Comparative Study of Oral Midazolam vs. Oral Melatonin for Pre-Operative Anxiolysis in Paediatric Patients

Bheema Devanand[1], Shankar Sreenivasulu Raghunath[2], Bala Bhaskar S.[3], Srinivasalu Dammur[4], Charu Shrotriya[5], Sundeep Goud E.[6]

[1]Professor and HOD, Department of Anaesthesiology, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka. [2]Assistant Professor, Department of Anaesthesiology, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka. [3]Professor, Department of Anaesthesiology, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka. [4]Professor, Department of Anaesthesiology, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka. [5]Junior Resident, Department of Anaesthesiology, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka. [6]Junior Resident, Department of Anaesthesiology, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka.

ABSTRACT

BACKGROUND

Clinical trials with melatonin as a pre-medication agent in anxious children under nitrous oxide oxygen sedation for dental treatment have shown good results; but so far, only limited data is available. Midazolam is a benzodiazepine which produces anxiolytic, amnestic, hypnotic and skeletal muscle relaxant effects. We wanted to compare oral midazolam (0.5 mg/Kg) versus oral melatonin (0.5 mg/Kg) as a premedication in paediatric patients aged 1-6 years with regard to sedation and anxiolysis.

METHODS

This is a prospective, randomised double blind clinical study in which sixty children of ASA I and II in the age group 1-6 years, scheduled for elective general surgeries were included who were randomly allocated to two groups that would receive either 0.5 mg/Kg of oral midazolam or 0.5 mg/Kg of oral melatonin. The children were evaluated for sedation, anxiolysis, parental separation anxiety and acceptance of mask at induction.

RESULTS

Midazolam and melatonin were well accepted by the children. The quality and onset of sedation were similar in both the groups. The quality of anxiolysis is significantly better in the midazolam group, and the onset is earlier which is statistically significant. Melatonin group had a delayed onset and quality of anxiolysis was satisfactory and comparable to midazolam. The quality of parental separation and quality of mask acceptance was statistically insignificant in both the groups.

CONCLUSIONS

Oral melatonin can be an alternative premedication for sedation-anxiolysis in children. Oral midazolam had earlier onset and superior quality of sedation-anxiolysis compared to oral melatonin in the doses compared.

KEYWORDS

Melatonin, Midazolam, Pre-Operative Sedation-Anxiolysis, Paediatric Patients

Corresponding Author:
Dr. Raghunath S. S,
Assistant Professor,
Department of Anaesthesiology,
Vijayanagar Institute of Medical Sciences, Bellary, Karnataka.
E-mail: docraghu2009@gmail.com
DOI: 10.18410/jebmh/2019/668

Financial or Other Competing Interests: None.

How to Cite This Article:
Devanand B, Raghunath SS, Bala Bhaskar S, et al. Comparative study of oral midazolam vs. oral melatonin for pre-operative anxiolysis in paediatric patients. J. Evid. Based Med. Healthc. 2019; 6(51), 3184-3187. DOI: 10.18410/jebmh/2019/668

Submission 22-11-2019,
Peer Review 27-11-2019,
Acceptance 05-12-2019,
Published 20-12-2019.

BACKGROUND

Melatonin is secreted by the pineal gland in the brain when the body recognizes darkness.[1] Melatonin has intense effects on the sleep/awake cycle and in regulating the circadian rhythms of several biological functions.[2] Melatonin has documented effects on sleep disturbances, anxiety and pain.[3-7] Melatonin has a spectrum of important properties and plays several important physiological roles, many of which can have important clinical applications. Some experimental studies and clinical trials are providing the basis for future clinical applications of melatonin of use to the anaesthesiologist.[8] Clinical trials with melatonin as a pre-medication agent in anxious children under nitrous oxide oxygen sedation for dental treatment have shown good results, but so far, only limited data are available.[9] Midazolam is a benzodiazepine which produces anxiolytic, amnestic, hypnotic and skeletal muscle relaxant effects. It can be administered via the intranasal, sublingual, rectal and the oral routes. It has been the pharmacological agent of choice for pre-operative anxiety in day care surgery because of its rapid onset and short half-life. Although midazolam is an effective agent in alleviating anxiety in children, it is not without its own disadvantages. In some investigations, its use has been associated with a delay in either the discharge of the patients from the hospital or in the recovery time. Furthermore, some children, after the premedication with midazolam, experience maladaptive behavioural changes.[10] A number of drugs, other than midazolam, are preferable in the context of paediatric premedication.

METHODS

A prospective, double blind, randomised, observational study was conducted in a tertiary hospital. Institutional ethical committee approval and written consent were obtained from the persons legally responsible for children included in the study. Sixty children, American Society of Anaesthesiology (ASA) Grade I-II, aged 1-6 years scheduled for surgery under general anaesthesia were randomly assigned to receive either preparation which contained either midazolam 0.5 mg/ kg or melatonin 0.5 mg /Kg which were prepared by a resident blinded to the study. The children were administered the study drug an hour before the scheduled surgery in pre-op room the drug acceptance which was noted on three point scale: 1=good, 2=indifferent, could not asses, 3=bitter and unpleasant. The heart rate, blood pressure, respiratory rate, oxygen saturation and the sedation and anxiety levels are noted at the time of administration of the premedication and then they are monitored continuously. The readings are recorded every 15 minutes for up to 60 minutes. The onset of the sedation was defined as the minimum time interval which was necessary for the child to become drowsy or asleep. The level of sedation is assessed by using a 3-point scale: 1= awake, 2= drowsy and 3= asleep. A sedation score of ≥2 was considered as satisfactory.

Anxiety is evaluated by a 4-point scale: 1= crying, very anxious, 2= anxious, not crying, 3= calm, but not cooperative and 4= calm, cooperative or asleep. The anxiolysis score of ≥3 was considered as satisfactory. The onset of anxiolysis is defined as the minimum time interval necessary to achieve a satisfactory anxiolysis. Any untoward side effect like apnoea, hypoxaemia, bradycardia, hypotension and any other if present, was looked for and recorded. When a sedation score of 2 or 3 was reached, the children were transferred to the induction room. If no satisfactory sedation level was achieved, the children were excluded from further studies. The separation of the children from their parents was evaluated on a three point scale: 1= Poor: Anxious or combative, 2= Good: Anxious but easily assured and 3= Excellent: Calm/Sleeping. If the children came to the induction room while they were already asleep, a steal induction was attempted. All the children received sevoflurane, nitrous oxide and oxygen via a mask to facilitate venous cannulation. The quality of the induction and the mask acceptance was immediately evaluated on a 5-point scale: 1= combative, crying, 2= moderate fear of the mask, not easily calmed, 3= cooperative with reassurance, 4= calm, cooperative and 5= asleep, steal induction. A mask induction score of 3-5 was regarded as a successful response to the premedication. An intravenous line was secured and an intravenous infusion was started with ringer lactate with 5% dextrose.

All the children received intravenous glycopyrrolate 0.01 mg/Kg body weight. Anaesthesia was induced by giving propofol 2 mg/Kg body weight intravenously, plus 60% nitrous oxide and 40% oxygen with incremental sevoflurane administration from the start of 0.5% induction up to 3%, depending on the requirement. The muscle relaxant, vecuronium 0.1 mg/Kg body weight was used to facilitate endotracheal intubation. After the effect of vecuronium wore off, the neuromuscular blockade was supplemented with vecuronium 0.08 mg/Kg body weight intravenously and the IPPV was maintained with 8% sevoflurane and 60% nitrous oxide in 40% oxygen. No opioids or any other sedatives were administered intra-operatively. All the patients received rectal acetaminophen for post-operative analgesia. At the end, sevoflurane was discontinued and nitrous oxide was switched off. The neuromuscular blockade was reversed with glycopyrrolate 0.01 mg/Kg and neostigmine 0.04 mg/Kg body weight intravenously. The children were extubated after adequate neuromuscular recovery and when they made purposeful movements and had regular respiratory patterns. Post-operatively the children were shifted to post-operative observation room and were monitored for one hour and followed up for recovery from sedation, PONV, and shivering. All the adverse effects including hypotension, bradycardia, respiratory depression, nausea/vomiting and shivering were recorded in the proforma sheets.

RESULTS

Patients in both groups had comparable demographic characteristics, (age, sex, weight and ASA grade) (Table 1) There was good acceptability of both the drugs. Group-1(Midazolam) was found to be tasting good for 22 subjects, indifferent for 4 subjects, and bitter tasting for 2 subjects, and could not be assessed for 2 subjects. Group -2 (Melatonin) was found to be tasting good for 26 subjects, indifferent for 2 subjects, and could not be assessed for 2 subjects. There was no significant difference in the sedation in both groups (Table 2). A satisfactory sedation was achieved in both the groups. The onset of anxiolysis was earlier in midazolam group, and was satisfactory by thirty minutes (p= 0.005). Melatonin took a longer time for onset of anxiolysis but was comparable to midazolam (p>0.05). (Figure 1) There was no significant difference in the quality of parental separation anxiety, both the groups achieved good quality of parental separation (p>0.05). (Figure 2). The mask acceptance and quality of induction was satisfactory in both the groups and there was no statistical difference (p>0.05). (Figure 3). No adverse effects like bradycardia, hypotension, hypoxaemia or apnoea were observed during the pre-operative, intra-operative or the post-operative periods in both the midazolam and melatonin groups. (Figure 4, 5) Post-operative nausea and vomiting (PONV) was seen in 6.7% in midazolam group and 3.30% in melatonin group and was statistically insignificant (p=0.554) Shivering was seen in 6.7% in both the groups and results were statistically insignificant (p=1).

Variable	Group 1	Group 2	p
Age	2.93±1.14	3.13±1.3	0.53**
Sex	11(45.8)	13(54.2)	0.792*
	19(52.8)	17(47.2)	
Weight	12.03±2.67	11.33±2.49	0.299**
Height	88.4±10.3	94.07±12.8	0.065**
ASA 1	26(49.1)	4(57.1)	0.688*
ASA 2	27(50.9)	3(42.9)	
*chi square test			
**t test			

Table 1. Demographic Characteristics

Time in Minutes		Group 1	Group 2	p
Fifteen	Asleep	1	0	0.126
	Awake	24	29	
	Drowsy	5	1	
Thirty	Asleep	1	0	0.44
	Awake	7	10	
	Drowsy	22	20	
Forty-five	Asleep	9	6	0.667
	Awake	1	1	
	Drowsy	20	23	
Sixty	Asleep	20	13	0.084
	Awake	1	0	
	Drowsy	9	13	

Table 2. Assessment of Sedation in Both Groups

The level of sedation is assessed by using a 3-point scale: 1= awake, 2= drowsy and 3= asleep. A sedation score of ≥2 was considered as satisfactory. Anxiety is evaluated by a 4-point scale: 1= crying, very anxious, 2= anxious, not crying, 3= calm, but not cooperative and 4= calm, cooperative or asleep. The anxiolysis score of ≥3 was considered satisfactory. (Figure 1).

The separation of the children from their parents was evaluated on a three-point scale: 1= Poor: Anxious or combative, 2= Good: Anxious but easily assured and 3= Excellent: Calm/Sleeping (Figure 2)

The quality of the induction and the mask acceptance was immediately evaluated on a 5-point scale: 1= combative, crying, 2= moderate fear of the mask, not easily calmed, 3= cooperative with reassurance, 4= calm, cooperative and 5= asleep, steal induction. A mask induction score of 3-5 was regarded as a successful response to the premedication. (Figure 3)

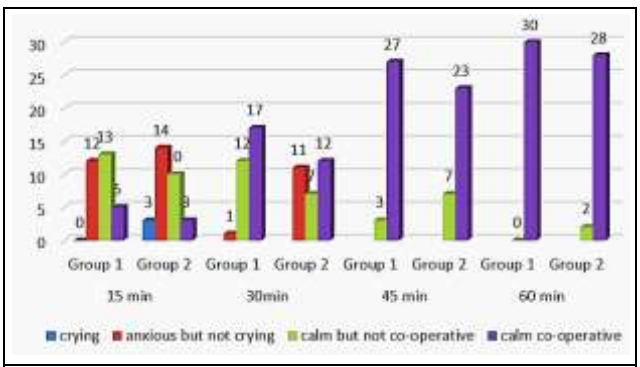

Figure 1. Comparison of Anxiety Among Groups

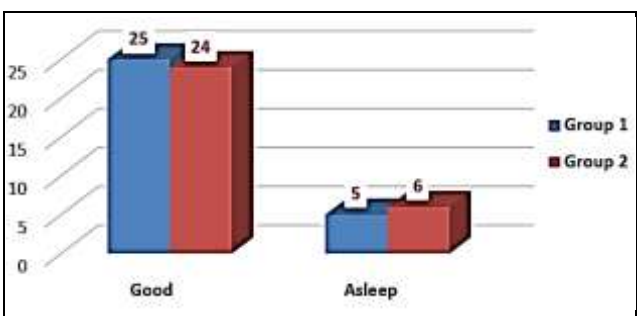

Figure 2. Comparison of Parental Separation Anxiety

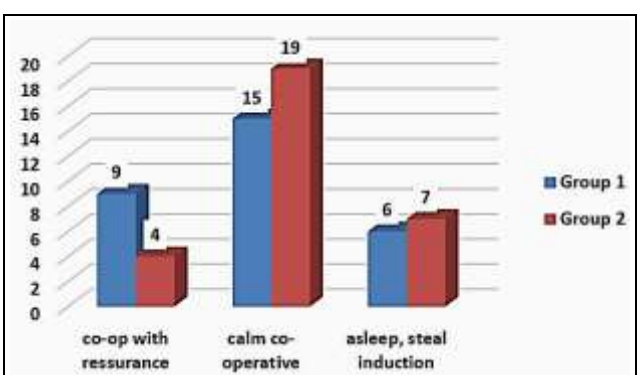

Figure 3. Comparison of Quality of Induction

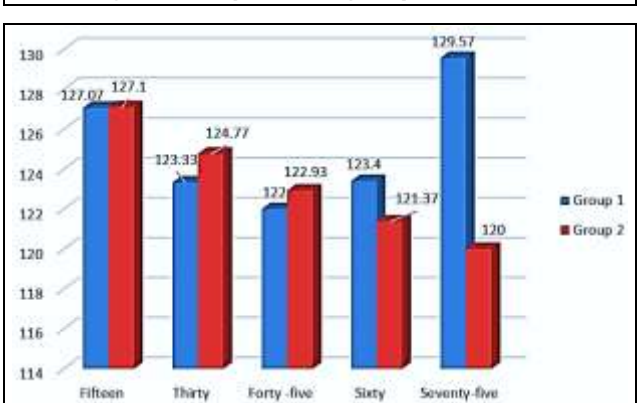

Figure 4. Comparison of Intra Operative Blood Pressure Rate among Both Groups

DISCUSSION

This study demonstrated that melatonin was an alternative to midazolam as a pre-medication in children. In this study both midazolam and melatonin were well accepted by the children. The quality and onset of sedation and was similar in both the groups. The quality of anxiolysis was significantly better in the midazolam group, and the onset was earlier which is statistically significant. Melatonin group had a delayed onset and quality of anxiolysis was satisfactory and comparable to midazolam. The quality of parental separation and quality of mask acceptance was statistically insignificant in both the groups. No adverse effects like bradycardia, hypotension, hypoxaemia were observed. PONV is comparatively less in our study because opioids were avoided, and paracetamol suppository was used as analgesic. Shivering in both the groups was similar and statistically insignificant.

Several studies reported that melatonin was useful for reducing anxiety prior to surgery, presumably due to its sedative effects. The anxiolytic effect of melatonin may be mediated through γ-aminobutyric acid system activation. Melatonin did not significantly reduce anxiety in older patients undergoing elective surgery.[11,12] There are studies in children which show that melatonin is as effective as midazolam in reducing preoperative anxiety and more rapid recovery, a reduced incidence of emergence delirium and decreased incidence of sleep disturbance 2 weeks after surgery when compared to midazolam.[13,14] 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 and 20 mg.[13] A study which compared three doses of midazolam (0.25 mg/Kg, m 0.5 mg/Kg and 1 mg/Kg up to 20 mg) found all the three doses to be effective in terms of sedation-anxiolysis but that a more rapid onset was produced with 0.5 mg and 1 mg/Kg.[14] In another study midazolam 0.25 mg/Kg dose was found to have equal efficacy to the higher doses in nearly 400 patients.[16] This study which compares 0.5 mg/Kg midazolam and 0.5 mg/Kg melatonin demonstrated that both were effective as premedicants in alleviating separation anxiety and anxiety associated with mask induction. And the onset of sedation-anxiolysis with midazolam was earlier compared to melatonin group. Further studies would be required comparing lower dose of midazolam 0.25 mg comparing higher dose of melatonin up to 1 mg/Kg.

CONCLUSIONS

Oral melatonin can be an alternative premedication for sedation-anxiolysis in children. Oral midazolam had earlier onset and superior quality of sedation-anxiolysis compared to oral melatonin in the doses compared.

REFERENCES

[1] Zee PC, Manthena P. The brain's master circadian clock: implications and opportunities for therapy of sleep disorders. Sleep Med Rev 2007;11(1):59-70.

[2] Brzezinski A. Melatonin in humans. N Engl J Med 1997;336(3):186-195.

[3] Dawson D, Encel N. Melatonin and sleep in humans. Journal of Pineal Research 1993;15(1):1-12.

[4] Khezri MB, Merate H. The effects of melatonin on anxiety and pain scores of patients, intraocular pressure, and operating conditions during cataract surgery under topical anesthesia. Indian J Opthalmol 2013;61(7):319-324.

[5] Khezri MB, Merate H. The effects of melatonin on anxiety and pain scores of patients, intraocular pressure, and operating conditions during cataract surgery under topical anesthesia. Indian J Opthalmol 2013;61(7):319-324.

[6] Caumo W, Torres F, Moreira NL, et al. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg 2007;105(5):1263-1271.

[7] Yousaf F, Seet E, Venkatraghavan L, et al. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomised trials. Anesthesiology 2010;113(4):968-976.

[8] Yousaf F, Seet E, Venkatraghavan L, et al. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. Anesthesiology 2010;113(4):968-976.

[9] Rodello LF, Labanca M, Foglio E. Melatonin in dentistry. In: Watson RR, ed. Melatonin in the promotion of health. 2nd edn. USA: Taylor and Francis Group 2012:219-231.

[10] Wright KD, Stewart SH, Finley GA, et al. Prevention and intervention strategies to alleviate pre-operative anxiety in children: a critical review. Behav Modif 2007;31(1):52-79.

[11] Capuzzo M, Zanardi B, Schiffino E, et al. Melatonin does not reduce anxiety more than placebo in the elderly undergoing surgery. Anesth Analg 2006;103(1):121-123.

[12] Brzezinski A, Vangel MG, Wurtman RJ, et al. Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev 2005;9(1):41-50.

[13] Samarkandi A, Naguib M, Raid W, et al. Melatonin vs midazolam premedication in children: a double blind, placebo-controlled study. Eur J Anaesthesiol 2005;22(3):189-196.

[14] Cote CJ, Cohen IT, Suresh S, et al. A comparison of three doses of a commercially prepared oral midazolam syrup in children. Anaesth Analg 2002;94(1):37-43.