

COMPARISON OF ORAL CLONIDINE WITH ORAL MIDAZOLAM IN MANAGING AGITATION FOLLOWING SEVOFLURANE ANESTHESIA: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLINDED STUDY

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ABSTRACT

Objective: Emergence agitation is a major problem during recovery from anesthetic agents like sevoflurane, particularly in children. This study had compared the effects of oral clonidine with oral midazolam in reducing the incidence of emergence agitation following sevoflurane anesthesia.

Methods: A total of 50 children of ASA Status I and II aged between 3 and 8 years were randomly allotted to one of the two groups, each group comprising 25 children. Group I children were given oral midazolam 0.5 mg/kg and Group II children were given oral clonidine 4 mcg/kg 30 minutes before the induction of anesthesia. The emergence reaction was analyzed using modified objective pain scale in all children following sevoflurane administration.

Results: The total agitation score was significantly less in clonidine group in comparison to midazolam group during the 1st hr of post-operative period ($p < 0.05$). No remarkable change in the hemodynamics or oxygen saturation was observed in both groups.

Conclusion: Premedication of oral clonidine 4 mcg/kg is superior to oral midazolam 0.5 mg/kg in reducing the incidence of emergence agitation following sevoflurane anesthesia.

Keywords: Sevoflurane, Recovery, Emergence agitation, Clonidine, Midazolam.

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INTRODUCTION

Although sevoflurane has good properties like quicker induction and recovery, making it an ideal agent for children, it has some drawbacks of which emergence agitation is worth mentioning because it is common during recovery period [1]. Disorientation, hypersensitivity to stimuli and hyperactive motor behavior are the characteristics of this emergence reaction [1]. The exact cause for this reaction is not known. It is believed that pain is a contributing factor since analgesics reduce the incidence of this emergence reaction [2,3]. Restless recovery from anesthesia may not only cause injury to the child or to the surgical site but may also lead to accidental removal of surgical dressings, intravenous catheters, and drains. Additional nursing care may often be necessary as well as supplemental sedative and/or analgesic medications, which may delay the discharge from the hospital. Clonidine, an alpha 2 agonist, has both sedative and analgesic effects [4,5]. Intravenous administration of clonidine, after induction of anesthesia reduces the incidence of emergence reactions following sevoflurane administration [6-8]. Tropisetron, the serotonin antagonist, used as an anti-emetic, also found to be useful in reducing the incidence of the emergence agitation following sevoflurane anesthesia [9]. Midazolam, which is a short-acting benzodiazepine, is commonly used as pre-medication to reduce pre-operative anxiety and for smooth induction of anesthesia. However, its efficacy in reducing the emergence reactions following sevoflurane anesthesia is questionable [10-12].

This study was done to assess the effect of oral midazolam in reducing the emergence reaction of sevoflurane in comparison to oral clonidine and also the effects of these two drugs on the hemodynamics and oxygen saturation during the perioperative period.

METHODS

After approval from the ethical committee of the institute, this study was conducted on 50 children, randomly divided into two groups of 25

each as per the inclusion/exclusion criteria to assess the efficacy of oral clonidine and oral midazolam in the prevention of sevoflurane-induced agitation in children during the post-operative period. The study was conducted in a medical college in south India from December 2008 to July 2010.

Inclusion criteria

A total of 50 children of ASA Status I and II aged between 3 and 8 years who were undergoing circumcision, tonsillectomy, adenoidectomy, myringotomy and herniotomy.

Exclusion criteria

1. Patients of ASA Status III and IV
2. Family history of malignant hyperthermia, mental retardation, and a history of agitation or any other neurological disease, potentially associated with symptoms of agitation.

After approval from the Institute Ethical Committee, this study was conducted on 50 children as per the inclusion/exclusion criteria. After obtaining the written informed consent from the parent, the children were randomly allotted into one group - Group I or II, by block randomization method.

After a fasting period of 6 hrs, Group I children were given oral midazolam 0.5 mg/kg and Group II children were given oral clonidine 4 mcg/kg 30 minutes before the induction of anesthesia. This premedication was mixed with 3 ml of sugar syrup/juice. Anesthesiologist involved in the study was blinded to the premedication.

After connecting the monitors (electrocardiogram, non-invasive blood pressure and pulse oximeter), anesthesia was induced by a single breath induction method using sevoflurane (8%) in a 50:50% mixture of nitrous oxide and oxygen with a fresh gas flow of 6 L/minute. For children weighing ≤ 20 kg, Jackson-Rees circuit was used, whereas in

children weighing ≥ 20 kg, circle system was used. After achieving adequate depth of anesthesia (Guedel phase 3), the inspired sevoflurane concentration was reduced to 4%.

After securing intravenous cannulation, injection glycopyrrolate 10 mcg/kg was given intravenously. Injection succinylcholine 2 mg/kg was given to facilitate endotracheal intubation with appropriate size. Injection fentanyl 2 mcg/kg was given before incision and inspired sevoflurane concentration was adjusted to 1.5%. All the children were given paracetamol 30 mg/kg body weight in suppository form at this point.

At the beginning of skin closure, sevoflurane concentration was reduced to 0.7% and was stopped at the time of last suture, while maintaining a 50:50% mixture of nitrous oxide and oxygen until the end of the wound dressing. Systolic and diastolic blood pressure, heart rate and oxygen saturation were measured every 5 minutes throughout the procedure. The child was allowed to breathe 100% O₂ until complete recovery of reflexes.

Systolic and diastolic blood pressure, heart rate and oxygen saturation were measured every 10 minutes for a period of 2 hrs in the post-operative period. In addition, all the children were evaluated for the state of agitation as per the modified objective pain scale [13], every 15 minutes in the recovery room during the 1st hr after surgery, in the presence of one of the parents. The full objective pain scale included five criteria, namely, the blood pressure, crying, agitation, behavior, verbal or body expressions whereas the modified objective pain scale constituted only three [14,15]. Tears (crying), movements (agitation), behavior were those three criteria used in the modified scale. Each criterion has scores from 0 to 2, so the maximum score possible is six. Total score of three or more is considered as agitation (Table 1).

Statistical analysis

Proportion, mean and standard deviation were used as descriptive statistics. Independent *t*-test was used for inferential statistics. All analyses were carried out using EPI INFO 6 version.

RESULTS

A total of 50 patients were recruited for this study of these 27 males and 23 females. The gender distribution was 12 males and 13 females in Group I and 15 males and 10 females in the Group II. The mean values for age and weight did not differ significantly between groups.

Table 1: The modified objective pain scale

Score	
Tears	
Absent	0
Present, but child can be consoled	1
Present and child cannot be consoled	2
Movements	
Absent	0
Moderate agitation (does not sit still)	1
Intense agitation (risk of trauma)	2
Behavior	
Sleeping or calm	0
Grimacing, trembling voice, can be calmed down	1
Frightened, sticks to parents, cannot be calmed down	2

Table 2: Comparison of modified objective pain scores of patients given midazolam and clonidine

Time	Total agitation score with midazolam		Total agitation score with clonidine		p	t	dz
	n (%)	Mean±SD	n (%)	Mean±SD			
15 minutes	25 (100)	3.96±1.21	25 (100)	1.92±0.76	0.0001	7.14	48
30 minutes	25 (100)	3.16±0.85	25 (100)	1.40±0.82	0.0001	7.54	48
45 minutes	25 (100)	2.72±0.94	25 (100)	1.08±0.86	0.0001	6.45	48
60 minutes	25 (100)	2.28±0.94	25 (100)	0.80±0.82	0.0001	5.90	48

The pre-operative hemodynamic parameters heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation did not differ significantly between groups.

There were no remarkable events like severe tachycardia or bradycardia, hypotension or hypertension, fall in saturation observed in both the groups.

The total agitation score was significantly less in clonidine group in comparison to midazolam group during the 1st hr of post-operative period (Table 2).

DISCUSSION

This was a prospective, randomized, double-blinded, comparative study. Our study has demonstrated that oral clonidine at a dose of 4 mcg/kg is more effective than oral midazolam of 0.5 mg/kg in preventing the post-operative agitation following sevoflurane anesthesia. Tazeroualti *et al.* had done a study on 68 children to compare the effects of oral clonidine with oral midazolam in preventing the sevoflurane-induced agitation [15]. They found that the modified objective pain score was significantly lower in the clonidine 4 mcg/kg group (median score 3) when compared to clonidine 2 mcg/kg (median score 5.5) or midazolam 0.5 mg/kg (median score 6.5) groups. They had also observed that the proportion of children with agitation in the 1st hr of recovery was significantly lower in the clonidine 4 mcg/kg group compared with midazolam group. The results of our study fairly correlate with that of Tazeroualti *et al.* [15]. We had not studied the prolonged agitation unlike them. They found that the proportion of children with prolonged agitation (agitation lasting for more than 15 minutes) was also significantly lower in the clonidine 4 mcg/kg group.

Bergendahl *et al.* had compared the effects of midazolam 0.3 mg per kg with clonidine 5 mcg/kg administered rectally as premedication [16]. They observed that clonidine group had significantly lower objective pain scale score. Our results also correlate with them although the route of administration was different. Almenrader *et al.* had done a study comparing the effects of oral midazolam 0.5 mg/kg with oral clonidine 4 mcg/kg in children [17]. They observed that clonidine was superior in acceptance, anxiolysis, recovery profile and parental satisfaction although the anesthetic agent was not specific like in our study which was sevoflurane. Kulka *et al.* also observed that clonidine significantly reduces the incidence and severity of post-operative agitation in children after sevoflurane anesthesia and also safe [6]. However, they had used clonidine intravenously 2 mcg/kg and also after the induction of anesthesia.

Lankinen *et al.* had done a study comparing the effects of intravenous clonidine 1.5 mcg/kg and tropisetron 0.1 mg/kg and found that tropisetron was more effective in reducing the incidence of emergence agitation after sevoflurane anesthesia [9]. We think that it could be due to the dosage of clonidine because intravenous clonidine 2 mcg/kg was effective according to Kulka *et al.*, Tesoro *et al.* and Malviya *et al.*, although it was compared with placebo [6-8].

Thus, we believe that oral clonidine is better than oral midazolam in preventing the emergence reaction following sevoflurane anesthesia. This is noteworthy because the incidence of emergence reaction following sevoflurane administration is significant [18]. Indeed, the

incidence of emergence delirium is more with sevoflurane than with desflurane administration, although desflurane produces quicker recovery [19].

The limitation of our study is that we did not evaluate the mask acceptance, anxiolysis and parental satisfaction.

CONCLUSION

We conclude that premedication of oral clonidine 4 mcg/kg is superior to oral midazolam 0.5 mg/kg in reducing the incidence of emergence agitation following sevoflurane anesthesia.

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