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Research Article

Melatonin, ketamine and their combination in half doses for management of sevoflurane agitation in children undergoing adenotonsillectomy

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KEYWORDS

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Abstract *Background:* The increased use of sevoflurane has been associated with an increased incidence of emergence agitation (EA), melatonin and ketamine were used for the management of sevoflurane agitation. But their combination was not evaluated up-to-date. So we designed this randomized double blinded controlled study to evaluate the effect of melatonin, ketamine and their combination in half doses in management of EA in children undergoing adenotonsillectomy.

Methods: One hundred twenty children (3–6 years) of both sex were randomly allocated into four equal groups (30 patients each); control group (C) received oral parecetamol 15 mg/kg 1 h before induction and 3 ml intravenous normal saline with induction, melatonin group (M) received oral melatonin 0.1 mg/kg with oral parecetamol 15 mg/kg 1 h before induction and 3 ml intravenous normal saline with induction, ketamine group received oral parecetamol 15 mg/kg 1 h before induction and intravenous ketamine 0.5 mg/kg in a total volume 3 ml with normal saline with induction and melatonin ketamine (MK) group received oral melatonin 0.05 mg/kg with oral parecetamol 15 mg/kg 1 h before induction and intravenous ketamine 0.25 mg/kg with induction in a total volume 3 ml with normal saline. General anesthesia was standardized for all children with inhaled sevoflurane. EA was assessed by 5 point scale at 5, 15 and 30 min.

Results: As regard the EA, there was significant difference between M, K and MK groups when compared to C group at 5 and 15 min. But there was no significant difference between M and K groups when compared with the MK group all over the time of the study.

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Conclusion: Melatonin and ketamine were effective in the management of EA. The combination of half doses of them was equally effective as the use of each of them alone.

1. Introduction

Emergence agitation was defined as a disturbance in a child's awareness of environment with disorientation and perceptual alteration including hypersensitivity to stimuli and hyperactive motor behavior in the immediate postanesthesia period [1].

Multiple factors cause EA, including pain, preoperative anxiety, type of surgical procedures, type of anesthetics, too rapid awakening, and personal character of the patient. No sole factor can explain the etiology of EA [2,3]. It is widely believed that reducing or eliminating pain decreases the incidence of EA after sevoflurane anesthesia. However, EA often occurs even after adequate pain treatment or after procedures that are not associated with pain. Weldon et al. demonstrated that sevoflurane is associated with an early, short-lived increase in the incidence of EA compared with halothane when reliable postoperative pain control is provided with a caudal block [4]. Also in Özcengiz et al., study esophageal dilatation is not a painful procedure; however, the patients in the placebo group had more agitation than the other patients [5].

Melatonin is synthesized from tryptophan and it is nocturnal neurohormone secreted by the pineal gland, retina, and gastrointestinal tract. It has several diverse functions, including antioxidant, antiinflammatory, and anticonvulsant activities, as well as regulation of circadian rhythms and the reproductive axis. Melatonin has numerous uses: treatment of sleep disorders [6], reduction of oxidative stress in neonates in the perioperative period [7] and treatment of psychosis in the intensive care unit [8]. Many studies had reported that melatonin was as effective in reducing preoperative anxiety as midazolam [9,10].

Ketamine has been reported to prevent EA associated with inhalation anesthetic agents. Khattab and El-Seify found that adding low dose oral ketamine to oral midazolam in children underwent dental surgery reduced sevoflurane agitation without delaying discharge [11].

Kawaraguchi et al. found that intravenous ketamine after induction of sevoflurane anesthesia in children undergoing strabismus surgery reduced the incidence of agitation [12].

In animal studies, ketamine was shown to potentiate the release of melatonin [13].

2. Materials and methods

After obtaining approval by the local ethics committee of El-Minia university hospital and informed consent from parents, one hundred twenty children (3–6 years) of both sex were randomly allocated into four equal groups (30 patients each) (randomization was done according to computer generated number); C group received oral parecetamol 15 mg/kg and 3 ml normal saline intravenous with induction, M group received oral melatonin 0.1 mg/kg with oral parecetamol 15 mg/kg 1 h before induction and 3 ml normal saline intravenous with induction, k group received oral parecetamol 15 mg/kg 1 h before induction and intravenous ketamine 0.5 mg/kg in a total volume 3 ml normal saline with induction and MK group received oral melatonin 0.05 mg/kg with oral parecetamol 15 mg/kg 1 h before induction and intravenous ketamine 0.25 mg/kg in a total volume 3 ml normal saline with induction. It was a double blinded study neither the observer nor the patients knew the group allocation or the drugs used.

Children with developmental, psychological, behavioral, or any medical problems were excluded.

Preparation of the oral medications was done as following; one tablet of melatonin 5 mg was dissolved in 10 ml glucose 5% and the calculated dose according to children body weight was added with parecetamol 15 mg/kg to be palatable for children and parecetamol also used as analgesic. Oral medications were given to children 1 h before induction.

In the operating room monitoring of heart rate, blood pressure and oxygen saturation was done. Induction of anesthesia was done with sevoflurane (3–8 MAC), started with 3 Mac and gradually increased to 8. Meanwhile intravenous line was inserted, and then atropine 0.01 mg/kg, cisatracurium 0.15 mg/kg and 3 ml of saline (with or without ketamine) were given. Maintenance of anesthesia was done by 1.5–2 MAC sevoflurane. At the end of operation discontinuation of inhalational anesthesia was done and muscle relaxant was reversed by neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. Then children were transferred to PACU till complete recovery then discharged to ward.

Parameters assessed were induction time (IT) time from the start of sevoflurane inhalation to the start of endtracheal tube insertion, duration of anesthesia (DA) time from the start of sevoflurane inhalation to discontinuation of sevoflurane inhalation, time up to spontaneous eye opening (time from removal of endotracheal tube till spontaneous eye opening), duration of stay in PACU and any side effects.

Agitation was also assessed by five-point scale (Table 1) at 5, 15 and 30 min after arrival to PACU; children with score 4 and 5 was considered agitated. Agitated children were considered uncontrolled if not respond to calming measures and the presence of parents and managed by 1 μg/kg intravenous fentanyl.

3. Statistical analysis

Data entry and analysis were done with IBM compatible computer using software (SPSS version 15, Chicago, Illinois, USA). Quantitative data were presented by mean and standard deviation and compared by analysis of variance (ANOVA) test

Table 1 Five-point emergence agitation scale.

1	Obtunded with no response to stimuli
2	Asleep, but responsive to movement and stimuli
3	Awake and appropriately responsive
4	Crying and difficult to console
5	Wild thrashing behavior that requires restraint

followed by post hoc test if there was significance. Qualitative data were presented by number and percentage and compared by Chi-square test. A P value $\leqslant 0.05$ was considered statistically significant.

The sample size was calculated according to the previous study that was done by Özcengiz et al. [5] as they assume that the probability of sevoflurane agitation was 30% or more. To find a significant difference with a power of 90% to detect a difference of 25%. Twenty-one patients per group would have been sufficient. And also we expected some exclusion from the protocol (which did not happen) so we increased the number to 30.

4. Results

There was no significant difference between the four groups as regard age, weight and sex distribution (Table 2).

There were no significant differences between the four groups as regard the IT and DA. But there was significant difference as regard the time to spontaneous eye opening as it was significantly longer in the M, K and MK when compared to C group. As regard the duration of stay in the PACU there were significant difference between the M, K and MK group when compared to the C group as it was significantly longer in the C group also significant difference was found when comparing M group with MK group being longer in the M group (Table 3).

As regard the EA, there was significant difference between M, K and MK groups when compared to C group at 5 and 15 min. But there was no significant difference between M and K groups when compared with the MK group all over the time of the study (Table 4).

5. Discussion

In our study as regard the M group we found that there was no significant difference between the M group when compared with control group in the ID and DA. But there was significant difference when compared with the C group in time for spontaneous eye opening as it was longer in the melatonin group. There was significant difference when compared with the C group in duration of stay in the PACU as it was shorter in melatonin group and this mostly explained by the more use of fentanyl in the C group to manage uncontrolled agitated children. Melatonin reduced the incidence of EA in children received oral melatonin when compared to children in the C group at 5 and 15 min.

In agreement with our result Kain et al. who study four groups of children assigned to receive preoperatively oral midazolam 0.5 mg/kg or oral melatonin 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg. The melatonin groups showed a dose–response effect on emergence behavior. Children who received melatonin developed less emergence delirium compared with those who received midazolam, and the effect was dose related; the incidence after 0.05 mg/kg melatonin was 25.0%, incidence after 0.2 mg/kg melatonin was 8.3%, and incidence after 0.4 mg/kg melatonin was 5.4%. They concluded that midazolam was more effective than melatonin in reducing children's anxiety at induction of anesthesia. Melatonin showed a direct dose-dependent effect on emergence delirium [14].

Also in agreement with our results Özcengiz et al., who studied 100 children (3–9 years old) who were scheduled to undergo general anesthesia for esophageal dilatation procedures. The patients were randomly assigned to four groups. The premeditations in the groups were saline, dexmedetomidine 2.5 μg/kg, 0.5 mg/kg midazolam, and melatonin 0.1 mg/kg, given orally. They found that oral melatonin, dexmedetomidine, and midazolam reduced the incidence of EA in children after sevoflurane anesthesia [5].

Samarkandi et al. 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 [9].

Caumo et al. 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 [15].

In our study as regard the K group we found that there were no significant difference between the K group when compared with C group in the ID and DA. But there were significant difference when compared with the control group in time for spontaneous eye opening as it was longer in K group and duration of stay in the PACU as it was shorter in the K group this mostly explained by the more use of fentanyl in the C group to manage uncontrolled agitated children. Ketamine reduced the incidence of EA in children received intravenous ketamine when compared to children in the C group at 5 min and 15 min.

In agreement with our results, Khattab and El-Seify who studied 92 children classified into two groups; oral midazolam 0.5 mg/kg mixed with 10 mg/kg ibuprofen or oral midazolam 0.5 mg/kg with 2 mg/kg ketamine mixed with 10 mg/kg ibuprofen. They found that adding low dose oral ketamine to oral midazolam in children underwent dental surgery reduced sevoflurane agitation from 37% to 11% without delaying discharge [11].

Also in agreement with our results Kawaraguchi et al. who used ketamine 1 mg/kg intravenously after induction of sevoflurane anesthesia in 55 children undergoing strabismus surgery. Children were classified into three groups; ketamine, pentazocine, and flurbiprofen. Ketamine group received ketamine 1 mg/kg intravenously, followed by infusion of ketamine 1 mg/kg/h during surgery, pentazocine group received pentazocine 0.2 mg/kg intravenously after induction of anesthesia, and flurbiprofen Group received intravenous flurbiprofen 1 mg/kg 15 min before the end of surgery. They found that

Table 2 Demographic data.

	C	M	K	MK	P value
Age (year)	5.58 ± 1.18	5.40 ± 1.22	5.92 ± 1.63	5.80 ± 1.09	0.41718
Weight (kg)	18.33 ± 4.43	18.10 ± 1.60	19.18 ± 4.76	19.37 ± 3.94	0.511
Sex (male/female)	16/14	15/15	16/14	17/13	0.966

Table 3 The parameters assessed in the four groups.

	C	M	K	MK	C and M	C and K	C and MK	M and MK	K and MK
Induction Time (minute)	4 ± 0.91	4.43 ± 2.09	3.98 ± 2.35	3.63 ± 1.37	0.402	0.965	0.222	0.084	0.436
Duration of anesthesia (minute)	27.63 ± 9.22	31 ± 9.82	29.79 ± 7.99	27.27 ± 8.48	0.172	0.336	0.875	0.120	0.602
Time up to spontaneous eye opening (minute)	3.98 ± 1.85	5.87 ± 2.83	6.46 ± 2.23	7.07 ± 2.84	0.0002	0.0001	0.0001	0.106	0.373
Time of stay in PACU (minute)	40.43 ± 5.56	37.09 ± 4.46	35.67 ± 2.76	34.67 ± 3.65	0.012	0.00001	0.0001	0.022	0.143

Table 4 Emergence agitation in the four groups.

	C		M		K		MK		C and M	C and K	C and MK	M and MK	K and MK
	4	5	4	5	4	5	4	5					
5 min	9	6 15/30 (50%)	6 6/30 (20%)	–	5	– 5/30 (16.7%)	4 4/30 (13.3%)	–	0.029	0.012	0.004	0.731	1
15 min	14	4 18/30 (60%)	9 9/30 (30%)	–	6	– 6/30 (20%)	5 5/30 (16.7%)	–	0.037	0.001	0.003	0.552	1
30 min	9	2 11/30 (36.7%)	7 7/30 (23.3%)	–	5	– 5/30 (16.7%)	3 3/30 (10%)	–	0.398	0.143	0.071	0.506	1

the incidence of agitation in ketamine group was less than that of flurbiprofen group and pentazocine group [12].

Also Kararmaz et al. found that 6 mg/kg oral ketamine given to children 30 min before adenotonsillectomy under desflurane anesthesia reduced EA incidence from 56% to 18% [16].

In agreement with our results, Dalens et al. showed a reduced incidence of EA in children given 0.25 mg/kg of ketamine administered intravenously at the end of MRI procedures under sevoflurane anesthesia (12% vs. 36% in the control group) [17].

Also administration of ketamine 0.25 mg/kg reduced EA in 85 children undergoing dental repair under sevoflurane from 34.2% in the control group to 16.6% in ketamine group [18].

In our study as regard the MK group we found that there were no significant difference between the MK group when compared with C group in the IT and DA. But there was significant difference when compared with the C group in time for spontaneous eye opening as it was longer at MK group and duration of stay in the PACU as it was shorter in the MK group this mostly explained by the more use of fentanyl in the C group to manage uncontrolled agitated children. Combination of melatonin and ketamine reduced the incidence of EA in children when compared to children in the C group at 5 min and 15 min.

As regard the melatonin and ketamine groups when compared to combination of melatonin and ketamine in half doses there was no significant difference as regard IT, DA, Time up to spontaneous eye opening and EA. Only time of stay in PACU was significantly longer in the M group when compared with MK group.

6. Conclusion

Melatonin and ketamine were effective in the management of EA. The combination of half doses of them was equally effective in reducing EA as the use of each of them alone without any additional improvement in IT, DA, time up to spontaneous eye opening but shorter PACU stay was noticed in children received the combination than those received melatonin only which may attributed to the need of more use of fentanyl in uncontrolled agitated children in melatonin group which need longer follow up.

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