A Comparison Between Oral Melatonin and Oral Dexmedetomidine As Premedication In Paediatric Anesthesia.

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Abstract

Background:

Preoperative anxiety in children is a common challenge, often triggered by the anticipation of pain, separation from parents, and fear of surgery. Effective premedication can significantly improve perioperative experiences and outcomes. This study aimed to compare the efficacy of oral dexmedetomidine and melatonin in alleviating preoperative anxiety in paediatric patients.

Materials and methods:

This prospective observational study was done in 92 children aged 2-10 years, belonging to ASA I and II, undergoing elective infraumbilical surgeries under general anesthesia. Patients were allocated into two groups: Group D received oral dexmedetomidine 3 µg/kg, and Group M received oral melatonin 0.5 mg/kg, administered orally 40 minutes prior to induction. Vital signs were monitored at 5-minute intervals. Sedation levels were assessed using the Ramsay Sedation Score and ease of parental separation by the Child–Parent Separation Score. Prior to induction, mask acceptance was assessed with Mask acceptance score. Postoperative sleep disturbances were assessed two weeks later using Post-Hospitalization Behaviour Questionnaire.

Results:

Group D demonstrated significantly higher sedation levels, smoother parental separation, and better mask acceptance compared to Group M ($p < 0.001$). No significant difference was observed in postoperative sleep disturbances between the groups as per Post-Hospitalization Behaviour Questionnaire findings.

Conclusion:

Oral dexmedetomidine provides superior preoperative sedation, facilitates easier parent–child separation, and improves mask acceptance in pediatric patients compared to melatonin.

Keywords:

Dexmedetomidine, Melatonin, Oral premedication, Paediatric, Sedation.

Introduction:

Preoperative anxiety, often manifesting as crying, agitation, and restlessness prior to surgery is distressing to parents and a challenge to anaesthesiologist. It can complicate anaesthetic induction, increase emergence delirium and pain perception, prolong recovery, and lead to negative postoperative behavioral changes such as sleep disturbances, enuresis, feeding issues, and parental stress [1,2]. Hence, premedication should be an integral component of paediatric anaesthesia.

Melatonin, a pineal hormone, is used for treatment of sleep disorders in adults and children and for premedication in adult patients. The high safety profile and cost effectiveness are the notable advantages of melatonin [3]. Dexmedetomidine, a selective alpha

2 agonist with sedative and analgesic effects, produces analgesia and sedation. It reduces the need for rescue analgesics and incidence of postoperative delirium in paediatric patients [4,5].

There is paucity of evidences on melatonin compared to other premedicats in children. This prospective study aimed to evaluate the effectiveness of melatonin compared to dexmedetomidine as oral premedicant in children.

Materials and methods:

This prospective observational study was conducted in a tertiary care teaching institute during the year 2021-2022, after obtaining clearance from the institutional research and ethics committee (Ref No: GMCKKD/RP2021/IEC/103). Study followed the principles of the Declaration of Helsinki (2013) and Good Clinical Practice guidelines.

Sample size was calculated based on a previous study by Malini et al, to detect a 0.3-point difference between groups with a 95% confidence level and 80% power, 42 subjects per group were required. To account for attrition, 10% was added, resulting in 46 children per group. We included 92 children aged 2-10 years, of either gender belonging to American society of Anaesthesiologist (ASA) physical status I-II, scheduled for infraumbilical surgeries under general anaesthesia. Children with sleep disorders, previous history of multiple surgeries or prolonged hospitalization, intellectual disability, neurodevelopmental problems, children who had any recent stressful life experience (death in the family, separated parents etc), children requiring postoperative ventilation and known allergy to study drugs were excluded from the study. Primary objective of the study was to assess the preoperative sedation with premedication. Secondary objectives were ease of parental separation, mask acceptance and any sleep disturbance after two weeks postoperatively.

Standard pre-anaesthetic evaluation and preparation including fasting guidelines followed. Premedication was administered in the preoperative holding area, 40 minutes

before anaesthesia, in presence of parent. Patients were divided into two groups of 46 each. Group D received dexmedetomidine 3μg/kg and group M received melatonin 0.5mg/kg orally. Melatonin syrup available as 3mg in every 5 ml and injectable preservative-free preparation of dexmedetomidine mixed with sugar syrup was used for premedication. Baseline heart rate (HR) and oxygen saturation (SpO_2) were noted before giving premedication and every 15 minutes until transfer to the operation theatre.

Preoperative sedation and anxiety were assessed at 15, 30, 45 minutes after premedication and before shifting to operation theatre using Ramsay sedation score of 1-6 (level 1- awake, anxious, level 2- awake cooperative, level 3- responds to commands only, level 4-asleep, brisk response to light glabellar tap, level 5- asleep, sluggish response to light glabellar tap, level 6- asleep, no response)**.** Level 1-2 are considered as poor sedation and 3-5 are good sedation and 6 as unresponsive. Ease of parental separation assessed using Child-parent separation score (1- poor, 2- fair, 3- good, 4- excellent). In the operation theatre, after attaching standard monitors, mask acceptance was assessed with Mask acceptance score of 1-3 (1- child is calm, cooperative, 2- moderate fear of mask. 3- cries, needs restraining). Intravenous access was obtained under sevoflurane induction and a balanced salt solution infusion was started. All children received caudal epidural analgesia (Bupivacaine 0.25%, 1ml/kg) after inducing with propofol. Anaesthesia maintained on spontaneous ventilation through mask with oxygen in nitrous oxide and sevoflurane. Vitals monitored (HR, SpO_2, NIBP) every 5 mins till surgery was over. After the surgery, children were monitored in recovery and discharged to the ward when fully alert and hemodynamically stable. Any incidence of hypotension, bradycardia, nausea or vomiting was noted.

Two weeks later, parents were contacted telephonically and asked for sleep disturbances using the Post-Hospitalization Behaviour Questionnaire (PHBQ), a validated

27-item tool covering six anxiety domains. Sleep related items included fussing at bedtime, difficulty falling asleep, and fear of the dark, scored from -2 to +2 relative to preoperative behavior. This scoring reflects the behaviors referenced to normal (much less, less, same, more and much more) before surgery.

Statistical analysis:

Initial data entered in an excel spreadsheet and analyzed using Statistical Package for the Social Sciences SPSS Statistics for Windows, Version 20.0 software (IBM, Bengaluru, India). Quantitative data expressed as mean and standard deviation, qualitative data as number and percentages. The categorical data analyzed with chi-square test and quantitative data using unpaired student's t-test and a *P* value <0.05 was considered statistically significant.

Results:

In this study, all 92 enrolled children completed the study. Both the groups were comparable with respect to demographics and duration of surgery (Table 1).

When the vital parameters were compared, baseline HR and SpO_2 were comparable. The HR at 30 and 45 min after premedication showed a significant difference between groups. Compared to group M, HR was significantly lower in group D (Table 2) but there was no significant bradycardia. Mean SpO_2 was higher in the melatonin group, however there was no statistically significant difference between the groups.

When sedation score was analyzed, at 15 minutes after premedication, 27 children (58.7%) in group D and 40 (87%) in group M showed level 1 sedation scores, while 19 (41.3%) of group D and 6 (13%) of group M showed level 2 scores. Children in group D showed better sedation scores at all time points and was statistically significant. At the

time of parental separation, more patients in group D were satisfactorily sedated compared to group M (Table 3).

In group D, 22 children were easily separated from their parents, whereas none of the children in the melatonin groups were easily separated. Only 4 of the group D kids were clinging on to their parents (Table 3). Between the groups, there was a statistically significant difference (p =0.001) with children in group D showing better ease of parental separation score.

With respect to mask acceptance, there was a significant statistical difference between the groups (Figure 1). Seven children in group D were cooperative and calm but 10, who cried and needed to be restrained. In contrast, 14 participants in group M were calm and cooperative, but 16 participants cried and required restraint.

During the intra operative period, heart rate was lesser in Group D but, no significant bradycardia occurred. The heart rates at different follow up intervals after premedication were significantly different between group D and group M.

In terms of post-hospitalization behaviour questionnaire, there was no statistically significant difference between the two groups, among the 3 questions asked regarding sleep disturbances (Table 4).

Discussion:

Preoperative anxiety affects 60 - 70% of paediatric patients [6]. Untreated anxiety cause difficulties during anaesthetic induction, necessitates higher postoperative pain and requirement for rescue medications, emergence delirium, postoperative psychological impacts and behavioural issues [7]. Premedication aims to ensure anxiolysis and sedation without delaying recovery or compromising hemodynamic stability [8,9]. This prospective

observational study compared dexmedetomidine and melatonin as oral premedication in paediatric anaesthesia.

Dexmedetomidine, a highly selective alpha-2-agonist exerts sedative and analgesic properties by inhibiting norepinephrine release pre-synaptically [10]. But, post-synaptic activation of alpha-2 receptors can cause bradycardia and hypotension. Oral bioavailability of dexmedetomidine is merely 16% because of significant first-pass metabolism [11]. In our study, we found that, dexmedetomidine provided better sedation scores compared to melatonin at 15, 30 and 45 min after premedication. These results were consistent with the study carried out by Syed T. Ali et al [8]. In their study comparing the effects of oral clonidine, dexmedetomidine, and melatonin as premedicants, they found that the sedative effects of clonidine versus dexmedetomidine and clonidine versus melatonin were comparable, while dexmedetomidine was superior to melatonin. In contrast to our study, it was found that all groups experienced parental separation in a comparable way. Dexmeditomidine premedication provided better sedation, smoother induction and recovery compared to midazolam [12].

Melatonin, a natural hormone valuable in regulating the normal circadian rhythm, also has antioxidant, anticonvulsant and anti-inflammatory properties. Melatonin provides anxiolysis with minimal sedation without impairing orientation by facilitating γ-aminobutyric acid (GABA) transmission [13] with a peak effect at 60-150 min [14]. It facilitates faster recovery, and causes fewer sleep disturbances compared to benzodiazepines [12,15]. The high safety profile and cost effectiveness are the notable advantages. Several studies demonstrated effective sedation and parental separation with melatonin premedication in children [16,17].

In a network meta-analysis by Chuan-Qi Yang et al [18], which included a total of 48 trials, showed that the effectiveness of dexmedetomidine, midazolam, clonidine, and

ketamine was superior to that of placebo in satisfactory sedation, parental separation and mask acceptance. Contrary to our results, melatonin and placebo did not significantly differ in these areas. Similar to our observation, dexmedetomidine caused haemodynamic changes like hypotension and bradycardia, but were within safe limits. They concluded that dexmedetomidine has the potential to be the best sedative to choose when premedicating children. Sedation scores, parental separation and mask acceptance was superior to dexmedetomidine compared to melatonin in other studies also [19].

Preoperative anxiety if not controlled adequately can result in post-hospitalization behavioral issues in children like sleep disturbance, separation anxiety, new onset enuresis, eating problems and heightened fear of physicians [20]. In our study, children did not have any sleep disturbances, and there was no statistical difference between the groups. Studies had reported reduced incidence of post-hospitalization sleep disturbance with melatonin premedication compared to midazolam or placebo [15]. Melatonin and dexmedetomidine also reduce emergence agitation after sevoflurane anaesthesia [20,21]. Dexmedetomidine showed better prevention of emergence agitation compared to midazolam [20,22].

Limitations of the study:

Some of the limitations of this study include the observational study design and single center experience which may not be applicable generally. Parental satisfaction was not assessed. Other post-hospitalization behavioural changes in PHBQ were also not assessed in the study.

Conclusion:

Dexmedetomidine in a dose of 3μg/kg found to be superior compared to melatonin at 0.5mg/kg as oral premedicant in paediatric patients with respect to preoperative sedation,

parental separation and mask acceptance. Both drugs did not show any post-hospitalization sleep disturbance at two weeks.

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Tables and Figure legends:

Table 1:

Category	Group D(n=46)	Group M(n=46)	*P* value
Age (years).	4.6 ± 2*	4.7 ± 2.2*	0.7
Gender, *n* (%) Male	36(78.3%)	38(82.6%)	0.793

Female	10(21.7%)	8(17.4%)	
ASA status, *n* (%)	ASA I = 41(89.7%) ASA II =5(10.9%)	ASA I= 46(100%) ASA II= 0(0.0%)	0.056
Duration of surgery (min)	34 ±4.6*	32 ± 6.8*	0.067

*Data as Mean ± Standard deviation

Table 2: HR evaluation post-premedication:

Heart Rate	Group D (n = 46)	Group M (n = 46)	*P* value
15 Min	103.5 ± 13.28	105.4± 11.21	0.468
30 Min	100.3 ± 13.23	106.8 ± 10.35	0.011
45 Min	97.54 ± 13.54	107.7 ± 12.73	<0.001

*Data as mean ± Standard deviation

Table 3: Sedation and parental separation score before taking to operation theatre

Outcome measured	Group D (n =46)	Group M (n =46)	*P* value
Sedation score at 40 min			
Level 1	0	0	
Level 2	5 (10.9)	25 (54.3)	
Level 3	35 (76.7)	21 (45)	*<0.01*

Level 4	6 (13)	0	
Separation score			
Poor(crying)	4(8.7)	22(47.8)	
Fair (crying not clinging)	20(43.5)	24(52.2)	<0.001
Good (whimpers, reassured)	22(47.8)	0	

*Data as number (percentage)

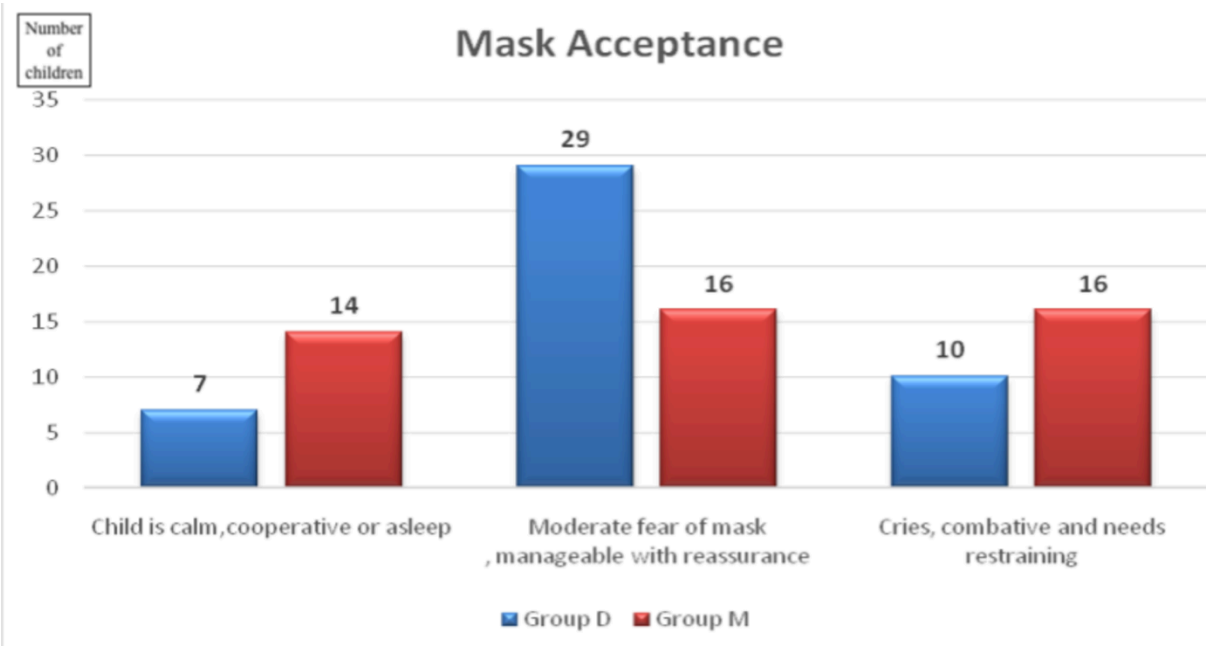
Table 4: Posthospitalization sleep disturbance by PHBQ

Question	Answer	Group D	Group M	*P* value
Is the child making any fuss about going to bed	Less	3(6.5)	3(6.5)	
	Same	43(93.5)	43(93.5)	0.9
Is the child afraid of darkness	Less	8(17.4)	3(6.5)	
	Same	38(82.6)	43(93.5)	0.197
Is there any trouble getting sleep at night	Less	8(17.4)	11(23.9)	
	Same	38(82.6)	35(76.1)	0.197

*Data as number (percentage)

Figure legends:

Figure 1: Mask acceptance at induction.


Mask Acceptance
Number of children
35
30
25
20
15
10
5
0
7
14
29
16
10
16
Child is calm,cooperative or asleep
Moderate fear of mask , manageable with reassurance
Cries, combative and needs restraining
Group D
Group M