European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 07, 2022

Original research article

A Comparative Study of Two Different Doses of Oral Melatonin for Premedication in Children Posted For Elective Paediatric Surgery

Mekha Elizabeth Mathew[1], Ritika Negi[2], Amit Kumar Prasad[3], R L Gogna[4]

[1]Senior Resident, Department of Anaesthesiology, MGM Medical College and Hospital, Navi Mumbai. Maharashtra. India.
[2]Assistant Professor, Department of Anaesthesiology, MGM Medical College and Hospital, Navi Mumbai. Maharashtra. India.
[3]Assistant Professor, Department of Anaesthesiology, RDJM Medical College and Hospital, Muzaffarpur. Bihar. India.
[4]Retired Professor and HOD, Department of Anaesthesiology, MGM Medical College and Hospital, Navi Mumbai. Maharashtra. India.

Email - bablooprasad11@gmail.com

Corresponding Author – Dr. Amit Kumar Prasad

ABSTRACT

Background and Aims: Preoperative anxiety and psychological trauma due to separation from parents before shifting to operation theatre are the major challenges in paediatric anaesthesia. Premedication in children aims at relieving anxiety and facilitates a smoother induction of anaesthesia. Melatonin (N-acetyl-5-methoxytryptamine), a naturally occurring sleep inducing hormone, available commercially is used as an effective premedicant without altering haemodynamic parameters. Thus we aimed at comparing the efficacy of two doses of oral melatonin i.e. 0.5mg/kg and 0.75mg/kg as premedication in children undergoing elective surgery under general anaesthesia.
Methods: Sixty patients of either sex of American Society of Anaesthesiologists (ASA) physical status I and II scheduled for elective paediatric surgery were randomly assigned to one of the two groups of 30 patients each in a double blind manner after taking written informed consent from their parents. Group A received oral Melatonin 0.5mg/kg and Group B received oral Melatonin 0.75mg/kg, 45 minutes prior to surgery in the preoperative area in presence of their parents. Patients were assessed on Modified Yale Pre-operative Anxiety scale, Sedation Score, Behaviour score and Mask acceptance score.
Results: The demographic characteristics of the two groups were comparable. Anxiety scores reduced significantly in both groups ($P < 0.01$) and were lower than baseline at the time of introduction of mask; but the reduction in anxiety score was more with 0.75mg/kg of oral melatonin. The sedation score was comparable in both groups. Mean parent child separation scale score was comparable at the baseline between study groups (3.4 vs 3.19: $P = 0.19$). The scores significantly fell in both groups till 30 minutes after premedication (2.2 vs 1.72; $P < 0.01$). The mask acceptance score was significantly lower in group B as compared to group A (1.77 vs 2.27; $P < 0.01$). No difference was observed between study groups

in terms of heart rate, mean arterial pressure, oxygen saturation and respiratory rate at baseline and its mean change during follow up till 30 minutes.

Conclusion: Our study concluded that premedication with oral Melatonin (0.5 mg/kg and 0.75 mg/kg) in children significantly decreases pre-operative anxiety without impairing cognitive and psychomotor functions with 0.75 mg/kg dose being more effective.

Keywords: Premedication, Oral Melatonin, Preoperative anxiety, Paediatric surgery.

Introduction

Anxiety and fear of unknown and new environment are significant determinants of preoperative agitation in children, manifesting as tearfulness, screaming, clinging to parents, apathy, and withdrawal.[1–4] Apart from undesirable effects of increased sympathetic tone and increased levels of catecholamines secondary to stress response, immunological, metabolic, and hormonal changes also occur.[5] Studies have demonstrated relationship between preoperative anxiety and emergence delirium, increased analgesic requirements, negative behavioral changes, sleep disturbances, and separation anxiety in postoperative period.[6]

Allaying this anxiety is of primary importance to prevent any adverse impact on the child. Various pharmacological and non-pharmacological modalities are commonly utilized to decrease preoperative anxiety. Non-pharmacological therapies, though effective, have variable results.[7] Sedative premedicants are the mainstay of pharmacological therapy.[8] An effective premedication facilitates a smoother induction of anaesthesia with minimal haemodynamic alterations and minimizes the emotional trauma in children undergoing surgery. Premedication can be administered orally, intramuscularly, intravenously, rectally, sublingually, or nasally. However, premedication is best given by an oral route in children, as children often exhibit an exaggerated psychological response to a needle, and it is easier to administer a medication orally than to use nasal or rectal routes.[9] Many drugs like benzodiazepines, opioids, pregabalin, gabapentin, alpha 2 agonists etc. have been used as premedicant to decrease preoperative anxiety and to provide post-operative analgesia with their own associated benefits and risks. Currently, Midazolam is the preferred premedication more than 90% of the time.[10,11] It acquired widespread acceptance because of its rapid absorption after oral ingestion; it can also be administered via multiple routes and confers a reduced incidence of nausea compared with other benzodiazepines.[12] However, midazolam has several drawbacks, including paradoxical reactions, interactions with opioids, variable bioavailability and elimination half-life, and delayed discharge from the post anaesthesia care unit after brief procedures.[12] Moreover, the effects of midazolam have been shown to vary with the age and temperament of the child.[13] In light of these drawbacks, an alternative to midazolam might have widespread appeal. Melatonin or N-acetyl-5-methoxytryptamine, a naturally occurring sleep inducing hormone secreted by pineal gland, also available commercially has got sedative, hypnotic, analgesic, anti-inflammatory, antioxidant, regulation of circadian rhythm and chronobiotic properties that distinguishes it as an attractive alternative premedicant.[14] By virtue of its multiple actions, Melatonin has the potential to be used as an alternative premedicant, as an anxiolytic, sedative and analgesic without significant haemodynamic alterations in patients undergoing surgical procedures under general or regional anaesthesia. It also helps in restoring sleep rhythm in postoperative period. It has no hangover effects on the day following its intake and has no negative effects like addiction, dependence as compared to benzodiazepines.[15] Melatonin is considered to be as effective in reducing preoperative anxiety as midazolam.[16,17] Moreover, Melatonin was associated with a more rapid recovery, a reduced incidence of emergence delirium, and sleep disturbances two weeks after surgery when compared to midazolam.

There are no studies on optimal dose of Melatonin as premedication in children. In present study, we thus aimed at comparing the efficacy of two doses of oral melatonin i.e. 0.5mg/kg and 0.75mg/kg as premedication in children undergoing elective surgery.

ISSN 2515-8260 Volume 09, Issue 07, 2022

Material And Methods

Study setting

This double-blind randomized controlled study was done in a tertiary care centre and medical college from December 2019 to September 2021. This study included a total of 60 patients posted for elective paediatric surgery. Institutional ethical committee approval (Approval number: N-EC/2020/SC/03/50) was taken. Written informed consent from all the parents/guardians were obtained after informing them the nature of the study and complications. Children in the age group of 2 to 10 years of either sex belonging to American Society Of Anaesthesiologists (ASA) physical status I and II undergoing elective surgery were included in this study. Exclusion criterias were children with history of sleep disorders, any chronic illness, developmental delay, prematurity children who spit, sniff or refuse taking the study drug and parent refusal.

The patients were randomly divided into 2 groups of 30 each (by using opaque sealed envelope) to receive one of the two doses of the study drug pre-medication. Group A received oral Melatonin in a dose of 0.5mg/kg and Group B received oral Melatonin in a dose of 0.75mg/kg.

We used oral Melatonin commercially available as Melatonin syrup. Melatonin was administered with the dropper. 1ml is equivalent to 3mg of Melatonin. Calculated dose of Melatonin was administered 45 minutes prior to induction of anaesthesia in the pre-operative area in the presence of parents. The time of administration of the drug was noted. Child was observed and heart rate, respiratory rate, oxygen saturation and non invasive blood pressure was monitored.

The patients were assessed on the basis of:

a) Modified Yale Pre-operative Anxiety scale
b) Sedation score
c) Ease of parent child separation (Behaviour score)
d) Ease of induction (Mask acceptance).

The temperament of the child was assessed by a parent using the Emotionality, Activity, Sociability, Impulsivity (EASI) score of child temperament. Each category consists of 5 items and a score of 5 [from 1(a little) to 5 (a lot)] is allocated to each item. The maximum score in each category is 25. Higher scores indicate high baseline values of EASI. Children's anxiety was assessed by the modified Yale Preoperative Anxiety Scale (mYPAS) before premedication (baseline) and at 10, 30, 45 minutes after premedication and at separation from parents and at introduction of the anaesthesia mask. Score > 30 was considered as severe anxiety. The degree of sedation was assessed at every 5 minutes with a 5 point Michigan Scale, A sedation score of 2 and above was considered satisfactory. At 30 minutes the child was separated from parents and was taken to the procedure room. Behaviour score was noted on a 4 point Parent child separation scale. Mask Acceptance score was evaluated by the attending anaesthesiologist at induction of anaesthesia using the Mask acceptance score scale. Multiparameter monitor was attached before induction of anaesthesia in the operating room and mode of induction (IV vs inhalational) and management of anaesthesia was decided by the attending anaesthesiologist.

Statistical Analysis

All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-Square test. Quantitative data was represented using Mean ± SD. Analysis of Quantitative data between the two groups was done using unpaired t-test if data passed 'Normality test' and by Mann-Whitney Test if data failed 'Normality test'. A P value < 0.05 was taken as level of significance.

Results were graphically represented where deemed necessary. SPSS Version 21.0 was used for most analysis and Microsoft Excel 2010 for graphical representation.

Results

The demographic characteristics in the two groups were comparable with no statistically significant difference (P= 0.443 for age, P =1 for gender distribution) [Table 1 & 2].

Table 1: Distribution of study groups as per mean age

Variables	Group	N	Mean	SD	P- value
Age (years)	A	30	4.57	1.45	0.443
	B	30	4.30	1.21	

Table 2: Distribution of study groups as per gender

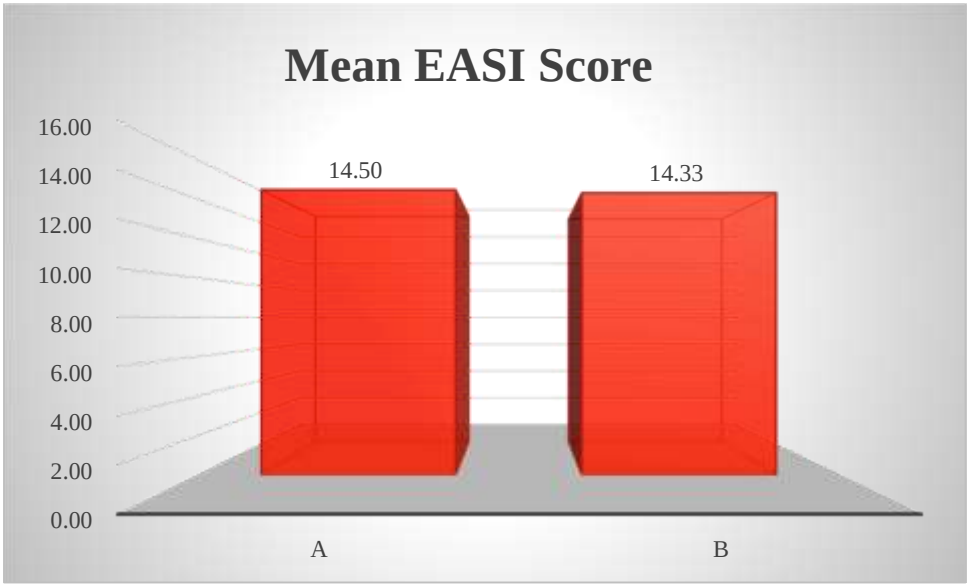
Gender	Group		Total
	A	B	
Female	13	12	25
	43.3%	40.0%	41.7%
Male	17	18	35
	56.7%	60.0%	58.3%
Total	30	30	60
	100.0%	100.0%	100.0%
P = 1.0			

Mean EASI Score was comparable between both the groups (14.50 vs 14.33; P = 0.79), showing that the temperament of the children in both the study groups were similar [Table 3, Figure 1].

Table 3: Mean Emotionality, Activity, Sociability, Impulsivity (EASI) score comparison among study groups

Variables	Group	N	Mean	SD	P- value
EASI Score	A	30	14.50	2.56	0.79
	B	30	14.33	2.50	

Figure 1: Mean Emotionality, Activity, Sociability, Impulsivity (EASI) score comparison among study groups



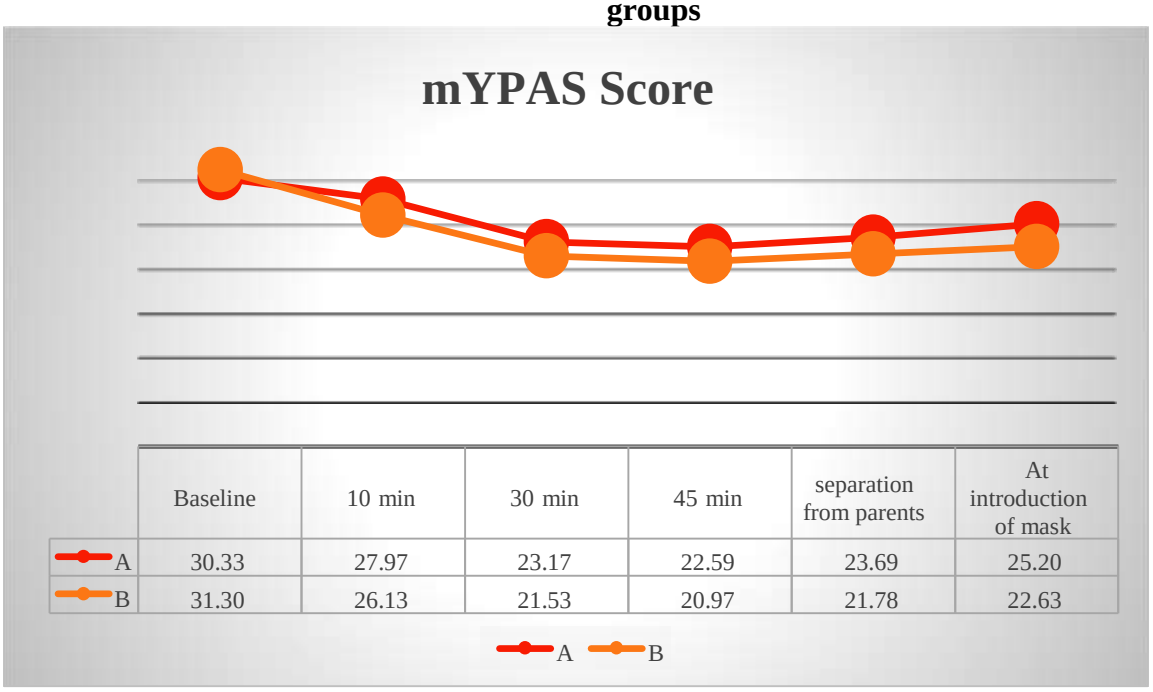
Mean anxiety score was comparable among both groups at baseline (30.33 vs 31.30; P = 0.258). After premedication, anxiety scores reduced significantly in both groups (P <0.01) and were lower than baseline at the time of introduction of mask. The score was however lower in 0.75 mg/kg melatonin group as compared to 0.5 mg/kg group after pre-medication till introduction of mask (P <0.01) [Table 4, Figure 2].

Table 4: Mean modified Yale Preoperative Anxiety Scale (mYPAS) comparison among study groups

mYPAS	Group	N	Mean	SD	P- value
Baseline	A	30	30.33	3.26	0.258
	B	30	31.30	3.29	
10 mins	A	30	27.97	3.34	0.46
	B	30	26.13	3.29	
30 mins	A	30	23.17	1.19	<0.01
	B	30	21.53	0.70	
45 mins	A	30	22.59	3.80	<0.01
	B	30	20.97	3.43	
	A	30	23.69	3.95	<0.01

Separation from parents	B	30	21.78	3.65	
At introduction of mask	A	30	25.20	3.83	<0.01
	B	30	22.63	2.70	

Figure 2: Mean modified Yale Preoperative Anxiety Scale (mYPAS) comparison among study groups

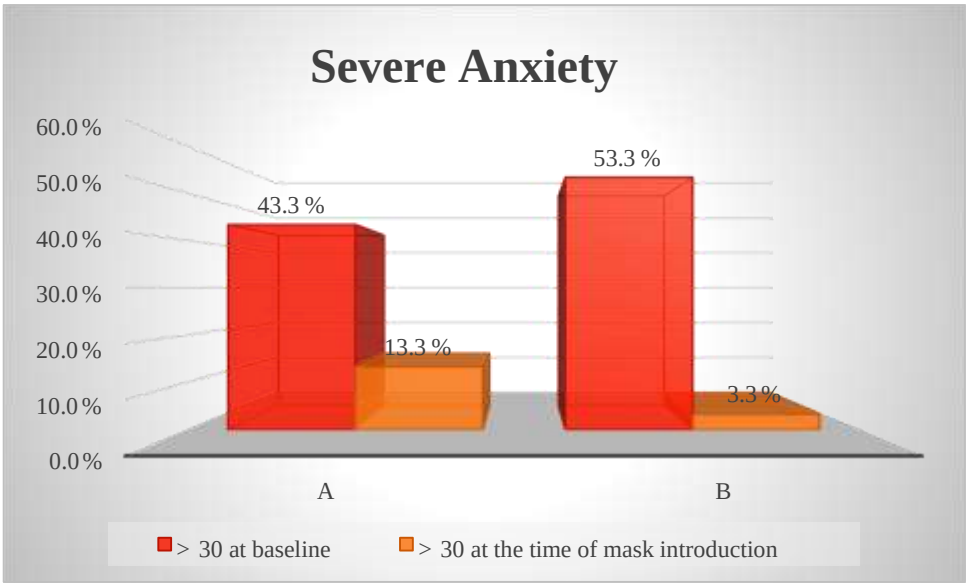


Severe anxiety as defined by mYPAS score of over 30 was observed in 43.3% cases of group A and 53.3% cases of group B at baseline (P = 0.21). However at the time of introduction of mask, only 13.3% and 3.3% cases of group A and B had severe anxiety, showing significant decrease in the anxiety levels after melatonin. The decrease was significantly more with higher dose of melatonin (P < 0.01) [Table 5, Figure 3].

Table 5: Comparison of cases with severe anxiety among study groups

mYPAS Score	Group		Total	P-value
	A	B		
> 30 at baseline	13	16	29	0.21
	43.3%	53.3%	48.3%	
> 30 at the time of mask introduction	4	1	5	<0.01
	13.3%	3.3%	8.3%	

Figure 3: Comparison of cases with severe anxiety among study groups



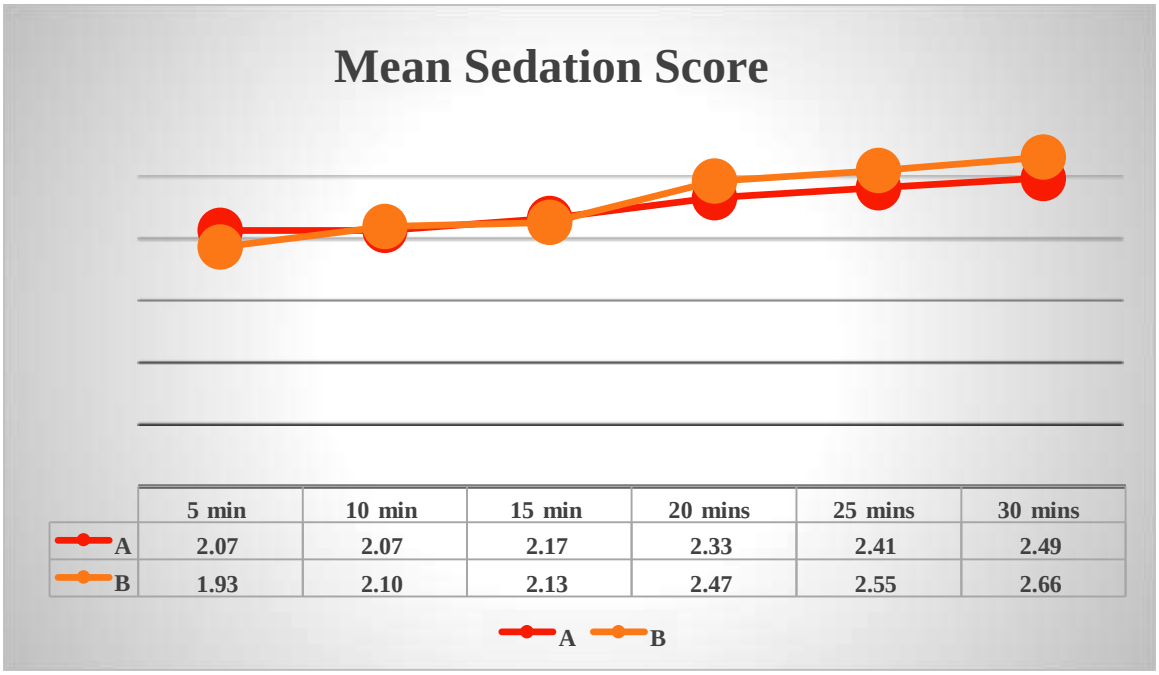
Mean sedation score was comparable between study groups at baseline (2.07 vs 1.93). The sedation score significantly increased in both groups but the increase was comparable among study groups (P > 0.05) [Table 6, Figure 4].

Table 6: Mean comparison of study groups as per sedation score

Sedation Score	Group	N	Mean	SD	P- value
5 mins	A	30	2.07	0.45	0.26
	B	30	1.93	0.45	
10 mins	A	30	2.07	0.45	0.78
	B	30	2.10	0.48	
15 mins	A	30	2.17	0.38	0.72
	B	30	2.13	0.35	
20 mins	A	30	2.33	0.48	0.30
	B	30	2.47	0.51	
25 mins	A	30	2.41	0.58	0.88
	B	30	2.55	0.58	

30 mins	A	30	2.49	0.65	0.72
	B	30	2.66	0.76	

Figure 4: Mean comparison of study groups as per sedation score



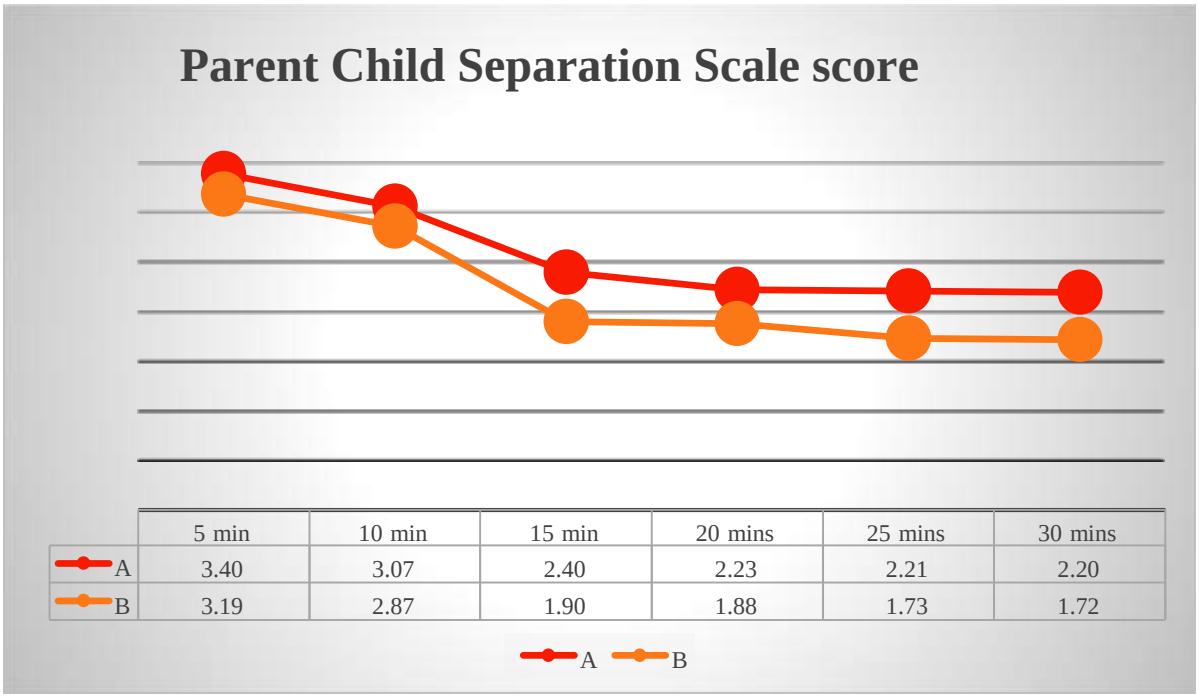
Mean parent child separation scale score was comparable at the baseline between study groups (3.4 vs 3.19; P = 0.19). The scores significantly fall in both groups till 30 mins follow up (2.2 vs 1.72; P < 0.01). The decrease was however significantly more with higher dose of melatonin (0.75 mg/kg) [Table 7, Figure 5].

Table 7: Mean comparison of study groups as per Parent Child separation Scale score

Parent Child Separation Scale score	Group	N	Mean	SD	P- value
5 mins	A	30	3.40	0.50	0.19
	B	30	3.19	0.59	
10 mins	A	30	3.07	0.37	0.06
	B	30	2.87	0.51	
15 mins	A	30	2.40	0.50	<0.01
	B	30	1.90	0.59	

20 mins	A	30	2.23	0.50	<0.01
	B	30	1.88	0.59	
25 mins	A	30	2.21	0.43	<0.01
	B	30	1.73	0.52	
30 mins	A	30	2.20	0.41	<0.01
	B	30	1.72	0.43	

Figure 5: Mean comparison of study groups as per Parent Child separation Scale score



The mask acceptance score was significantly lower in group B as compared to group A (1.77 vs 2.27; P < 0.01). This showed that acceptance of mask was significantly better in group B (0.75 mg/kg) as compared to group A (0.5 mg/kg) [Table 8, Figure 6].

Table 8: Mean comparison of study groups as per mask acceptance score

Mask Acceptance Score	Group	N	Mean	SD	P- value
	A	30	2.27	0.52	<0.01
	B	30	1.77	0.63	

Figure 6: Mean comparison of study groups as per mask acceptance score

No statistically significant difference was observed between study groups in terms of heart rate, respiratory rate, oxygen saturation, mean arterial pressure at baseline and their mean change during follow up till 30 minutes (P >0.05) [Table 9,10,11,12].

Table 9: Mean comparison of study groups as per heart rate

Heart Rate	Group	N	Mean	SD	P- value
5 mins	A	30	115.53	13.58	0.67
	B	30	112.23	16.52	
10 mins	A	30	112.93	15.75	0.52
	B	30	109.27	17.82	
15 mins	A	30	108.60	14.54	0.49
	B	30	105.67	18.78	
20 mins	A	30	105.07	12.68	0.81
	B	30	104.10	16.72	
25 mins	A	30	103.27	11.91	0.83

	B	30	102.02	16.76	
30 mins	A	30	101.27	11.69	0.88
	B	30	100.40	16.79	

Table 10: Mean comparison of study groups as per respiratory rate

RR	Group	N	Mean	SD	P- value
5 mins	A	30	28.88	3.40	0.93
	B	30	28.56	4.13	
10 mins	A	30	28.23	3.94	0.69
	B	30	27.82	4.45	
15 mins	A	30	27.15	3.64	0.63
	B	30	26.67	4.69	
20 mins	A	30	26.27	3.17	0.61
	B	30	25.53	4.18	
25 mins	A	30	25.82	2.98	0.27
	B	30	24.10	4.19	
30 mins	A	30	25.32	2.92	0.19
	B	30	24.60	4.20	

Table 11: Mean comparison of study groups as per oxygen saturation

SpO2	Group	N	Mean	SD	P- value
5 mins	A	30	99.13	0.86	0.15
	B	30	99.43	0.73	
10 mins	A	30	99.67	0.55	0.18
	B	30	99.83	0.38	
15 mins	A	30	99.87	0.35	1.00

	B	30	99.87	0.35	
20 mins	A	30	99.87	0.35	0.40
	B	30	99.93	0.25	
25 mins	A	30	99.77	0.57	0.60
	B	30	99.83	0.38	
30 mins	A	30	99.77	0.50	0.37
	B	30	99.87	0.35	

Table 12: Mean comparison of study groups as per mean arterial pressure

MAP	Group	N	Mean	SD	P- value
5 mins	**A**	30	72.21	8.49	0.00
	B	30	63.90	10.33	
10 mins	**A**	30	70.58	9.85	0.51
	B	30	68.04	11.14	
15 mins	**A**	30	67.88	9.09	0.72
	B	30	66.17	11.74	
20 mins	**A**	30	65.67	7.93	0.13
	B	30	62.81	10.45	
25 mins	**A**	30	64.54	7.44	0.19
	B	30	62.25	10.47	
30 mins	**A**	30	63.29	7.30	0.12
	B	30	61.88	10.49	

Discussion

Melatonin is a naturally occurring sleep inducing hormone. It has got sedative, hypnotic, analgesic, antiinflammatory, antioxidant, regulation of circadian rhythm and chronobiotic properties that distinguishes it as an attractive alternative premedicant.[14]

By virtue of its multiple actions, Melatonin has the potential to be used as an alternative premedicant, as an anxiolytic, sedative, and analgesic without significant haemodynamic alterations in patients undergoing surgical procedures under general or regional anaesthesia. It also helps in restoring sleep

rhythm in postoperative period. It has no hangover effects on the day following its intake and has no negative effects like addiction, dependence as compared to benzodiazepines.[15]

Studies involving children have reported that melatonin is as effective in reducing preoperative anxiety as midazolam.[16,17] However, there are no studies on optimum dose of oral melatonin as premedication in children. We also don't know the effect of higher melatonin dose in terms of anxiolysis, sedation and adverse effects. In present hospital based comparative study we thus aimed to compare the effects of two different doses of oral melatonin on pre-operative anxiety in children of age group 2 to 10 years undergoing elective paediatric surgery.

Mean age of the study group was 4.43 years with no statistically significant difference between study groups (P= 0.443). Study groups were also comparable with regard to gender distribution (58.5% males and 41.7% females: P =1.0). The temperament of the child was assessed by a parent using the Emotionality, Activity, Sociability, Impulsivity (EASI) score of child temperament. Mean EASI Score was comparable between both the groups (14.5 vs
14.33; P =0.79), showing that both groups were similar with regards to temperament of the study children.

The anxiolytic effect of melatonin occurs following the activation of the GABAergic system.[18] Melatonin produces a marked dose-dependent increases in GABA concentrations in the central nervous system.[14] This property of melatonin is likely to result from the mutual interaction between GABA and MT2 receptor systems.[18] In adults, several studies demonstrated that 5mg oral melatonin given preoperatively had a clinically significant anxiolytic effect[19] and improved the control of post-operative pain. In the paediatric population, melatonin has been successfully used in the treatment of anxiety associated to sleep disorders while data on lowering of preoperative anxious status are discordant. In fact, for Samarkandi and co-workers[20] the administration of melatonin or midazolam, each in doses of 0.25 or 0.5 mg/kg, was equally effective in alleviating anxiety in children undergoing surgery. Conversely, other studies did not confirm this result.[21,,22] In present study, we observed that after premedication, anxiety scores reduced significantly in both melatonin groups (P <0.01) and were lower than baseline at the time of introduction of mask. The score was however lower in 0.75 mg/kg melatonin group as compared to 0.5 mg/kg group from 30 mins after premedication till introduction of mask (P <0.01). Severe anxiety as defined by mYPAS score of over 30 was observed in 43.3% cases of group A and 53.3% cases of group B at baseline (P = 0.21). However, at the time of introduction of mask, only 13.3% and 3.3% cases of group A and B respectively had severe anxiety, showing significant decrease in the anxiety levels after premedication with melatonin. The decrease was significantly more with higher dose (0.75 mg/kg) of melatonin (P <0.01). Similarly, mean parent child separation scale score was comparable at the baseline between study groups (3.4 vs 3.19; P = 0.19). The scores significantly fell in both groups till 30 minutes follow up (2.2 vs 1.72; P <0.01). The decrease was however significantly more with higher dose of melatonin (0.75 mg/kg). The mask acceptance score was also significantly lower in group B as compared to group A (1.77 vs 2.27; P <0.01). This showed that acceptance of mask was significantly better in group B (0.75 mg/kg) as compared to group A (0.5 mg/kg). This was comparable with study done by Lofty M et al.[23]

Lotfy M et al[23] in their study compared the effects of Melatonin in a dose of 3mg and 6mg . Preoperative anxiety was scored using the Anxiety Specific to Surgery Questionnaire. Scores determined prior to administration of medications showed non-significant differences between the groups. ASSQ scores determined at 1 hour after receiving the study medication were lower in group M2 as compared to M1 (P =0.36). The calculated ΔASSQ was significantly higher in M2 group in comparison to M1 (P <0.01). Significantly higher frequency of patients had ΔASSQ of >25% in M2 in comparison to M1 group (P <0.01). The calculated ΔASSQ for patients of M2 group was higher than that of patients of M1 group by 36.9% (P <0.01). These findings point to the dose related anxiolytic effects of melatonin. The results were in accordance with the findings of our study.

Clinical trials with melatonin as a pre-medication agent for sedation in children have shown good results, but so far, only limited data are available.[24] In our study, the degree of sedation was assessed every 5 minute with a 5 point Michigan Scale. A sedation score of 2 and above was considered satisfactory. We observed that mean sedation score was comparable between study groups at baseline (2.07 vs 1.93). The sedation score significantly increased in both groups, but the increase was comparable among study groups (P >0.05). This observation was consistent with the findings of study conducted by Nethra S et al. [25]

Nethra S et al[25] in their study assessed the effectiveness of preoperative oral melatonin. Ramsay Sedation Scores (RSS) was higher in Melatonin group up to 2 hours after surgery as compared to placebo with P <0.01. Currently, there is no consensus on the appropriate dose of melatonin for sedation in children. Melatonin dosing for children is reported to be between 0.3 mg and 20 mg.[26]

In our study, no difference was observed between study groups in terms of heart rate, respiratory rate and mean arterial blood pressure at baseline and during follow up till 30 minutes (P > 0.05). None of the study groups reported any adverse events during and after the procedure which is consistent with the study shown by Nethra S et al.[25] In their study no haemodynamic or any other adverse effects after preoperative oral melatonin in patients undergoing surgical procedures under subarachnoid block were observed. Lofty M et al[23] in their study also observed no adverse events following melatonin pre-medication. Ali S et al [27] compared premedication efficacy of melatonin, clonidine, and dexmedetomidine. No adverse events were observed in cases of melatonin group.

Thus, to summarize, present study concluded that oral melatonin is effective for premedication in children, with higher dose of 0.75 mg/kg showing better results as compared to 0.5 mg/kg. The anxiety scores and mask acceptance improved with melatonin; however, it was significantly better in children with dose of 0.75 mg/kg. The sedation scores were comparable and there were no reported adverse effects in both the groups.

Conclusion

From our study, we concluded that oral melatonin (0.75 mg/kg) is superior to oral melatonin (0.5 mg/kg) in premedication for children. The anxiety scores after premedication was significantly lower in cases with 0.75 mg/kg dose. Parental separation and mask acceptance was also better in these children. The sedation scores were comparable and there are no reported adverse effects in both the groups. Thus, oral melatonin in a dose of 0.75 mg/kg may be used as an effective premedication in paediatric patients. However future comparative studies with other pre-medication drugs are required to establish the overall superiority of melatonin.

References

1. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: Predictors and outcomes. Arch Pediatr Adol Med 1996;150:1238-1245.
2. Kain ZN, Wang SM, Mayes LC, Caramico LA, Hofstadter MB. Distress During Induction of Anesthesia and Postoperative Behavioral Outcomes. Anesth Analg. 1999;88:1042-7.
3. Kain ZN. Postoperative maladaptive behavioral changes in children: incidence, risks factors and interventions. Acta Anaesthesiologica Belgica. 2000;51:217–26.
4. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, et al. Preoperative anxiety, emergence delirium and postoperative maladaptive behaviors: are they related? A new conceptual framework. Anesth Analg 2004;99:1648–54.
5. Kain ZN, Maclaren J, Mayes LC. Perioperative Behavior Stress in Children. In: Cote CJ, Lerman J, ID Todres, Eds. A Practice of Anesthesia for Infants and Children. Philadelphia, PA: Saunders Elsevier 27, 2009
6. McCann ME, Kain ZN. Management of Preoperative anxiety in children: an update. Anesth Analg; 2001, 93:98-105.

7. Manyande A, Cyna AM, Yip P, Chooi C, Middleton P. Non pharmacological intervention for assisting the induction of anaesthesia in children. Cochrane Database Syst Rev 2015;14:CD006447
8. Fradkin DM, Scott-Warren VL, Vashisht R, Rolfe SE. An evidence based guideline for the preoperative sedation of children. J Pediatr Neonatal care 2015;2:00095.
9. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. Miller's anesthesia e-book. Elsevier Health Sciences; 2014.
10. Kain ZN, Caldwell-Andrews AA, Krivutza DM, LoDolce ME, Wang SM, Gaal D: Trends in the practice of parental presence during induction of anesthesia and the use of preoperative sedative premedication in the United States, 1995-2002: Results of a follow up study. Anesth Analg 2003; 98:1252–9
11. Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S: Premedication in the United States: A status report. Anesth Analg 1997; 84:427–32. McCann M, Kain Z: Management of preoperative anxiety in children: An update. Anesth Analg 2001; 93:98– 105
12. McCann M, Kain Z: Management of preoperative anxiety in children: An update. Anesth Analg 2001; 93:98–105
13. Kain ZN, MacLaren J, McClain BC, Saadat H, Wang SM, Mayes LC, Anderson GM: Effects of age and emotionality on the effectiveness of midazolam administered preoperatively to children. Anesthesiology 2007; 107:545–52.
14. Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: A qualitative systemic review of randomized trials. Anaesthesiol 2010;113:968-76.
15. Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. J Pineal Res 2011;52:365-75.
16. Samarkandi A, Naguib M, Riad W, Thalaj A, Alotibi W, Aldammas F, Albassam A: Melatonin versus midazolam premedication in children: A double-blind, placebocontrolled study. Eur J Anaesthesiol 2005; 22:189–96
17. Johnson K, Page A, Williams H, Wassemer E, Whitehouse W: The use of melatonin as an alternative to sedation in uncooperative children undergoing an MRI examination. Clin Radiol 2002; 57:502–6.
18. Wan, Q.; Man, H.Y.; Liu, F.; Braunton, J.; Niznik, H.B.; Pang, S.F.; Brown, G.M.; Wang, Y.T. Differential modulation of GABAA receptor function by Mel1a and Mel1b receptors. Nat. Neurosci. 1999, 2, 401–403.
19. Naguib, M.; Samarkandi, A.H. The comparative dose-response effect of melatonin and midazolam for premedication of adult patients: A double-blinded placebo-controlled study. Anesth. Analg. 2000, 91, 473–479.
20. Samarkandi, A.; Naguib, M.; Riad, W.; Thalaj, A.; Alotibi, W.; Aldammas, F.; Albassam, A. Melatonin vs. midazolam premedication in children: A double-blind, placebo-controlled study. Eur. J. Anaesthesiol. 2005, 22, 189–196.
21. Kain, Z.N.; MacLaren, J.E.; Herrmann, L.; Mayes, L.; Rosenbaum, A.; Hata, J.; Lerman, J. Preoperative melatonin and its effects on induction and emergence in children undergoing anesthesia and surgery. Anesthesiology 2009, 111, 44–49.
22. Isik, B.; Baygin, O.; Bodur, H. Premedication with melatonin vs. midazolam in anxious children. Paediatr. Anaesth. 2008, 18, 635–641.
23. Lotfy, M., Ayaad, M. Preoperative oral melatonin can reduce preoperative anxiety and postoperative analgesia in a dose-dependent manner. Ain-Shams J Anesthesiol **13,** 32 (2021).
24. Isik B, Baygin O, Bodur H. Premedication with melatonin vs midazolam in anxious children. Paediatr Anaesth. 2008 Jul; 18(7):635-41.
25. Nethra S.S, Madhu K. P, Sagar Srinivas K, Sudheesh K, Shubha. S. Efficacy of preoperative oral melatonin on post-operative pain in patients undergoing infraumbilical surgeries under

subarachnoid block: A double blind randomized control study. Indian J Clin Anaesth 2019;6(3):420-4
26. Bajaj P. Melatonin for Anxiolysis in children. Indian J Anaesth. 2009;53:504–5.
27. Ali ST, Asthana V, Gupta D, Singh SK. A Comparative Evaluation of Oral Clonidine, Dexmedetomidine, and Melatonin As Premedicants in Pediatric Patients Undergoing Subumbilical Surgeries. Romanian Journal of Anaesthesia and Intensive Care. 2020 Jul;27(1):35.

Received: 10-07-2022. Revised:16-08-2022. Accepted:12-10-2022