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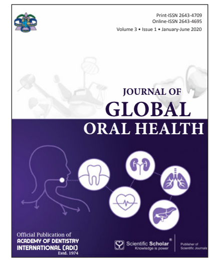
Journal of Global Oral Health

Article in Press



Research Article

Melatonin as a Noble approach for un-cooperative child –An observational study

Sonal Gupta[1], Abhinandan Patra[1], Asmita Das[1]

[1]Department of Pedodontics and Preventive Dentistry, KD Dental College and Hospital, Mathura, Uttar Pradesh, India.

***Corresponding author:**
Sonal Gupta,
Department of Pedodontics and Preventive Dentistry, KD Dental College and Hospital, Mathura, Uttar Pradesh, India.

sonalpedo@gmail.com

Received: 27 January 2024
Accepted: 24 May 2024
EPub Ahead of Print: 17 October 2024
Published:

DOI
10.25259/JGOH_7_2024

Quick Response Code:

ABSTRACT

Objectives: Melatonin is a naturally occurring hormone. It is secreted from the pineal gland in the human body. It is also used for preoperative anxiolysis and sedation. Thus, this study aims to evaluate the before and after effects of melatonin medication on sedation, anxiety, and cognitive and psychomotor functions before and after dental procedures. **Materials and Methods:** A total of 45 patients aged between 4 and 8 years scheduled to undergo dental treatment were randomly assigned for medication administration to evaluate changes in behavior, anxiety, orientation, and sedation scale between pre- and post-medication. Data were analyzed using a paired *t*-test and Wilcoxon test, and $P < 0.05$ was considered statistically significant. **Results:** Cognitive scores and anxiety scores were decreased significantly, and sedation scores were increased significantly after 60 min of melatonin medication. There were significant differences in trail-making test scores between premedication and 60 min after melatonin medication. **Conclusion:** Thus, it can be used as a potent premedication drug in children as an anti-anxiety drug.

Keywords: Oral sedation, Anxiety, Melatonin

INTRODUCTION

Pediatric and preventive dentistry is one of dentistry's most difficult speciality.[1] It provides good quality clinical work to child patients not only based upon the clinical expertise of the operator, but more importantly on the behavior guidance skills.[1,2] Invasive dental procedures with their barrage of instrumentation, smells, sounds, and new places often considered as one of the most fear and anxiety-producing events in the pediatric dental clinic. Dental anxiety is ranked ninth among intense fears and fourth among common fears.[2] Thus, fear and anxiety are common problems in pediatric dentistry, which could affect the correct treatment and involve failure.[1,3] Most children are easily managed with non-pharmacological behavior management and modification techniques and parental support, but some will require pharmacological management to endure the procedures.[4]

The oral route of drug administration is the most frequently used for sedating children in the dental operatory.[3,4] To reduce pre-operative anxiety in dental clinics, drugs such as midazolam and diazepam are used widely in children as premedication.[4] Although effective, these drugs are associated with an increased sedative effect that may delay post-sedation recovery.[4,5] However, midazolam has several side effects, including excessive sedation interaction with opioids, paradoxical reactions, disorientation, impaired psychomotor performance, and postoperative sleep disturbance. Hence, keeping this in mind, melatonin has been proposed as pre-medication, which is an alternative to midazolam.[5]

Melatonin is used in newborns and children to control a multitude of illnesses, including sleep, neonatal infection, and seizure disorders. Starting at 3 months of age, low levels are secreted during the day, and high levels of melatonin are secreted at night.[6] Melatonin has a Circadian phase-shifting or chronobiotic action, as well as a less recognized sleep-promoting and hypnotic impact. The half-life of melatonin is 40 min, and it has extensive first-pass metabolism.[7] Melatonin will reach its peak concentration within 1 hour of administration. It has also been evaluated for its use as a pre-operative sedative effect and anxiolytic in adults.[5-7] Its anxiolytic properties are a consequence of its acceleratory role as y-aminobutyric acid transmission. Melatonin offers greater taste acceptance, which is better than the bitter flavor of conventional benzodiazepines.[8] It is difficult to overdose since it is a natural hormone, it has a short half-life and dose-dependent effect, and hence, prolonged sedation is unlikely.[9] Several studies established that melatonin is equally beneficial as midazolam in lowering preoperative anxiety in adults; however, the data does not support such a function in children. Hence, this study aims to evaluate the pre- and post-effect of medication on anxiety, cognitive, and psychomotor functions before and after 45 min of medication.[7-9]

MATERIALS AND METHODS

After obtaining informed consent from all the patients, 45 patients of American Society of Anesthesiologists (ASA) I and II physical status and Frankel's 1 and 2 behavior rating scale aged between 4 and 8 years scheduled to undergo dental treatment were randomly assigned for medication administration to evaluate changes of behavior in between pre- and post-medication. All children with ASA III and IV physical status, Frankel's 3 and 4 behavior rating scale, and a history of chronic illness, prematurity, and developmental delay were excluded from this study. The drugs used in our study were Altonil syrup, and the dose was calculated according to Young's rule for each child. Before and after 45 min of medicine administration, vital signs (SpO2, respiratory rate, and pulse rate), sedation scale, anxiety scale, orientation scale, and cognitive scale were studied.

Figure 1[10] showing Richmond Agitation-Sedation scale, used to measure the agitation or sedation level of the person. Figure 2[11] showing facial image scale, is a measure of children's dental anxiety and comprises a row of five faces ranging from happy to very afraid. Scores ranged from 1 to 5, with 5 indicating the most anxiety. The students were instructed to point to the face they felt most like at the time. Figure 3[12] showing the Glasgow coma scale which assesses the ability of a person to perform eye movements, speak, and move their body. These three behaviors make up three elements of scale, which are eye, verbal, and motor. A person's GCS score can range from 3 (completely unresponsive) to 15 (responsive). Thus, this scale was used to check the orientation of the child before and after 45 min of medication. Figure 4[13] showing Montreal Cognitive Assessment, used to check the cognitive capabilities of children (Total score 30) which include naming, memory, visuospatial, attention, abstraction, language, delayed recall, and orientation tests. Such study is important to research concerning the philosophy of mind and psychology, as well as the determination of human intelligence. The scoring was done based on normal (Score >24), mildly impaired (Score 18–24), and severely impaired (Score <18) state of the child's condition. Figure 5[14] showing trail making test to study psychomotor functions. The trail-making test (TMT) is a neuropsychological test often used for screening for cognitive impairment. In this test, the circles are numbered 1–8, and the patient should draw lines to connect the numbers in ascending order. The patient should be instructed to connect the circles as quickly as possible without lifting the pencil or pen from the paper. Time is noted

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Figure 1: Richmond agitation-sedation scale.

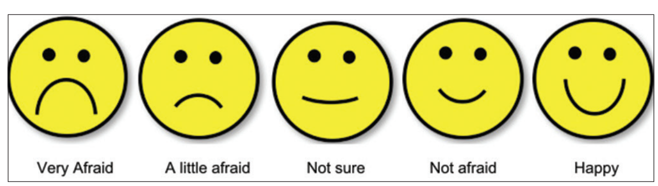


Figure 2: Facial image scale.

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Figure 3: The Glasgow coma scale.

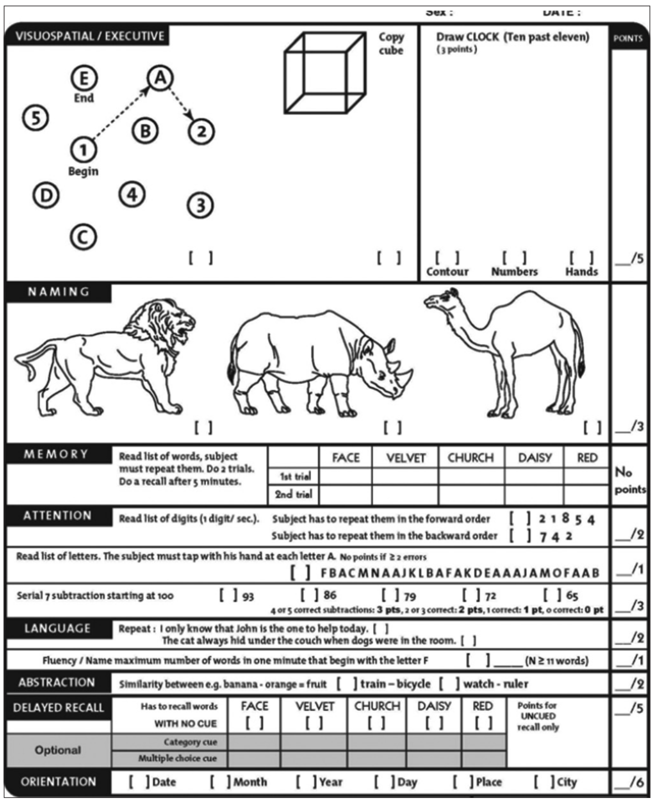


Figure 4: Montreal cognitive assessment.

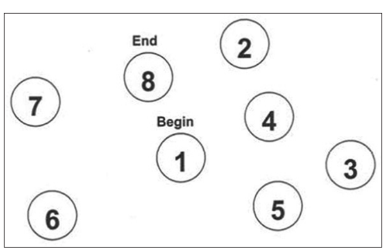


Figure 5: Trail-making test.

as the patient connects the trail. Data were noted and analyzed by the statistical computer software Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA) and are expressed as standard deviations, mean, and confidence interval (CI) 95%. The results were analyzed to verify the normality of the distribution. The data were normally distributed, and all inferential analyses were made using parametric statistical tests (*t* Student's test). $P < 0.05$ was set as statistically significant.

RESULTS

A total of 45 children were studied. The mean age of all patients enrolled was 6.28 ± 2.62 years, and the mean weight was 25.30 ± 6.42 kg. Here, paired *t*-test was done to compare the effect of premedication and 45–60 min after melatonin medication on SpO2, pulse rate, respiratory rate, general examination, Richmond Agitation-Sedation Scale,[10] Anxiety scale (Facial Imaging Scale),[11] Glasgow scale,[12] Montreal cognitive assessment scale,[13] and TMT.[14] Wilcoxon Signed-Ranks Test was done to compare the orientation scale (Glasgow Coma Scale) in between pre- and post-medication. As shown in Table 1, there were significant differences in decrease in pulse rate ($P = 0.003$) and respiratory rate ($P = 0.001$) between premedication and post-medication of melatonin but no significant changes in SpO2 level ($P = 0.088$). Anxiety scores ($P = 0.000$), cognitive score ($P = 0.001$) decreased significantly, and sedation score ($P = 0.000$) increased significantly after 60 min of melatonin medication ($P = 0.05$). There was a significant difference in TMT scores between premedication and 60 min after melatonin medication ($P = 0.001$). In TMT, the mean value of time in premedication is less than the time taken in post-medication due to reduction of cognitive scale, anxiety scale, and orientation scale. Table 2 shows, that the orientation scale is decreased significantly after 60 min of melatonin medication (*P* value of eye opening, verbal response, motor response is 0.014, 0.001, 0.014 respectively). Figure 6 shows no significant changes in before and after melatonin medication but little changes occurred in pulse rate and respiratory rate. Figure 7 shows that melatonin produced the decrease in anxiety score, orientation scale and cognitive function and increase sedation level after 60 min of melatonin medication.

DISCUSSION

In this study, melatonin was effective as a premedication in alternating separation anxiety and anxiety associated with dental procedures. Although midazolam is often used as a premedication in children, the results of the present study suggest that melatonin is an effective premedication for lowering fear and anxiety in pediatric patients.[15] When melatonin is administered orally, it has a sedative effect. According to Naguib and Samarkandi,[4] and Wilhelmsen *et al*.,[5] sedative effect of melatonin may be due to modulation of γ-Aminobutyric acid type A (GABAA) receptors in the brain through its action on melatonin receptors (MT1 and MT2) or due to its circadian rhythm regulation effect. After binding with the MT1 receptor, melatonin affects the GABAA receptor through the G-coupled protein pathway and enhances the binding of γ-Aminobutyric acid (GABA) to the GABAA receptor, which is like how other anesthetic drugs such as benzodiazepines and propofol exert their effects.[16]

Post-operative sleep disruption is typical following benzodiazepine medication. In the present study, melatonin was associated with less sleep disturbance at 15-day intervals, which is in accordance with Perez-Heredia *et al.*[6] We selected the dose of syrup oral melatonin as 5–7.5 mL, which is equivalent to 3–4.5 mg melatonin tablet.[17,18] We wanted the maximum effectiveness of oral melatonin as a sedative with the safest maximum dose previously used by various authors.[1,7] Kain *et al.*,[7] reported that oral melatonin in children with a maximum dose of 0.4 mg/kg is safe and without any major side effects. Melatonin in doses up to 10 mg has been used as an alternative to conventional sedatives and for uncooperative children. On the other hand, Acil *et al.*,[8] evaluated that 5 mg melatonin premedication was associated with pre-operative

Table 1: Significant differences in decrease in pulse rate (P=0.003) and respiratory rate (P=0.001) between premedication and post medication of melatonin.

Paired t-test								
Pair	**Group**	**N**	**Mean**	**SD**	**MD**	***t*-test**	***P*-value**	**Inferences**
SpO2	Pre	21	97.76	0.89	0.381	1.793	0.088	NS
	Post	21	97.38	0.59				
Pulse rate	Pre	21	89.95	11.92	4.048	3.378	0.003	S
	Post	21	85.90	9.94				
Respiratory rate	Pre	21	24.05	3.23	2.381	3.799	0.001	S
	Post	21	21.67	2.94				
General examination	Pre	21	70.59	4.71	2.270	4.638	0.000	S
	Post	21	68.32	3.77				
Sedation scale	Pre	21	4.00	1.00	-2.048	9.639	0.000	S
	Post	21	6.05	0.59				
Anxiety scale	Pre	21	2.71	0.78	-1.143	14.606	0.000	S
	Post	21	3.86	0.79				
Cognitive scale	Pre	17	1.00	0.00	-1.529	10.101	0.000	S
	Post	17	2.53	0.62				
Trial making test	Pre	19	20.58	5.85	-5.737	3.966	0.001	S
	Post	19	26.32	9.89				

N: number of samples; SD: standard deviation, MD; mean deviation, NS: no significant, S: significant

Table 2: The orientation scale decreased significantly after 60 min of melatonin medication (P-value of eye opening, verbal response and motor response).

Wilcoxon Signed Ranks Test											
Orientation scale	**N**	**Mean**	**Percentiles**			**Ranks**			**Z**	***P*-Value**	**Inferences**
			25th	**50th (median)**	**75th**	**Negative Ranks**	**Positive Ranks**	**Ties**			
Eye opening											
Pre A	6	1	1	1	1	0.00	3.50	0.00	-2.449	0.014	S
Post A	6	2	2	2	2						
Verbal response											
Pre B	11	1	1	1	1	0.00	6.00	0.00	-3.317	0.014	S
Post B	11	2	2	2	2						
Motor response											
Pre C	6	1	1	1	1	0.00	3.50	0.00	-2.449	0.014	S
Post C	6	2	2	2	2						

N: Number of samples, Z: Test value of significance, S: Significant

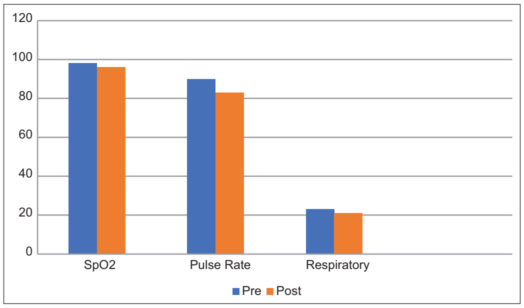


Figure 6: No significant changes before and after melatonin medication, but little changes occurred in pulse and respiratory rate.

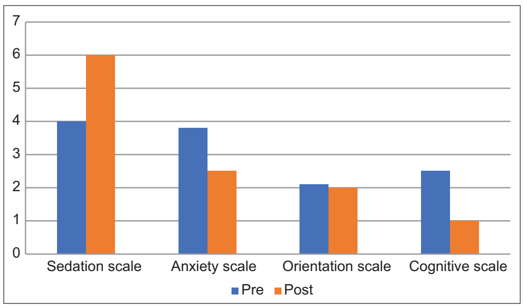


Figure 7: Melatonin produced a decrease in anxiety score, orientation scale, and cognitive function and an increased sedation level after 60 min of melatonin medication.

anxiolysis and sedation without post-operative impairment of psychomotor performance.[1,18] Melatonin is also used for the treatment of sleep disorders in children as it is a potent free radical scavenger, and it has been reported to improve survival rates in newborns with septic shocks. In addition, some melatonin formulations may offer greater taste acceptance compared to the bitter flavor of conventional premedication, which could potentially improve compliance in a pediatric population. All the evidence mentioned above attests to the safety of melatonin in children.[19]

In our study, the peak effect of exogenous melatonin ranges from 45 to 90 min. According to Patel and Kurdi, oral melatonin (0.4 mg/kg) given 60–90 min before surgery provides adequate anxiolysis comparable to that of oral midazolam (0.2 mg/kg) and provides sedation.[1] According to Patel and Kurdi,[1] melatonin was superior to midazolam in reducing the incidence of excitement at 10 min postoperatively.[1] According to Samarkandi *et al.*,[9] no patient in the melatonin group exhibited postoperatively excitement at 20, 30, and 40 min. They also quoted that no significant difference in behavior changes was observed in the melatonin group as compared to midazolam. In our study, anxiety scores decreased significantly after giving melatonin. This was in accordance with Samarkandi *et al.*,[9] and Perez-Heredia *et al.*[6] In our study, cognitive scores decreased significantly after giving melatonin.[6,9] However, according to Patel and Kurdi,[1] oral melatonin does not impair cognitive function. The present study also reported that melatonin does not affect psychomotor performance, such as working memory, memory retrieval, sustained attention, and flexibility of thinking.

In our study, sedation was increased after melatonin medication, and this was in accordance with Kain *et al.*,[7] and Patel and Kurdi.[1] The present study reported that melatonin causes little changes in orientation after giving melatonin medication. According to Patel and Kurdi, oral melatonin 0.4 mg/kg melatonin does not affect orientation.[1,6,20-22] TMT test was done for cognition, and in our study, there was a significant difference between pre- and post-medication. In our study, melatonin is effective for sedation in children after 60 min of medication. This was in accordance with Kain *et al.*,[7] and Khare *et al.*[15] Thus, it proves that melatonin can be used as premedication to reduce anxiety in children.[23] Melatonin offers several potential advantages: reduced post-operative sedation, less sleep disturbance, faster recovery, improved post-operative analgesia, and avoidance of respiratory depression. It produced increased sedation after 60 minutes of post-medication. Melatonin produced a reduction in anxiety score, orientation score, and cognitive function. Thus, it can be used as a potent premedication in children as an anti-anxiety drug.[24]

Limitation of the study

In the present study, the sample size was small. Thus, the study can be conducted to include a large population to understand the action of melatonin medication as an oral sedation during dental treatment.

Why this study is important in pediatric dentistry?

- Importance of oral sedation in pediatric dentistry as a pharmacological behavior management.
- Role of melatonin in oral sedation without any major orientation impairment.
- This study proved that melatonin has anti-anxiety and sedative effects for children.

CONCLUSION

Melatonin offers a number of potential advantages, reduced post-operative sedation, less sleep disturbance, faster recovery, improved post-operative analgesia, and avoidance of respiratory depression. Melatonin produces increase sedation after 60mins of post medication. It produces reduction in anxiety score, orientation score and cognitive function. Thus, it can be used as a potent premedication in children as anti-anxiety drug.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Gupta S, Patra A, Das A. Melatonin as a Nobel approach for un-cooperative child – An observational study. J Global Oral Health. doi: 10.25259/JGOH_7_2024