

Effect of Oral Melatonin in Attenuation of Emergence Delirium in Paediatric Patients Coming for Elective Tonsillectomy Under General Anaesthesia – Randomized Single Blind Controlled Study

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Abstract

Background: Melatonin is an endogenous sleep regulating hormone secreted by pineal gland. Emergence agitation and delirium in children remains a common clinical challenge in post anaesthetic care unit. Exogenous administration of melatonin causes sedation, anxiolysis and hypnosis by inhibitory action on central nervous system. Preoperative oral melatonin has been suggested as an effective drug in preventing emergence agitation with favourable safety profile.

Methods: Randomized single blind control study, consisting of 60 ASA 1 & 2 paediatric patients, belonging to the age group of 5-13 years, who were posted for elective tonsillectomy. Patients were randomly divided into group M (n=30) received oral melatonin 0.2mg/kg bodyweight 90 mins prior to surgery with sips of water and group C (control) (n=30) received oral multivitamin tablet 90 mins prior to surgery with sips of water. Primary objective of the study was induction compliance checklist and paediatric anaesthesia emergency delirium scale.

Results: We have noticed Induction Compliance checklist among the groups soon after the extubation, which was statistically highly significant in Group M when compared to Group C (p=0.000). Paediatric Anaesthesia emergence delirium Score among the groups which was highly statistically significant in group M when compared to Group C (p=0.000)

Conclusion: To conclude in paediatric surgical patients oral melatonin in the dose of 0.2 mg per kg given pre-operative does not affect, but it will impact their post-operative behaviour by reducing emergence agitation.

Keywords: Paediatric, Melatonin, Emergence Agitation.

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Introduction

Melatonin (5-methoxy-N-acetyltryptamine) is an endogenous sleep regulating hormone secreted by pineal gland with nocturnal predominance. It plays an essential role in maintaining the body's circadian rhythm (sleep-wake "clock"). Beyond its primary role of regulating the sleep wake cycle, endogenous melatonin has been reported to be involved in the physiological maintenance of multiple homeostatic processes, which affects the mood, antioxidative processes and immunity.

Exogenous administration of melatonin causes sedation, anxiolysis, and hypnosis by inhibitory action on the central nervous system. It is different from benzodiazepines and their derivatives, it

produces natural sleep pattern that does not cause cognitive impairment [1,2,3,4]. Emergence delirium has been described as "a mental disturbance during the recovery from general anesthesia, consisting of hallucination, delusion, confusion which is manifested by moaning, restlessness, involuntary physical activity and thrashing about in bed" [5]. Agitation and delirium are common complications in preschool children during emergence from anesthesia. Several risk factors have been identified, which includes age, sex, choice of anaesthetics, type of surgery and preoperative behavioral traits [6].

Emergence delirium and agitation maybe not only distressing to the children and their parents, but it also delays the wound healing and prolongs the length of hospital stay. Lack of pharmacological premedication is a risk factor for the development of emergence delirium. Exogenous melatonin is considered to be beneficial in children, due to its high safety profile with minimal adverse effects when compared to placebo or midazolam in reducing emergence delirium. Since there are not many studies to prove that Melatonin is a better alternative for preoperative anxiolysis in pediatric patients, the aim of this study was to evaluate the effect of melatonin in reducing anxiety and agitation in pediatric patients coming for tonsillectomy.

Methods and Materials: The study was conducted in 60 ASA 1 and 2 pediatric patients belonging to the age group 5 – 13 years, who were posted for elective tonsillectomy surgery under general anaesthesia. After obtaining ethical and scientific committee clearance, preanaesthetic evaluation done day prior to the surgery. Randomization was done using shuffled closed opaque envelope technique. The study population was divided into two groups 30 each. (n = 30).

1. Group M – received oral melatonin 0.2mg/kg/body weight 90 mins prior to the surgery with sips of water.
2. Group C (control) – received oral multivitamin tablet 90 mins prior to surgery with sips of water.

On the previous day a thorough preanaesthetic evaluation of all the subjects of both groups with necessary basic investigation was done and informed consent was taken. All the subjects were kept nil per oral for 6 hours for solid food, 2 hours for clear fluids. On arrival to operation room IV access was taken by using appropriate gauge cannula on non-dominant hand. All the subjects were connected to multiparameter monitor. Ringer lactate fluid was started. All subjects were premedicated with 0.1 mg/kg bodyweight Ondansetron, 0.1mg/kg bodyweight IV Glycopyrrolate and 3mg/kg bodyweight IV Pentazocine. Preoxygenation was done for 5 mins with 100% oxygen. Subjects were induced with IV Thiopentone 5mg/kg bodyweight and IV Vecuronium 0.1 mg/Kg Bodyweight. The induction compliance was assessed by using the induction compliance checklist (ICC) which includes 11 items indicating compliance during induction of anaesthesia. The ICC score is a sum of items checked. A perfect induction during which the child does not exhibit negative behaviours, fear or Anxiety is scored as zero. All the subjects were intubated with appropriate size micro cuffed ET tube which was confirmed by EtCo₂. Anaesthesia was maintained with O₂ + N₂O + Inj. Vecuronium + 0.5 – 1 % Isoflurane. At the end of the surgery Subjects were Reversed with neostigmine and atropine 0.05 – 0.07 mg/kg bodyweight.

Table 1: Induction compliance checklist

Checklist	SCORE	
Perfect induction (does not exhibit negative behaviors, fear or anxiety)		
Crying, tears in eyes	0	1
Turns head away from mask	0	1
Verbal refusal, says “no”	0	1
Verbalization indicating fear or worry, “where’s mommy?” or “will it hurt?”	0	1
Pushes mask away with hands, pushes nurse/anaesthetist with hands/feet	0	1
Covers mouth/nose with hands/arms or buries face	0	1
Hysterical crying, may scream	0	1
Kicks/flails legs/arms, arches back, and/or general struggling	0	1
Requires physical restraint	0	1
Complete passivity, either rigid or limp	0	1
Total score	0	1

Total score= the number of categories checked, 0- Perfect, 1 to 3- moderate cooperation, >4- weak cooperation

Table 2: Paediatric Anaesthesia Emergence Delirium Scale

Clinical picture	PAEDS score
Child makes eye contact with care givers	4 = Not at all 3 = Just a little 2 = Quite a bit 1 = Very much 0 = Extremely
Child's actions are purposeful	4 = Not at all 3 = Just a little 2 = Quite a bit 1 = Very much 0 = Extremely
Child is aware of surroundings	4 = Not at all 3 = Just a little 2 = Quite a bit 1 = Very much 0 = Extremely
Child is restless	0 = Not at all 1 = Just a little 2 = Quite a bit 3 = Very much 4 = Extremely
Child is inconsolable	0 = Not at all 1 = Just a little 2 = Quite a bit 3 = Very much 4 = Extremely
Total PAEDS score	

A score greater than 10 was counted as emergence delirium. PAEDS = Paediatric anaesthesia emergence delirium scale

Primary Objectives: Induction Compliance Checklist Score and PAEDS Score (Paediatric Anaesthesia Emergence Delirium Score)

Inclusion Criteria: All ASA grade I and grade II patients between 5-13 years age group.

Exclusion Criteria: All children with a history of chronic illness, prematurity, or developmental delay were excluded from the study.

Definitions: Emergence Delirium: A score greater than 10 on PAEDS scale was defined as Emergence Delirium.

Statistical Methods: Sample size is calculated with $\alpha = 5\%$ and admissible error-10%. Numerical variables were presented as the mean and standard deviation or median, whereas categorical data were presented using counts and

percentages. The following tests were applied according to the type of variables.

Chi-square or Fisher exact test for categorical variables, one-way or two-way or repeated ANOVA for normally distributed variables as appropriate and a Kruskal-Wallis test for non-parametric data.

A post-hoc test was applied using the Bonferroni method for adjusting for multiple comparisons.

Results

Effect of oral melatonin in attenuation of emergence delirium in pediatric patients coming for elective tonsillectomy under general anesthesia – Randomized Single Blind Controlled Study.

The demographic data of the study like age, sex, weight and height among the groups, were not statistically significant. ($p > 0.05$)

Table 3: Age among the groups

Crosstab					
			Groups		Total
			Group M	Group C	
Ages	<6	Count	9	8	17
		% within groups	30.0%	26.7%	28.3%
	7-9	Count	5	12	17
		% within groups	16.7%	40.0%	28.3%
	10+	Count	16	10	26
		% within groups	53.3%	33.3%	43.3%
Total		Count	30	30	60
		% within groups	100.0%	100.0%	100.0%

Table 4: Chi- square test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4.326	2	0.115

Table 5: Cross tab

			Groups		Total
			Group M	Group C	
Sex	male	Count	13	14	27
		% within groups	43.3%	46.7%	45.0%
	female	Count	17	16	33
		% within groups	56.7%	53.3%	55.0%
Total		Count	30	30	60
		% within groups	100.0%	100.0%	100.0%

Table 6: Chi – Square test

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	0.067	1	0.795	
Fisher's Exact Test				1.000

Table 7: Descriptives

Age						
	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum
Group M	30	8.8667	2.87358	0.52464	4.00	12.00
Group C	30	8.3333	2.27934	0.41615	4.00	12.00
Total	60	8.6000	2.58549	0.33379	4.00	12.00

Table 8: T-Test (Group statistics of weight and height)

	Groups	N	Mean	Std. Deviation	Std. Error Mean
Weight	Group M	30	28.2967	7.85632	1.43436
	Group C	30	26.4067	6.29405	1.14913
Height	Group M	30	130.4333	15.71225	2.86865
	Group C	30	127.8000	12.57913	2.29662

Table 9: Independent Samples Test

		t-test for Equality of Means			
		t	df	Sig. (2-tailed)	Mean Difference
Weight		1.028	58	0.308	1.89000
Height		0.717	58	0.476	2.63333

Induction compliance Checklist**Table 10: T-Test**

Group Statistics					
	Groups	N	Mean	Std. Deviation	Std. Error Mean
ICC	Group M	30	0.9667	0.92786	0.16940
	Group C	30	5.9000	0.84486	0.15425

Table 11: Independent Samples Test

	t-test for Equality of Means			
	t	df	Sig. (2-tailed)	Mean Difference
ICC	-21.533	58	0.000	-4.93333

Above table shows Induction Compliance checklist among the groups, which was highly statistically significant in Group M when compared to Group C ($p=0.000$).

Paediatric Anaesthesia Emergence delirium Score

Table 12: T-Test

Group Statistics					
	Groups	N	Mean	Std. Deviation	Std. Error Mean
PAEDS_score	Group M	30	2.5667	1.40647	0.25679
	Group C	30	10.8000	0.92476	0.16884

Table 13: Independent sample test

	t-test for Equality of Means			
	t	df	Sig. (2-tailed)	Mean Difference
PAEDS_score	-26.791	58	0.000	-8.23333

The Above table shows Paediatric Anaesthesia Emergence Delirium Score among the groups, which was highly statistically significant in Group M when compared to Group C ($p=0.000$).

Discussion

Melatonin (5 methoxy – N – Acetyl tryptamine is an endogenously secreted sleep regulating hormone secreted by Pineal Gland. It is essential for sleep control through Mp1 and Mp2 receptors. Many studies have been done to investigate its perioperative application for sedative, anxiolytic and analgesic effect. Children's preoperative anxiety is linked to a variety of post-operative outcomes, including eating disorders, bedwetting, longer recovery phase sufferings and post-operative regressive behavioural abnormalitie. [7,8,9]

Systemic Review and Meta-Analysis conducted by Dongni zhang suggests that the prophylactic use of melatonin significantly decreases emergence agitation incidence compared with use of placebo and midazolam.

The current study's demographic data's, age, sex and weight and height were comparable among the groups which was not statistically significant. Several prior studies claimed that children who underwent sevoflurane anaesthesia had a higher incidence of emerging agitation, than those who underwent General anaesthesia with halothane.

However, some prospective studies assessing this emergence agitation among the groups was not statistically significant between Sevoflurane and Halothane Groups but in recent days halothane is not used in clinical practice, most of the time it is Sevoflurane or Isoflurane. Our study can be comparable with Systemic review and meta-analysis which was conducted by Dongni zhang, he has taken 9 studies conducted among 951 participants. The study showed Melatonin significantly reduces the incidence of emergence

agitation (EA) when compared to placebos (risk ratio 0.40, 95% CI, 0.26 – 0.61, $p<0.01$). [10]

Our study can also be comparable with Haider Muhy Al Bareh. He has done the study with two different doses of melatonin (0.4mg/kg/body weight, 0.2mg/kg body weight) they have also used ICC and PAEDS and along with this, the Orientation Scale. They have concluded that Patients who received 0.4 mg/kg had better outcome than patients who received 0.2mg/kg bodyweight.[11]. Our study can also be comparable with Hussein A Hussein Sr. They have conducted the study in 80 children who were undergoing elective cardiac catheterization. Group A received 0.5 mg/kg bodyweight melatonin as premedication while group B received Placebo. They concluded that Melatonin is an effective drug in reducing EA and Psychomotor impairment when compared to placebo which was significant ($p<0.05$).

Conclusion

In paediatric surgical patient the dose of the melatonin does not affect the induction dosage of anaesthesia drug but it will impact their post-operative behaviour by reducing emergence agitation. Hence, we conclude that administering oral melatonin to pediatric patients coming for any kind of surgery could potentially aid in managing pre-operative anxiety and post-operative emerging agitation.

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