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ORIGINAL ARTICLE

Oral melatonin, dexmedetomidine, and midazolam for prevention of postoperative agitation in children

Dilek Özcengiz · Yasemin Gunes · Ozlem Ozmete

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Abstract
Purpose Several studies have reported that sevoflurane was associated with a relatively high incidence of emergence agitation in children even in the absence of any surgical intervention. The aim of this study was to compare early agitation characteristics of oral melatonin, dexmedetomidine, and midazolam premedication in children who were given sevoflurane anesthesia for esophageal dilatation.
Methods Following Internal Review Board approval and parental informed consent, 100 ASA physical status I–II children (3–9 years old) who were scheduled to undergo general anesthesia for esophageal dilatation procedures were enrolled. The patients were randomly assigned to four groups ($n = 25$ in each). The premedications in the groups were saline (group P), dexmedetomidine 2.5 μg/kg (group D), 0.5 mg/kg midazolam (group MD), and melatonin 0.1 mg/kg (group ML), given orally. All premedication drugs were given with paracetamol 2–2.5 mg/kg to be easily drinkable 40–45 min before anesthesia induction. Anesthesia was maintained with sevoflurane 2–4%, N_2O 50% in oxygen. No supplemental analgesic agent was given, and an emergence agitation scale (EAS) was measured on admission to the PACU, then every 5 min, and recorded during the postoperative period: 1, awake and calm, cooperative; 2, crying, requires consoling; 3, irritable/restless, screaming, inconsolable; 4, combative, disoriented, thrashing. Children with an agitation score of 3 or 4 were classified as agitated.
Results There were no significant differences among the four groups demographically. The emergence agitation scale was higher in the placebo group than in the others at 5, 10, and 15 min postoperatively ($P < 0.001$). EA was similar among group D, group MD, and group ML.
Conclusion We found that oral melatonin, dexmedetomidine, and midazolam reduced the incidence of emergence agitation in children after sevoflurane anesthesia.

Keywords Melatonin · Dexmedetomidine · Midazolam · Postoperative agitation

D. Özcengiz (✉) · Y. Gunes · O. Ozmete
Department of Anesthesiology, Medical Faculty, Cukurova University, Balcali, Adana, Turkey
e-mail: dilekozcengiz@gmail.com

Introduction

Emergence agitation (EA) or delirium is a frequent phenomenon in children recovering from general anesthesia that can create a challenging situation to their health care providers [1, 2]. Separation from the family, anticipation of postoperative pain, fear of surgery, incapacity, and loss of independence, and fear of death are factors that trigger EA [3].

Sevoflurane is a popular anesthetic for children because it is less pungent, and has a more rapid onset and recovery because of lower solubility in blood, a relative lack of airway irritation, and greater hemodynamic stability than other potent inhaled agents [4, 5]. However, a number of studies reported that sevoflurane was associated with a relatively high incidence of EA in children [6, 7], even in the absence of any surgical intervention [1]. EA is a term used to describe nonpurposeful restlessness and agitation, thrashing, crying or moaning, disorientation, and incoherence [8]. It was concluded that EA was seen 33% of the time when a high threshold for agitation was defined, and 80% of the time when using a lower threshold, in children

after sevoflurane anesthesia without surgery [1]. It was reported that midazolam, melatonin, and dexmedetomidine given preoperatively can prevent emergence agitation [3]; however, the influence of the agents on EA seems to be somewhat controversial.

In this study, we aimed to compare early agitation characteristics of oral melatonin, dexmedetomidine, and midazolam premedication in children who were given sevoflurane anesthesia for esophageal dilatation. We hypothesized that there would not be any significant difference among the treatment groups.

Methods

Following Internal Review Board approval and parental informed consent, 100 ASA physical status I–II children (3–9 years old) who were scheduled to undergo general anesthesia for esophageal dilatation procedures were included. This study was conducted prospectively; it was placebo controlled and double blinded. Exclusion criteria included lack of consent, known adverse reactions to dexmedetomidine, midazolam, or melatonin, mental retardation, developmental delay, or neurological or psychiatric illness that may be associated with agitation (cerebral palsy, seizure, etc.). One hour before sedation, children were transported to an isolated premedication room near the operating suite. Parental presence was allowed throughout the sedation and postsedation period. The patients were randomly assigned to four groups ($n = 25$ in each). The randomization was performed with using a table random method.

The premedications in the groups were saline (group P), dexmedetomidine 2.5 μg/kg (group D), midazolam 0.5 mg/kg (group MD), and melatonin 0.1 mg/kg (group ML), all given orally. All premedication drugs were given with paracetamol 2–2.5 mg/kg to be easily drinkable 40–45 min before induction of anesthesia. Study drugs were given by a trained nurse. For the purpose of creating double-blind conditions, neither the researcher who attended clinical applications and observations nor the parents were informed as to which drug was administered to which child. After the patients were taken to the operating room, routine anesthesia monitoring was obtained. Hemodynamic variables [HR (heart rate), electrocardiogram (ECG), SAP (systolic arterial pressure), DAP (diastolic arterial pressure), and peripheral oxygen saturation (SpO_2)] were recorded at preoperative (control) and intraoperative periods.

Anesthesia induction was obtained with sevoflurane 8%, N_2O 50% in oxygen with face mask. During the induction, response to the face mask was evaluated; then, the sevoflurane concentration was decreased. Anesthesia was maintained with sevoflurane 2–4%, N_2O 50% in oxygen. An intravenous access was obtained, and vecuronium was given for endotracheal intubation. No supplemental analgesic agent was given. Esophageal dilatation was applied, and anesthesia was ended. Neuromuscular block was antagonized with atropine sulfate 0.02 mg kg^{-1} and neostigmine 0.05 mg/kg. The trachea was extubated on resumption of spontaneus respiration and control of airway.

After the procedure, all the patients were transferred, still asleep, to the postoperative anesthesia care unit (PACU) and observed during 1 h. HR, SAP, DAP, and SpO_2 were recorded at entrance and at 5, 10, 15, 40, and 60 min, postoperatively. An emergence agitation scale (EAS) was measured on admission to the PACU, every 5 min, and recorded 5, 10, 15, 30, and 60 min thereafter and on arrival of the parent in the PACU (1, awake and calm, cooperative; 2, crying, requires consoling; 3, irritable/restless, screaming, inconsolable; 4, combative, disoriented, thrashing) [8]. All the patients were evaluated by the same researcher, who was unaware which drug was administered to which child. Children with an agitation score of 3 or 4 were classified as agitated. Although scoring agitation at 5-min intervals may not be ideal, in the busy milieu of our pediatric PACU it was the most expedient and practical approach. The parents were admitted 3–5 min after the children arrived to PACU. Children were considered severely agitated if they had an agitation score that remained at 3 for 5 min after the arrival of their parent.

Statistical evaluation was performed with SPSS 11.5 pocket program using the tests mentioned below; $P < 0.05$ was considered significant. The results are expressed as (mean ± SD).

The sample size was determined assuming that the probability of sevoflurane agitation was 30% or more. We wanted to find a significant difference ($P < 0.05$) ($\alpha = 0.05$, one-tailed) with a power of 90% (error = 0.1) to detect a difference of 25%. Twenty-one patients per group would have been sufficient, but we expected some exclusions from the protocol (which did not happen) and increased this number to 25 (which allowed finding the same significant difference with a power of 90%). A one-way analysis of variance (ANOVA) test was used in the intergroup comparisons of age, weight, duration of anesthesia, and emergence agitation score. Repeated measures variance analysis evaluated SAP, DAP, HR, and SpO_2. Bonferroni adjustment was used in the comparisons of intragroup values of SAP, DAP, HR, and SpO_2 in which the time factor was identified as important through repeated measures variance analysis.

Results

There were no significant demographic differences among the four groups. Demographic values of the patients are

Table 1 Demographic parameters in groups (mean ± SD)

Parameter	Group P ($n = 25$)	Group D ($n = 25$)	Group MD ($n = 25$)	Group ML
Gender (M/F)	13/12	10/15	14/11	13/12
Age (years)	6.2 ± 2.2	5.5 ± 2.4	4.9 ± 2.3	6.1 ± 2.4
(median)	(4)	(5)	(4)	(5)
Preschool age (3–6 years)	14	15	16	14
School age (7–9 years)	11	10	9	11
Weight (kg)	20.9 ± 7.9	20.4 ± 11.0	18.8 ± 9.4	22.0 ± 10.4
Duration of anesthesia (min)	24.4 ± 10.5	20.5 ± 8.3	20.4 ± 6.9	23.9 ± 8.6

Group P, placebo (saline); group D, dexmedetomidine 2.5 μg/kg; group MD, 0.5 mg/kg midazolam; group ML, melatonin 0.1 mg/kg

Table 2 Postoperative emergence agitation scales in groups (mean ± SD)

Time	Group P	Group D	Group MD	Group ML	*P*
Postop. 5 min	2.0 ± 0.7[a]	1.3 ± 0.6	1.6 ± 0.6	1.8 ± 0.8	0.001
Postop. 10 min	1.9 ± 0.8	1.3 ± 0.6	1.4 ± 0.6	1.3 ± 0.6	0.002
Postop. 15 min	1.5 ± 0.8[a]	1.3 ± 0.6	1.1 ± 0.5	1.1 ± 0.3	0.028
Postop. 30 min	1.4 ± 0.9[a]	1.2 ± 0.5	1.1 ± 0.4	1.0 ± 0.2	0.170
Postop. 60 min	1.4 ± 0.9[a]	1.1 ± 0.5	1.1 ± 0.4	1.0 ± 0.0	0.142

[a] Group P compared to group D, group MD, group ML

Table 3 Number of patients with emergence agitation (EA) of three or greater (≥3) (*n*, %)

Group P	Group D	Group MD	Group ML
8 (32%)	2 (8%)*	1 (4%)**	2 (8%)*

** $P = 0.01$, group P compared to group MD

* $P = 0.034$, group P compared to group D and group ML

shown in Table 1. The emergence agitation scale was higher in the placebo group than others at 5 min ($P < 0.001$), 10 min ($P < 0.002$), and 15 min ($P < 0.028$) postoperatively. EA was similar among groups D, MD, and ML (Table 2). More patients in group P had an EA of 3 or more (≥3) than those in the study groups (Table 3). There were no differences in HR, SAP, DAP, and SpO_2 among the groups ($P > 0.05$). No other clinically relevant adverse effect was observed in any group.

Discussion

This study was performed to evaluate the influence of preanesthesia administration of midazolam, dexmedetomidine, or melatonin on postoperative agitation. We found that all the drugs decreased postoperative agitation, with no statistically significant differences among the groups.

Several previous studies reported that sevoflurane anesthesia caused children to have a higher incidence of emergence agitation as compared with halothane, but some prospective studies performed to evaluate this point found no significant difference between the two anesthetics [9–12]. Kuratani and Oi [9] revealed that sevoflurane anesthesia more often resulted in emergence agitation than did halothane in pediatric patients. The results of their analysis are consistent with the current consensus among pediatric anesthesiologists.

The etiology of emergence agitation derives from multiple factors, including pain, preoperative anxiety, type of surgical procedures, personal character of the patient, too-rapid awakening, and type of anesthetics. No sole factor can explain the etiology of emergence agitation [3, 13]. Although pain is definitely a major reason for emergence agitation, screaming as a result of pain should be distinguished from emergence agitation. However, especially in younger children, it is sometimes not possible to distinguish between them. It is widely believed that reducing or eliminating pain decreases the incidence of emergence agitation after sevoflurane anesthesia. Several studies demonstrated that regional block, opioids, and nonsteroidal antiinflamatory drugs decrease the incidence of emergence agitation [10, 11, 13–15]. However, emergence agitation often occurs even after adequate pain treatment or after procedures that are not associated with pain. Weldon et al. [10] demonstrated that sevoflurane is associated with an early, short-lived increase in the incidence of emergence agitation compared with halothane when reliable postoperative pain control is provided with a caudal block. In addition, if we consider the fact that anesthesia for essentially pain-free procedural sedation can cause emergence agitation, complete pain treatment does not guarantee a calm awakening after sevoflurane [1]. In our study, ecophageal dilatation is not a painful procedure; however, the patients in the placebo group had more agitation than the other patients.

The reasons for a higher incidence of emergence agitation after sevoflurane are not fully understood. Sevoflurane in particular situations may exert an irritating side effect on the central nervous system, because epileptiform seizure activity in previously nonepileptic patients has been observed with electroencephalography during sevoflurane anesthesia [16, 17]. The mechanism of cortical epileptogenicity by sevoflurane is largely unknown [18]. Because volatile anesthetics with low blood solubility generally tend to cause a higher incidence of emergence agitation, rapid awakening has been posited as a cause for this phenomenon. However, rapid awakening after propofol has not been associated with emergence agitation [7]. Therefore, rapid awakening per se does not seem to be a factor in the causation of emergence agitation.

Giving sedative premedication before anesthesia to ameliorate preoperative anxiety has been tried, with hopes that it would decrease the incidence of emergence agitation. The influence of midazolam on emergence behavior seems to be somewhat controversial. Lapin et al. [19] and Ko et al. [20] reported a reduction of agitation in premedicated children, whereas McGraw and Kendrick [21] observed no difference at emergence and even an increased incidence of adverse postoperative behavior at 1 and 4 weeks after surgery. Breschan et al. [22] reported that their data could not detect an increase of effectiveness in reducing emergence agitation after a higher dose of rectal midazolam, 1 mg/kg compared with 0.5 mg/kg. The high incidence of severe agitation after both doses, especially in younger children, would rather suggest a complete lack of effectiveness, which is in agreement with other reports [23, 24]. In our study, midazolam was found to be very effective for postoperative agitation. Schmidt et al. [25] showed that the alpha-2 agonists dexmedetomidine and clonidine seem to be a better choice for premedication in children, as they were associated with lower levels of postoperative pain than midazolam. Furthermore, α2-agonists were related to a safe decrease of sympathetic tone, as no significant side effects were observed in this setting. Yuen et al. [26] suggested that intranasal dexmedetomidine produces more sedation than oral midazolam, but with similar and acceptable cooperation. Using more selective α2-agonists, an agitation incidence of 4.8% was observed among patients given dexmedetomidine, at a dosage of 1 μg/kg intravenously, compared with 47.6% in a placebo group, without detecting increases in emergence time or intraoperative hemodynamic repercussion [27].

Melatonin is a methoxyindole synthesized from tryptophan and secreted principally by the pineal gland. It has an endogenous circadian rhythm of secretion induced by the suprachiasmatic nuclei of the hypothalamus that is entrained to the light/dark cycle [28]. In mammals, melatonin is present in almost all tissues, with or without the melatonin receptors, because it acts as both a hormone and an antioxidant. Considering the time-dependent action of melatonin, it can be better classified as a chronohypnotic [29]. Oral melatonin at 5 mg/day has been used to alleviate jet lag and as a preoperative sedative [30–34]. Işık et al. [34] reported that, in anxious children, oral 3 mg or 0.5 mg/kg melatonin premedication is not a good choice for dental treatment. They suggested further clinical research with respect to melatonin with another dose or time regimen or in combination with other sedatives might be required. In this study, melatonin provided decreasing postoperative agitation compared to placebo and was as effective as dexmedetomidine and midazolam. Naguib and Samarkandi [32] found that melatonin (0.5 mg/kg) was associated with preoperative anxiolysis and sedation without impairment of cognitive and psychomotor skills or affecting the quality of recovery. Samarkandi et al. [35] reported that 0.25 and 0.5 mg/kg melatonin was not only as effective as midazolam in alleviating preoperative anxiety in children but also associated with a tendency toward faster recovery and lower incidence of excitement postoperatively. Caumo et al. [36] reported that patients treated with melatonin preoperatively had a significant decrease in pain and anxiety at all time points assessed during the first 36 h after surgery. Furthermore, they required less morphine in the postoperative period and had better recovery of the rhythmicity percentual in the first postoperative week after discharge. They also demonstrated that melatonin had a significant clinical effect on pain and anxiety during the first 24 h after surgery, which defines the treatment-specific effects of an intervention. In contrast, Kain et al. [37] determined whether the anxiolysis associated with 0.05, 0.2, or 0.4 mg/kg (maximum dose, 20 mg) oral melatonin differed from that of midazolam in children scheduled for surgery. They suggested that oral midazolam is a more effective anxiolytic than oral melatonin. In our study, melatonin and midazolam reduced EA very similarly.

Summarizing our findings, we believe that melatonin, dexmedetomidine, and midazolam given orally for premedication prevented postoperative early agitation in children after sevoflurane anesthesia.

References

1. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth. 2000;10:419–24.
2. Beskow A, Westrin P. Sevoflurane causes more postoperative agitation in children than does halothane. Acta Anaesthsiol Scand. 1999;43:536–41.
3. Silva LM, Braz LG, Módolo NS. Emergence agitation in pediatric anesthesia: current features. J Pediatr. 2008;84:107–13.

4. Goa KL, Noble S, Spencer CM. Sevoflurane in paediatric anaesthesia: a review. Paediatr Drugs. 1999;1:127–53.
5. Hatch DJ. New inhalation agents in paediatric anaesthesia. Br J Anaesth. 1999;83:42–9.
6. Keaney A, Diviney D, Harte S, Lyons B. Postoperative behavioral changes following anesthesia with sevoflurane. Pediatr Anesth. 2004;14:866–70.
7. Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. Rapid emergence does not explain agitation following sevoflurane anaesthesia in infants and children: a comparison with propofol. Paediatr Anaesth. 2003;13:63–7.
8. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology. 2004;100:1138–45.
9. Kuratani N, Oi Y. Greater incidence of emergence agitation in children after sevoflurane anesthesia as compared with halothane: a meta-analysis of randomized controlled trials. Anesthesiology. 2008;109:225–32.
10. Weldon BC, Bell M, Craddock T. The effect of caudal analgesia on emergence agitation in children after sevoflurane versus halothane anesthesia. Anesth Analg. 2004;98:321–6.
11. Galinkin JL, Fazi LM, Cuy RM, Chiavacci RM, Kurth CD, Shah UK, Jacobs IN, Watcha MF. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. Anesthesiology. 2000;93:1378–83.
12. Davis PJ, Greenberg JA, Gendelman M, Fertal K. Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion. Anesth Analg. 1999;88:34–8.
13. Veyckemans F. Excitation phenomena during sevoflurane anaesthesia in children. Curr Opin Anesthesiol. 2001;14:339–43.
14. Aouad MT, Kanazi GE, Siddik-Sayyid SM, Gerges FJ, Rizk LB, Baraka AS. Preoperative caudal block prevents emergence agitation in children following sevoflurane anesthesia. Acta Anaesthesiol Scand. 2005;49:300–4.
15. Cohen IT, Hannallah RS, Hummer KA. The incidence of emergence agitation associated with desflurane anesthesia in children is reduced by fentanyl. Anesth Analg. 2001;93:88–91.
16. Komatsu H, Taie S, Endo S, Fukuda K, Ueki M, Nogaya J, Ogli K. Electrical seizures during sevoflurane anesthesia in two pediatric patients with epilepsy. Anesthesiology. 1994;81:1535–7.
17. Woodforth IJ, Hicks RG, Crawford MR, Stephen JP, Burke DJ. Electroencephalographic evidence of seizure activity under deep sevoflurane anesthesia in a nonepileptic patient. Anesthesiology. 1997;87:1579–82.
18. Constant I, Seeman R, Murat I. Sevoflurane and epileptiform EEG changes. Paediatr Anaesth. 2005;15:266–74.
19. Lapin SL, Auden SM, Goldsmith LJ, Reynolds AM. Effects of sevoflurane anaesthesia on recovery in children: a comparison with halothane. Paediatr Anaesth. 1999;9:299–304.
20. Ko YP, Huang CJ, Hung YC, Su NY, Tsai PS, Chen CC, Cheng CR. Premedication with low-dose oral midazolam reduces incidence and severity of emergence agitation in paediatric patients following sevoflurane anesthesia. Acta Anaesthesiol Sin. 2001;39:169–77.
21. McGraw T, Kendrick A. Oral midazolam premedication and postoperative behaviour in children. Paediatr Anaesth. 1998;8:117–21.
22. Breschan C, Platzer M, Jost R, Stettner H, Likar R. Midazolam does not reduce emergence delirium after sevoflurane anesthesia in children. Paediatr Anaesth. 2007;17:347–52.
23. Viitanen H, Annila P, Viitanen M, Tarkkila P. Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. Anesth Analg. 1999;89:75–9.
24. Kulka PJ, Bressem M, Wiebalck A, Tryba M. Prevention of 'postsevoflurane delirium' with midazolam. Anaesthesist. 2001;50:401–5.
25. Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simões CM, Auler JO Jr. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Paediatr Anaesth. 2007;17:667–74.
26. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. Anesth Analg. 2008;106:1715–21.
27. Isik B, Arslan M, Tunga AD, Kurtipek O. Dexmedetomidine decreases emergence agitation in pediatric patients after sevoflurane anesthesia without surgery. Paediatr Anaesth. 2006;16:748–53.
28. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin (physiological review). Sleep Med Rev. 2005;9:11–24.
29. Scheer FA, Czeisler CA. Melatonin, sleep, and circadian rhythms. Sleep Med Rev. 2005;9:5–9.
30. Jaffe SE, Patterson DR. Treating sleep problems in patients with burn injuries: practical considerations. J Burn Care Rehabil. 2004;25:294–305.
31. Petrie K, Cognaglen JV, Thompson L, Chamberlain K. Effect of melatonin on jet lag after long haul flights. BMJ. 1989;298:705–7.
32. Naguib M, Samarkandi AH. Premedication with melatonin: a double-blind, placebo controlled comparison with midazolam. Br J Anaesth. 1999;82:875–80.
33. Naguib M, Samarkandi AH. The comparative dose-response effect of melatonin and midazolam for premedication of adult patients: a double-blinded, placebo-controlled study. Anesth Analg. 2000;91:473–9.
34. Işık B, Baygin O, Bodur H. Premedication with melatonin vs. midazolam in anxious children. Paediatr Anaesth. 2008;18:635–41.
35. 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;22:189–96.
36. Caumo W, Torres F, Moreira NL Jr, Auzani JA, Monteiro CA, Londero G, Ribeiro DF, Hidalgo MP. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg. 2007;105:1263–71.
37. Kain ZN, MacLaren JE, 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;111:44–9.