ORIGINAL ARTICLE

Oral midazolam plus ketamine compared to midazolam only to reduce agitation in children undergoing urological surgery after sevoflurane anesthesia

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ABSTRACT

Background and objectives: Sevoflurane is widly used in pediatric anesthesia as children tolerate it well, but it often gives postoperative agitation**.** The objective of this study was to test the effect of small doses of ketamine together with midazolan in reducing agitation from sevoflurane in children.

Methodology: We enrolled 80 children from 3-10 years old, undergoing urological surgery under general anesthesia, in this randomized double blind prospective study. Participants were randomly divided into two groups. The first group (Group M) received midazolam 0.5 mg/kg orally and the second group (Group KM) received oral midazolam plus ketamine 2 mg/kg. For general anesthesia, we used sevoflurane. Induction was done with fentanyl, thiopental and sexamethonium and then the patient was intubeted. Five different levels were used to measure the degree of agitation. Agitation was managed by fentanyl 1 μg/kg IV and total dose used was noted.

Results: The demographic data were statistically equivalent in both groups. There was no significant difference between two groups regarding awakening period or hospital discharge. Patients in Group KM had a significantly lower agitation score compared to Group M. (Mann Whitney T=15; $p<0.01$). Fentanyl consumption was significantly greater in Group M compared to the Group KM.

Conclusion: Adding small doses of ketamine by mouth beside midazolam reduces episodes of agitation after sevoflurane anesthesia in children undergoing urology procedures without delaying hospital discharge.

Key words: General anesthesia; Urology surgery; Fentanyl; Sevoflurane; Postanesthesia agitation

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INTRODUCTION

Sevoflurane is widely used in pediatric anesthesia because it is well tolerated by inhalation, gives fast induction and recovery, has lower level of hepatic toxicity and offers hemodynamic stability. Regardless of its advantages, there is a growing concern that sevoflurane causes postanesthesia agitation (PAA) in pediatric patients. Research shows that the incidence of agitation may be as high as 67%. Both desflurane and sevoflurane, which are more insoluble agents, have been associated with a higher level of postoperative emergence agitation as compared to halothane and propofol.[7,8-20]

Agitation in children can present as disorientation in time and place, confusion, and decreases child's level of responsiveness. Furthermore, it causes hypersensitivity to pain and motor hyperactivity in the immediate post procedure period. These changes can lead to serious complications including removal of surgical dressings, contaminating the wound, and removal of IV lines and/or Foley catheter. A situation like this is unacceptable by parents or attendants. Regardless of the use of anti-anxiety medication and analgesics, nothing has been effective in preventing agitation in children who received sevoflurane as an anesthetic. This complication may also lead to extended hospital stay and delayed recovery. Midazolam

and/or ketamine are widely used in pediatric anesthesia and are found to decrease emotional trauma, and secure gradual induction but their ability to decrease agitation has been controversial.[21-24]

The objective of this study is to discover the effect that ketamine has on agitation post surgery when ketamine is used with midazolam on children that used sevoflurane and are undergoing urology procedures, compare with cases when children used only midazolam.

METHODOLOGY

This study took place in UHC Mother Teresa for one year from September 2012-September 2013. In the urology clinic participants of this study were 80 healthy children between 3-10 years of age, operated in our clinic with no other active disease. All clinical and lab readings were within normal limits. Participants had urology surgery using general anesthesia. Participants were randomly divided into two groups, the first group, Group-M, received midazolam 0.5 mg/kg and the second group (Group-KM) received midazolam and ketamine 2 mg/kg.

Children with mental developmental problems such as Down syndrome and epilepsy were not included on the study. On the pre-op visit weight of all children was recorded to effectively calculate pre-medication dose. The drugs for pre-medication were prepared by one of the anesthesiologists in a syringe and was given to the nurse. With parents' cooperation this medication was given to children on the morning of the scheduled surgery. Anesthesia was induced with sevoflurane for 1-2 min, IV line established and atropine 0.015 mg/kg, fentanyl 1μg/kg, thiopental 8 mg/kg, and suxamethonium 1 mg/kg given and endotracheal intubation performed. Maintenance of anesthesia was carried with sevoflurane in O_2 and N_2O. After intubation 0.01 mg/kg pancuronium and ketoprofen were given to the child. All participant were continuously monitored with EKG, pulse oximeter and non-invasive arterial blood pressure every 5 min. At the end of the procedure sevoflurane was discontinued, O_2 100% started and muscle relaxation was reversed with neostigmine and atropine.

Statistical analysis: Statistical analysis of the data was performed using SPSS-11 software. Continuous variables were compared by means of t-test. Chi square was used to compare the proportions between variables and Mann-Whitney test was used to compare the score between groups. Statistical significance was set for $p \leq 0.05$. All tests are two-tailed.

able 1: Preoperative behavior scales

Acceptance score (palatability)	
Good	1: Readily accept
	2: Dislike but accept
Poor	3: Held down/forced to accept
	4: Refuses to open mouth after tasting

Table 2: Agitation level scale

Agitation level score	Description
1	Deep sleep not responding to stimulant
2	Sleeping, but responsive to stimulant and movement.
3	Awake and responds normal.
4	Crying and very difficult to comfort.
5	Unacceptable behavior, pt wild and dangerous Can be stopped only if is restrained.

Once the patients were out of the operating room the parents were required to stay with them.
To manage agitation we used fentanyl 1μ/kg IV.

RESULTS

The demographic data of the patients e.g. age, weight, sex of the patients and the duration of the operation in minutes is shown in Table 1. The mean duration of the surgery was 84.27 ± 17.02 in the midazolam group and 85.6 ± 23.31in ketamin plus midazolam group. The average age was equivalent in both groups 4.15 ± 1.07 vs. 4.18 ± 1.1 in the midazolam group vs. ketamine plus midazolam group respectively.

There was statistically no difference in average weight in the groups 18.5 ± 3.4 vs. 18.2 ± 3.1 (P 0.8). Similarly M:F ratio was equivalent in both groups (Table 3).

Table 3: Demographic data

Parameter		Group M N 40	Group KM N 40	test	p-value
Age in years (Mean ± SD)		4.15 ± 1.07	4.18 ± 1.1	t= -0.12	0.8
Weight in kg (Mean ± SD)		18.5 ± 3.4	18.2 ± 3.1	t= 0.41	0.5
Gender	Male	29 (72.5%)	28 (70%)		
	Female	11 (27.5%)	12 (30%)	χ^2=0	0.8
Surgery procedure in min (Mean ± SD)		84.27 ± 17.02	85.6 ± 23.31	t= -0.29	0.7

No statistical difference was observed between two groups with regard to baseline characteristics e.g. age, gender, weight and the health status of the children as well as the length of surgical procedures.

Table 4: Comparison of agitation level and fentanyl consumption between two groups

Parameter	Group M	Group KM
Fentanyl consumed (ug) (Mean±SD).	7.5±10.12	1.4±1.2
Agitation level		
Score 1	4	1
score 2	5	0
score 3	3	1
score 4	3	1
score 5	10	2

t-test = 3.7 p<0.001

Fentanyl consumption was significantly greater in Group M compared to the Group KM.

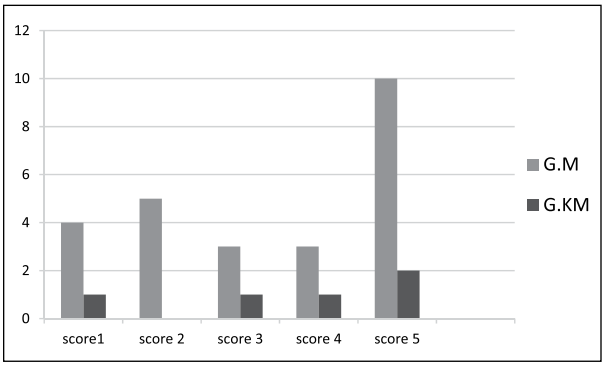

Figure 1. Comparison of agitation level between two groups

Mann Whitney T=15; p<0.01

Patients in Group KM had a significantly lower agitation score compared to Group M. (Mann Whitney T=15; p<0.01).

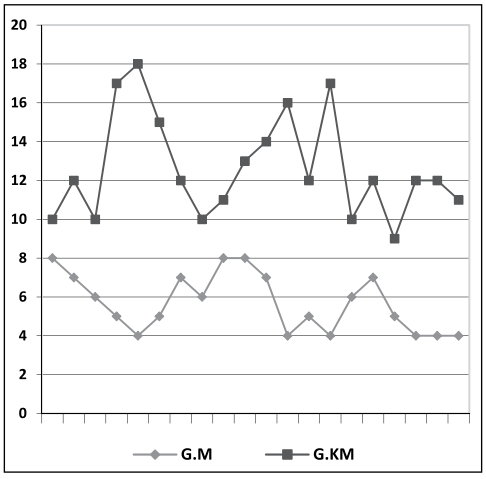

Figure 2: Time period that patients opened the eyes (min)

t = -14.6; p<0.001

The time period to open the eyes was greater among the patients in the Group KM (*t* = -14.6; p<0.001) but not significant statistically. The amount of fentanyl used was also more in the Group M compared to Group KM.

DISCUSSION

Even though there is an increased[3] level of postanesthesia agitation level with the use of sevoflurane, in the majority of cases the agitation level decreases after 20-30 min and children recovered by themselves. Pain could be a cause of agitation as well.[4] It has been seen that the intra-operative administration of non steroidal anti-inflammatory agents[5] decreases agitation due to sevoflurane. Use of clonidine, dexmedetomidine, and fentanyl has been proven to decrease agitation after anesthesia with sevoflurane. Agitation may be associated with pain, as there is evidence that it is reduced when both groups receive ketoprofen for pain. Agitation after propofol[6] has shown to be less severe and patients recover faster compared with to sevoflurane. Increased agitation level with the use of sevoflurane is explained with the effect of the gas on nervous system, especially in children. Episodes of epilepsy have been noted in the post-anesthesia period with sevoflurane in non-epileptic children. This reaction can be connected with the fast accumulation of sevoflurane in the brain. When γ-aminoabutric acid ergcproperties and sevoflurane can cause changes in balance between and innervations of synaptic neurons. Ketamine is an NMDA receptor antagonist and it can stop "wind up phenomenon" (central sensitization) on the spinal neurons.[7] Exactly in this effect are ketamine's analgesic, amnesic, psychomimetic and neuroprotective effects connected.[8] To some extent oral preventive use of ketamine gives a better analgesic effect compared with the group that received only midazolam; and it also leads to decreased post-anesthesia agitation level with sevoflurane. Some previous studies also mentioned this effect of ketamine and the use of ketamine as a preventive agent in pediatric anesthesia. In these studies ketamine was not used by mouth but by parenteral route, which can lead to high and fast build-up of concentration in the brain and may present with the side effect of this medication.

Limitations: A small sample size of the patients makes the significance of this study limited but it may serve to supplement other studies that have discussed the use of ketamine as a preventive measure for post-anesthesia agitation associated with sevoflurane.

CONCLUSION

Ketamine use, beside oral midazolam as pre-medication in children undergoing urology procedures decreased post-anesthesia agitation incidence when sevoflurane is used as inhalational agent without delaying recovery process or hospital discharge.

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Anesthetic aphorisms

DRUGS

- All 1 ml ampoules look the same – check very carefully.
- Always label all syringes.
- Atropine and adrenaline (epinephrine) are often stored next to each other.
- Suxamethonium can easily be given in error for all drugs found in 2 ml syringes. All unused drug drawn in a syringe must immediately be discarded.
- Thiopentone solution can look like augmentin and antibiotics do not induce anesthesia.
- Put the label on the syringe at the volume you fill it. You can check later how much you have given.
- Intravenous drugs go into veins so color code the three-way taps. Blue for venous, red for arterial. If the cannula has a filter it is in the epidural space!
- For a rapid sequence induction always have two doses of suxamethonium ready in case one goes over the floor/ ceiling etc.