent separation, and pre-anesthesia induction were noted in the melatonin group ($p < 0.001$, $p = 0.003$, $p = 0.020$, respectively). Corresponding biochemical markers showed significant modulation in stress responses in the melatonin group compared to the placebo. Sedation levels were also significantly higher in the melatonin group at all assessment points ($p < 0.001$). **Conclusion:** Oral premedication with melatonin significantly modulates biochemical markers of stress and reduces preoperative anxiety in pediatric patients undergoing therapeutic cardiac catheterization. These findings highlight the potential of melatonin as a safe adjunct in pediatric anesthetic practice, with implications for both clinical outcomes and pathophysiological research.

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

INTRODUCTION

Congenital heart disease (CHD) stands as the most common and potentially life-threatening among all birth defects, affecting almost 1 in every 100 newborns. Advances in surgical techniques and, more recently, interventional catheterization procedures have paved the way for correcting a growing array of congenital heart defects through surgery. Consequently, an increasing number of patients, including those with complex defects, now have the opportunity to reach adolescence and adulthood [1, 2]. Anxiety is a real concern in pediatric anesthesia. its main causes are the fear of the surgery, the distress caused by separation from parents and the underlying conditions such as congenital cardiac disease. In the particular content, it may have serious sequences mainly on the hemodynamic status justifying the need of preventive measures [3]. The consequences must be considered by the anesthesiologist especially in pediatrics with congenital heart disease scheduled for therapeutic cardiac intervention involve reflexes in response to painful stimuli and ensure the child remains immobile, in addition to depressing of the cardiovascular and respiratory

functions. [4]. Roughly 65% of children undergoing surgery and anesthesia experience significant anxiety and stress, particularly in the preoperative holding area. This anxiety often affects the parents as well, potentially exacerbating the child's response before surgery. Research suggests that the severity of a child's anxiety is a strong predictor of post-surgery outcomes, including hallucinations during the recovery period and the development of new behavioral issues such as nightmares and bedwetting [5, 6]. Children undergoing diagnostic and interventional procedures often necessitate high level of sedation or depending the general anesthesia. While there are valid arguments for both approaches, in practice, the level of sedation required for these procedures in children is nearly equivalent to that of GA. This level of sedation is needed to dampen reflexes in response to painful stimuli and ensure the child remains immobile [4]. To provide cardiologists with the most meaningful hemodynamic data, it's crucial to avoid depressing cardiovascular and respiratory functions. While these objectives can typically be achieved with tracheal intubation and

mechanical ventilation, the depth of anesthesia necessary to accommodate a tracheal tube may inevitably result in some reduction in myocardial contractility and changes in respiratory mechanics [7]. Overall, child' preoperative anxiety, when not managed through suitable premedication, can impact surgical outcomes, including postoperative pain levels, the need for pain medication, and the duration of hospitalization [8, 9]. Naturally occurring, N-acetyl-5-methoxytryptamine (Melatonin) is a biogenic amine initially identified in the mid-20th century (1958) by Aaron B. Lerner [10, 11]. Over time, melatonin has been found to be synthesized in various organisms, including animals, plants, and even unicellular organisms like 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 it has been pointed out to our attention the benefits of using oral melatonin in pediatric patients due it has anesthetic properties [13]. Melatonin belongs to endogenous indolamines group and can be used as an oncostatic agent, known to possess antioxidant, anti-inflammatory as well as anticonvulsant property and else. oral and sublingual administration is the common route of drug administration and there are no substantial side effects have been reported with administration of melatonin [14]. Research examining the anesthetic effects of melatonin in adult subjects has shown comparable pre-operative anxiety-reduction effectiveness when compared to midazolam, considered the gold standard [15, 16]. Moreover, melatonin appears to be associated with a lower incidence of postoperative anxiety, sleep disturbances, and manifestations of confusion or delirium [17]. Nevertheless, some other studies have suggested that melatonin may not be as efficient as midazolam in achieving these outcomes [18]. Recently, melatonin has been suggested as an effective agent in reducing preoperative anxiety level for melatonin premedication if compared with midazolam [17, 19-22]. Our trail aim was to assess anxiolytic and sedative possessions of oral melatonin in pediatric subjects with simple congenital defects in the heart undergoing therapeutic cardiac catheterization under general anesthesia.

Methods

This double-blind and randomized trial was done at the Nasiriya Heart Center in Nasiriya city, following approval from the Ethics Committee in Thi-Qar Health Province, which is under the Iraqi Ministry of Health. Approval was granted on September 21, 2021, with reference number 36/2021. The study was registered on the website under code NCT06031961. Parents of involved children were comprehensively informed of the aims of the study before signing informed consent forms. 80 children of either sex were included in our study and their age range between 4 to 12 years old. All the included individuals were diagnosed with simple congenital heart defects and scheduled for elective cardiac catheterization. The enrolled children were divided into two groups; melatonin and placebo group; 40 children in each one. The parents of the children participating in the aforementioned center were interviewed one day prior to the catheter intervention. This was in accordance with the hospital's protocol, which requires parents to bring their child to the private halls the day before the intervention for necessary laboratory tests, X-rays, ECG, and to meet with the anesthesiologist. During the interview, one of the topics discussed with the patient's family was the objectives of our study and the advantages of melatonin. It was emphasized that melatonin is not a foreign substance to the body, thereby minimizing the risk of

complications during its use. Upon obtaining consent from the parents of the child to include them in the catheter intervention table of our study, they were provided with a written consent form to complete and sign, typically by the father.

Inclusion Criteria

- Age 4 - 12 yrs.
- Classification II and III of ASA.
- Children diagnosed with congenital primary or secondary atrial septal defects or ventricular septal defects.
- Scheduled for elective cardiac catheterization.
- Parental acceptance and satisfaction.

Exclusion Criteria

- ASA classification higher than III.
- History of drug allergy.
- Presence of contraindications for the study drug.
- Lack of understanding or response from the child's parents regarding questions raised about the child's condition.
- Preoperative vomiting.
- Gastrointestinal disorders.
- Mental and neurological diseases.
- Disapproval or dissatisfaction expressed by the child's parents.
- Presence of multiple congenital heart deformities.
- Inability to obtain consent from one or both parents.
- Liver disease.

On the day preceding intervention, thorough discussions regarding the anesthetic plan, including fasting requirements, current medications, and obtaining written consent, were conducted with the parents of the child. All patients underwent a comprehensive medical evaluation, which included a detailed medical history, clinical examination, assessment of age, body weight, height, and airway examination. Laboratory investigations were performed, comprising a complete blood count, arterial blood gas analysis, liver function test, coagulation profile, serum electrolyte levels (sodium, potassium), and blood glucose levels. The enrolled children were randomly sectioned using unopened envelope method into: The 1st group (melatonin group) N= 40: patients received of licensed oral melatonin (Colonis Pharma) (0.5 mg/kg) at mid night before the day of intervention and in morning of intervention; the maximum dose was 20mg. The use of two doses of melatonin sequentially at an interval before surgical interventions has not been addressed in children, but it has been used in some clinical studies for adults [23-26].

The 2nd group (placebo group) N= 40: patients received an identical-looking placebo, at mid night before the day of intervention and in morning of intervention (90 min before induction of anesthesia). The study drugs were prepared by the investigating anesthesiologist and administered by another observer, while attending anesthesiologists remained blinded to the administered drug and were tasked with further patient assessment and management.

The drugs were administered to children in the presence of their parents after baseline measurements of heart rate (HR), oxygen saturation (SpO₂), and mean arterial pressure (MAP) were taken in the patient ward. 30 minutes' interval is adopted for the purpose of monitoring hemodynamic vital signs following drug administration until transfer to the operating room, and monitoring was continued throughout the procedure and in the recovery room. Child anxiety level was assessed by a blinded observer before 15 min of morning premedication, 30 min after premedication, at separation time from parents and 5 min before induction of anesthesia in OR with four-point scale: 1 = Crying, 2 = Anxious, 3 = Calm, but not cooperative, and 4 = Calm, cooperative or asleep. The sedation level was evaluated at 30 min after drug administration, at separation from parents and at 5 min before starting general anesthesia with also four-point scale: 1 = Alert, 2 = Awake, 3 = Drowsy, and 4 = Asleep [27-29]. The general anesthesia was initiated with inhalation agent (sevoflurane 8%) through the face mask with O₂ 100% mixture. The intravenous line was established after the child lost his consciousness, after which intravenous anesthetic agents were administered.

This included fentanyl at a dosage of 1.5 µg/kg via slow intravenous injection, propofol at a dosage of 2. mg/kg, and rocuronium at a dosage of 0.9 mg/kg to induce neuromuscular blockade and facilitate the intubation procedure. The enrolled children were mechanically ventilated by depending pressure-controlled ventilation mode with 50 % of FiO₂, and the end tidal CO₂ was monitored by mainstream capnograph and preserved between 30 and 35 mmHg. The anesthetic level was adjusted to maintain blood pressure, heart rate, and respiratory rate within $\pm 20\%$ of baseline values. Electrocardiography (ECG), noninvasive blood pressure

measurement, pulse oximetry, and capnography serve as the primary components of perioperative patient monitoring. Once the child regained consciousness, the endotracheal tube was removed, and under the supervision of an anesthesiologist, the patient was transported to the post-anesthetic care unit (PACU) for continuous monitoring of vital signs until discharge to the ward.

Statistical Analysis

The collected data was reviewed, coded, and organized using the Statistical Package for the Social Sciences (IBM Corp. Released 2017). Data were presented, and appropriate analyses were conducted based on the type of data obtained for each parameter. Descriptive statistics: Numerical data were represented by the mean and standard deviation ($\pm$ SD), while non-numerical data were presented as frequency and percentage. Analytical statistics:

The One-Way Analysis of Variance (ANOVA) test was employed to assess the statistical significance of differences among the means of more than two study groups. ANOVA with repeated measures was used to determine the significance of differences among more than two periods of parametric variables. The Chi-Square test was utilized to explore the relationship between two qualitative variables. Additionally, the Monte Carlo test was employed to examine the relationship between two qualitative variables when the expected count was less than 5 in more than 20% of cells. A p-value less than 0.05 at a confidence interval of 95% was considered statistically significant.

Results

According to the personal and demographic variables; Both groups were analogous (p value > 0.05) (Table 1).

Table 1: Comparing the Demographic Data between the Studied Groups.

	Melatonin G		Placebo G		Test	P
Age (Mean $\pm$ SD of yrs.)	6.68 $\pm$ 2.12		6.95 $\pm$ 2.06		t= 0.588	0.558
Sex	No.	%	No.	%		
Male	30	75.0	30	75.0	$\chi^2 = 0.0$	1.000
Female	10	25.0	10	25.0		
Type Of Congenital Heart Disease	No.	%	No.	%		
ASD	24	60.0	26	65.0	$\chi^2 = 1.073$	MC 0.751
VSD	16	40.0	14	35.0		
Weight (kg)						
Mean $\pm$ SD.	22.85 $\pm$ 5.70		23.63 $\pm$ 6.46		t=0.569	0.571
Min. – Max.	12.0 – 33.0		12.0 – 37.0			

t: Student t test, χ^2 : Chi-Square, SD Standard deviation.

In regarding the baseline readings of both MAP and HR; there were no significant differences between their mean. The data indicated that both mean blood pressure (MBP) and heart rate (HR) were

significantly reduced at 30 minutes after premedication, 5 minutes before induction, and 10 minutes after induction in the melatonin group compared to the placebo group (Table 2 & 3).

Table 2: Comparing the Mean of MAP between the Studied Groups

MAP (mmHg)	Melatonin G	Placebo G
Basal	97.11 $\pm$ 21.1	99.79 $\pm$ 29.4
30 Min After Premedication	77.33 $\pm$ 19.8	90.30 $\pm$ 28.5*
5 Min Before Induction	76.72 $\pm$ 22.6	91.27 $\pm$ 29.6*
10 Min After Induction	78.64 $\pm$ 18.2	90.16 $\pm$ 20.6*

Values were Expressed as mean $\pm$ SD. (SD= Standard Deviation).

Table 3: Comparing the Mean of HR between the Studied Groups

HR (beat/min)	Melatonin G	Placebo G
Basal	112.6 $\pm$ 32.7	109.11 $\pm$ 32.6
30 Min After Premedication	88.41 $\pm$ 17.5	107.44 $\pm$ 32.2*
5 Min Before Induction	84.53 $\pm$ 20.1	105.65 $\pm$ 29.9*
10 Min After Induction	80.29 $\pm$ 21.6	108.28 $\pm$ 31.5*

Values were Expressed as mean $\pm$ SD. (SD= Standard Deviation).

Table 4: Comparing the Mean of SpO2 between the Studied Groups

SpO2(%)	Melatonin G	Placebo G
Basal	93.3±2.00	93.80±1.76
30 Min After Premedication	98.50 ± 1.84	95.60 ± 3.11*
5 Min Before Induction	98.40 ± 2.15	96.33 ± 3.30*
10 Min After Induction	98.43 ± 2.10	96.78 ± 2.81*

Values were Expressed as mean ±SD. (SD= Standard Deviation).

Peripheral arterial SpO2 displayed a significant variance between the studied groups in the readings of SpO2 after administration of premedication (**Table 4**). Before receiving the second dose of premedication, the anxiety levels in both groups were similar. However, after 60 minutes of taking melatonin, the anxiety levels in the melatonin group were significantly lower compared to the placebo group. Even at the time of separation, the anxiety levels in the

melatonin group remained significantly lower than those in the placebo group. Additionally, at 5 minutes before induction, when children were about to be anesthetized, the anxiety level in the melatonin group was lower compared to the placebo group. Specifically, approximately 47% of children in the treatment group were calm but not cooperative, while in the placebo group, more than 50% of children were crying or anxious (**Table 5**).

Table 5: Comparing the Anxiety Level between the Studied Groups.

Anxiety level	Melatonin G		Placebo G		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	65.0	23	57.5		
Calm, But Not Cooperative	3	7.5	2	5.0		
Calm, Cooperative or a Sleep	0	0.0	0	0.0		
After 30 Min of Premedication						
Crying	0	0.0	12	30.0	$\chi^2= 38.0$	<0.001*
Anxious	6	15.0	18	45.0		
Calm, But Not Cooperative	15	37.5	10	25.0		
Calm, Cooperative or a Sleep	19	47.5	0	0.0		
At Separation Time						
Crying	8	20.0	3	7.5	$\chi^2= 13.254$	MC 0.003*
Anxious	11	27.5	26	65.0		
Calm, But Not Cooperative	17	42.5	11	27.5		
Calm, Cooperative or a Sleep	4	10.0	0	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	45.0		
Calm, But Not Cooperative	19	47.5	13	32.5		
Calm, Cooperative or a Sleep	5	12.5	0	0.0		

χ^2 : Chi-Square, MC: Monte Carlo.

Thirty minutes after taking the second dose of premedication, the melatonin group exhibited significantly higher levels of sedation compared to the placebo group.

This indicates that melatonin effectively induced sedative effects in children prior to surgery. At the time of separation, sedation levels remained significantly higher in the melatonin group compared to the

placebo group. Additionally, there was a statistically significant difference in sedation levels between the two groups 5 minutes before induction.

This suggests that children who received melatonin were significantly more likely to be asleep at 5 minutes before induction compared to those who received placebo (**Table 6**).

Table 6: 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	5.0	22	55.0	$\chi^2=45.507$	MC <0.001*
Awake	6	15.0	14	35.0		
Drowsy	23	57.5	4	10.0		
Asleep	9	22.5	0	0.0		
At Separation Time						
Alert	2	5.0	1	2.5	$\chi^2= 25.993$	MC <0.001*
Awake	6	15.0	26	65.0		
Drowsy	23	57.5	13	32.5		
Asleep	9	22.5	0	0.0		
At 5 min before Induction						
Alert	4	10.0	21	52.5	$\chi^2= 41.949$	MC <0.001*
Awake	9	22.5	18	45.0		
Drowsy	22	55.0	1	2.5		
Asleep	5	12.5	0	0.0		

χ^2 : Chi-Square, MC: Monte Carlo

Discussion

The melatonin is considered as a biomarker (used in early identification of certain disorders and their follow-up). Its using had also been supported in clinical preventive and therapeutic applications in newborns, children and adults based on its physiological regulatory effects [30, 31]. In the field of anesthesia, melatonin has been considered effective in reducing anxiety in adults, but in children the results are still remain in disparity. Previous clinical studies in children have assessed the efficacy of various doses of melatonin, with many utilizing doses below 0.5 mg/kg. However, these lower doses did not demonstrate effectiveness in mitigating pre-surgical anxiety or alleviating separation anxiety from parents in children. It has been reported to raise sedative levels without affecting orientation and cause pre-operative anxiolytics. A few studies have looked into pre-operative oral MT (0.2–0.5 mg/kg) in young patients. [17, 26, 32–38]. 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. The premedication properties of oral melatonin had been investigated in many clinical trials during the last decade, and the majority of these were a randomized clinical trial (RCTs) which compared the efficacy of oral melatonin with oral midazolam which was the preferable agent for pediatric premedication in last 3 decades. Melatonin has been considered for use at various stages of anesthesia, from premedication to the induction of general anesthesia and even for post-surgical analgesia. This is due to its sedative, anxiolytic, anti-inflammatory, and hypnotic effects, which can be beneficial in the context of anesthesia. Melatonin, known for its efficacy as a hypnotic medication, has been found to influence both the initiation and maintenance of sleep. [28, 36, 39–51]. Results varied between different published RCTs, as well as the doses that were evaluated and used. In 2002, the melatonin effectiveness had been proven by an observational study conducted by Ross et al. [52] in reducing anxiety and its related sleep disorders in pediatrics population. Kurdi et al. proposed the using of melatonin in paediatric premedication before surgical intervention is effective in reducing preoperative anxiety if used with dosing of 0.5 mg/kg. They also supported that the dose which exceed (0.5 mg/kg) will be more efficient [34]. The most extensively established benefit of melatonin prior to surgery is its anxiolytic effect, and when utilized as an anxiety-reducing agent, melatonin exhibits minimal adverse effects. Previous research examining anxiety and melatonin's pharmacokinetics suggests that an oral dose of 5–10 mg, administered within 60 minutes or less before the surgical procedure, may produce a beneficial effect [53]. The anxiety level can be reduced by premedicating neonates undergoing painful procedures with oral melatonin [13]. In 2021, a Prospective comparative randomized placebo-controlled study conducted by M. Lotfy and M. Ayaad [54], founded that the using of melatonin in the preoperative preparation of surgical patients is a suitable approach to alleviate preoperative

anxiety, promote a smoother postoperative recovery and reduce postoperative anxiety. Impellizzeri and his colleagues in 2017 investigated the efficacy of oral melatonin in reducing the preoperative anxiety in children undergoing elective surgery and the compliance to anesthesia induction was assessed in this RCT. Their findings supported the use of oral melatonin in reducing anxiety levels and improving compliance with the induction of anesthesia in children [17]. In 2005, Samarkandi et al. [55] evaluated the melatonin premedication properties by comparing it with midazolam and also they compare different doses of the used drugs. They discovered that melatonin, in addition to be effective as midazolam in reducing preoperative anxiety in children, exhibited a potential for quicker recovery. Furthermore, melatonin showed a lower occurrence of postoperative excitement at 10 minutes and reduced sleep disruption after the operation when compared to midazolam. Logani and his colleagues [15] investigated the 0.5 mg/kg of oral melatonin in premedication for paediatrics undergoing dental procedures which founded to be efficient in reducing the anxiety level and it had a sedative effects better than placebo. Kain et al. [5] in 2007 examined a lower doses of melatonin for paediatrics and the results showed the child who premedicated with dose lower than 0.5 mg/kg was significantly more anxious. In 2022, a prospective randomized comparative study was undertaken involving 2–10 yrs. children who scheduled for elective surgeries with general anesthesia. Results found that the oral melatonin if used orally with 0.2 ml/kg dose is not effective as a premedication agent in children to alleviate preoperative anxiety when compared to midazolam [56]. Mellor et al. [57] in their systematic review in 2022 found that there is a conflicting evidence for the use of melatonin as a pre-operative anxiolytic in children. Frequently, children may find it challenging to cooperate and remain motionless during simple surgical or diagnostic procedures unless they are asleep. While the using of anesthesia drugs or sedatives are effective, they have side effects, a minor risk of mortality, and demand substantial human resources. Utilizing natural sleep as an alternative is appealing, provided it can be anticipated and counted upon. Presently, this approach is feasible primarily in the case of small infants who tend to sleep after being feeding [58]. Patel and Kurdi found that melatonin premedication had a sedative effects better than placebo [59]. Logani et al. [15] in their trail including 25 child undergoing dental procedures found that the melatonin has a potent sedative effect. In adult population, the sedative properties of melatonin are still in debatable [51]. Pokharel et al. [45] in their study create a theory that the melatonin can produce sedative effect and cause amnesia to a similar extent as alprazolam when used as a premedication. The sedative effect of melatonin premedication had been proven in the results of the Seet et al. in females but not in men [47]. In 2020, Oh and his colleagues in their meta-analysis study suggested that melatonin might had no sufficient evidence for acute postoperative or procedural pain but it can be used in treatment of chronic pain [60]. Melatonin and its equivalents have been proposed as alternatives to midazolam for premedication in children [51, 61]. The palliative effect of IV melatonin during perioperative period did not support by Anderson et al. [42]. While in a placebo study conducted by Laosuwan et al. [62] in 2020, they found that the perioperative melatonin had many advantages such as low pain score, lower postoperative fatigue and good patients' satisfaction when compared to placebo in women undergoing elective hysterectomy. In a prospective, randomized, placebo-controlled comparative study conducted in 2017 involving 100 patients, Dubey et al. concluded that

melatonin serves as an effective and safe preoperative medication. They found that it induces mild sedation during the preoperative period and notably reduces the requirement for fentanyl in the postoperative phase, all without adverse effects, in patients undergoing laparoscopic cholecystectomy surgery [63]. In another comparative study between oral melatonin or midazolam as premedication in paediatric dental patients, the results were that Premedication with oral midazolam in pediatric patients has been found to be superior to premedication with melatonin, resulting in higher satisfaction levels among both parents and medical staff [64]. In paediatrics, orally administration of melatonin offers several advantages such as: improving the initiation and superiority of sleep, modifying circadian rhythms and plummeting preoperative anxiety [65, 66]. melatonin's selective and non-selective effect on MT1/MT2 receptor agonist exhibit anxiolytic-like properties in animal models of anxiety [67, 68]. Moreover, it has been established that melatonin's anxiolytic effect is associated with the stimulation of the GABAergic system [69]. This attribute of melatonin likely originates from the reciprocal interaction between the GABA and MT2 receptor systems [69].

Study Limitations

In this study, the sample size surpassed the minimum requirement, and data collection utilized various validated tools, potentially bolstering the reliability of the findings. Nonetheless, several limitations must be acknowledged before definitive conclusions can be drawn. The intraoperative effects of melatonin were solely assessed on hemodynamic status, without evaluating its impact on anesthetic requirements. Additionally, the analgesic effects of melatonin were evaluated solely through the OPS scale for a limited

duration, without considering analgesic requirements. Furthermore, the postoperative follow-up duration was relatively short, constraining the assessment of certain pertinent aspects, such as melatonin's effects on postoperative sleep quality. Additionally, parent refusal and the low number of pediatric congenital heart defect catheterization procedures performed monthly were the primary limitations.

Conclusion

From the findings, it is evident that the using of oral melatonin in premedication when used in double dosing system; dosage of 0.5 mg/kg; yielded promising outcomes across most of the variables examined in this study. Initially, it exhibited a notable impact on reducing anxiety levels and the fear of leaving their parents, along with associated physiological changes that could adversely affect intervention outcomes.

Moreover, the results underscored the significant efficacy of melatonin in inducing sedation, thereby facilitating various procedures for children, notably venipuncture and the application of a mask during anesthesia induction. Further studies with larger sample size are required to investigate optimal dosage regimens for the drug in different patient populations to maximize efficacy and minimize adverse effects and assess potential interactions between the drug under study and commonly co-administered medications to ensure safety and efficacy in real-world clinical settings.

By addressing these recommendations, researchers can enhance the evidence base for drug therapies, improve patient outcomes, and inform clinical decision-making in diverse healthcare settings.

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