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Original Article

Effect of Midazolam and Propofol in Prevention of Emergence Agitation in Paediatric Patients Under Sevoflurane Based Anaesthesia: A Comparative Study

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Abstract
Introduction: *Sevoflurane is the most commonly used inhalational anaesthetic agent in paediatric setup. The incidence of emergence agitation (EA) is high in children after sevoflurane anaesthesia. The efficacy of propofol and midazolam in preventing EA remains debatable. This study was conducted to compare the effects of administration of a single dose of propofol or midazolam on sevoflurane-based general anaesthesia on EA during the recovery period.*
Methods: *One hundred and thirty two children, ASA I-II, aged 2 to 10 years undergoing abdominal and urogenital surgeries were enrolled in this prospective,double blind study. Children were randomly allocated to receive propofol 1 mg/kg (group P, n=66) or midazolam 0.1 mg/kg (group M, n=66) 5 minutes before the end of surgery. Aonosfour point scale and Paediatric Anaesthesia Emergence Delirium (PAED) scale were used to evaluate the incidence and severity of EA, respectively.*
Results: *The incidence of EA in group M was 43.9% (29/66) and 83.3% (55/66) in group P. PAED scores were significantly lower in group M. Duration of PACU stay was delayed in group P than in group M.*
Conclusion: *Administration of midazolam (0.1 mg/kg) prevents incidence and severity of EA more effectively than propofol (1 mg/kg)in paediatric patients receiving sevoflurane based general anaesthesia.*
Keywords: *children, emergence agitation, midazolam, propofol, sevoflurane.*

Introduction

Sevoflurane is a volatile inhalational anaesthetic agent with low pungency, non-irritant odour and a low blood : gas coefficient. This is widely used in paediatric patients due to fast and well tolerated induction, low hepatotoxicity, hemodynamic stability and rapid emergence from anaesthesia. Emergence agitation (EA) in children after sevoflurane anaesthesia is very common, with a reported incidence from 10 – 80 %.[1]

The exact cause of EA is unknown but several risk factors may be encountered such as intrinsic characteristics of an anaesthetic, rapid emergence from anaesthesia, postoperative pain, preschool

age, preoperative anxiety and child temperament.[2] Multiple randomized controlled trials revealed that EA occurred more frequently with sevoflurane than other inhalational agents.[3] Different drugs such as propofol, α_2 adrenoreceptor agonists, midazolam and ketamine have been used to allow a smooth emergence from sevoflurane anaesthesia. However, their efficacy remains the subject of debate.

Based on previous studies, propofol seems to be effective in preventing EA.[4] Midazolam is reported to significantly reduce EA frequency after sevoflurane anaesthesia in paediatric surgery and non-surgical procedures.[5]This study was conducted to compare the effects of administration of a single dose of propofol or midazolam on sevoflurane based anaesthesia on the incidence and severity of EA as well as emergence and discharge time in children.

Methods

After institutional review board approval and written informed consent from parents, 132 healthy children of either sex, aged 2 to 10 years, with American Society of Anaesthesiologists (ASA) physical status I or II, scheduled to undergo abdominal and urogenital surgeries under general anaesthesia using sevoflurane. The patients were randomized in two groups using computer generated randomization table : group P (patients receiving propofol) and group M (patients receiving midazolam). Children were fasted for 6 hours before the procedure; clear liquids were permitted until 2 hours prior to surgery. After establishment of intravenous access, an electrocardiogram, pulse oximeter and non-invasive arterial blood pressure monitor was attached. Ondansetron 0.15 mg/kg i.v was given. General anaesthesia was induced with 8 vol % sevoflurane in 70% nitrous oxide in oxygen, via a facemask and atracurium 0.5 mg/kg i.v. Orotracheal intubation was performed and maintained with 60% nitrous oxide in oxygen and sevoflurane 2-2.5 vol% and intermittent doses of atracurium . Mechanical ventilation was done to maintain an end-tidal carbon dioxide ($EtCO_2$) between 30 and 35 mm Hg. All patients was given 15 mg/kg i.v paracetamol for the control of post-operative pain.

Around 5 minutes before the termination of surgery, patients in group P received propofol 1 mg/kg while patients in group M received midazolam 0.1 mg/kg. Towards the end of surgery after discontinuation of sevoflurane and nitrous oxide, residual muscle relaxation was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/kg for every 1 mg of neostigmine. Extubation was performed when the patients' gag reflex was restored and showed facial grimaces or purposeful motor movements, and the rate of train of four (TOF) was higher than 0.8 by a nerve stimulator (TOF-Watch, Organon, Ireland).

Children were transferred to the post anaesthesia care unit (PACU) where one of their parents/guardian was allowed to stay with them until discharge.

All above i.v agents was prepared, hidden behind drapes and administered by one resident anaesthesiologist according to the group to which the patient was randomized. The data was collected by another resident anaesthesiologist who was blinded to the group to which the patient was assigned in the PACU.

The incidence of EA was evaluated using Aonos four point scale: 1=calm; 2=not calm but could be easily consoled; 3=moderately agitated or restless and not easily calmed; 4=combative, excited, or disoriented, thrashing around. The severity of EA was evaluated using Paediatric Anaesthesia Emergence Delirium (PAED) scale, a five-point rating scale with five grades for each item. The incidence and severity of EA was measured upon admission to the PACU (T0) and in the PACU at 5 min (T5), at 15 min (T15) and 30 min (T30). Any adverse events such as respiratory depression, urinary retention, pruritus, hypotension, bradycardia, vomiting, laryngospasm, bronchospasm and oxygen desaturation were noted. Vomiting was treated with ondansetron 0.15 mg/kg. Thirty minutes after

entry into PACU, the agitated children were managed by giving intravenous increments of fentanyl 1 μg/kg with at least a 10 min time interval between each dose. Children were considered severely agitated if they had a PAED scale of 15/20 or higher. Children were discharged from the PACU when the modified Aldrete score was more than nine without agitation and vomiting.

Statistical Analysis

By using statistical program for social science (SPSS) software for windows, version 11 (SPASS Inc, Chicago, IL, USA), arithmetic mean and standard deviation values for different variables were calculated and statistical analyses were performed for each group. Independent sample t-test was used to compare continuous variables exhibiting normal distribution, and Chi-squared or Fisher exact test for non-continuous variables. Serial measurements such as PAED scores were reported as mean and inter quartile range and analysed by Mann-Whitnney U test. $P<0.05$ is considered significant.

Results

There were no significant differences ($p>0.05$) between demographic characteristics like age, sex, weight and ASA status. Similarly, the duration of surgery and sevoflurane administration were similar. Incidences of EA were significantly lower in group M than in group P. Statistically and clinically, number of patients suffering from EA were more in group P than in group M. However at T30, the difference was not significant.

The severity of EA as measured by PAED score was also significantly less in group M than in group P.

Incidence of nausea and vomiting were lower in group M.

However, frequency of children treated with fentanyl for post-operative pain were comparable between the two groups. Duration of PACU stay was lower in group M.

Comparison of Demographic chacteristics and anaesthesia details(n=66)

	Group M	Group P	*P*
Age(yrs)	8.78±1.05	8.89±1.24	0.58
Sex(M:F)	32:34	40:26	0.64
ASA status(I:II)	61:05	58:08	0.34
Body weight(kg)	19.87±3.14	20.34±4.12	0.46
Surgery time(min)	52.12±10.12	54.64±8.54	0.12
Sevoflurane administration time(min)	58.34±8.04	60.54±6.78	0.09

Data presented as mean±SD. Group M received 0.1mg/kg Midazolam and Group P received 1mg/kg Propofol. ASA=American society of anesthesiologists, SD=Standard deviation

Comparison of Emergence Agitation with time (n=66)

	Group M	Group P	*P*
Incidence of emergence agitation with time			
T_0	18	28	0.025
T_5	6	13	0.027
T_{15}	3	9	0.029
T_{30}	2	5	0.051
PAED score with time			
T_0	**10.6±1.2**	**14.1±1.6**	**0.001**
T_5	**6.8±0.3**	**8.4±1.2**	**0.030**
T_{15}	**3.5±0.4**	**5.8±0.2**	**0.002**
T_{30}	**2.7±0.8**	**3.1±0.5**	**0.112**

Group M received 0.1mg/kg Midazolam and Group P received 1mg/kg Propofol. The severity of emergence agitation was assessed with PAED scale upon admission (T0), after 5 min (T5), 15 min (T15) and 30 min (T30). SD=Standard deviation, PAED=Pediatric anesthesia emergence delirium

Comparison of PACU management parameters (n=66)

	Group M	Group P	*P*
No of children complaining of nausea ,vomiting	9	15	0.040
Ondansetron used to control nausea and vomiting	4	9	0.059
No of children treated with Fentanyl for analgesia	3	6	0.267
Duration of PACU stay (min)	74±2.3	81±1.6	0.001

Group M received 0.1mg/kg Midazolam and Group P received 1mg/kg Propofol.Data presented as mean±SD. SD=Standard deviation, PACU=Postanesthesia care unit

Discussion

EA may arise as a serious problem in paediatric surgery because EA itself and its treatment using sedatives or analgesics may cause undue delay in patient discharge. Extended hospital stay is a problem for both patients and their caregivers. Therefore several medications have been used for prevention of EA to provide efficient and high quality care.[3] Among these drugs, propofol and midazolam have shown promising results.

In this prospective, double blinded trial, we have compared the effects of propofol 1 mg/kg and midazolam 0.05 mg/kg administered 5 minutes before end of surgery on incidence, severity of EA, duration of PACU stay and no. of children treated with fentanyl and ondansetron.

Demographic profile of patients were statistically insignificant between two groups. This finding was quite similar to other research investigations.

In our study, incidence and severity of EA was significantly lower in group M than in group P. Similarly, Chen J*et al*[6] found in their study that administration of a subhypnotic dose of midazolam just before discontinuation of sevoflurane anaesthesia was better than propofol. They concluded that midazolam was more effective in decreasing the incidence and severity of EA in children undergoing cataract extraction without significant delay in recovery time and discharge.

Abu-Shahwan's study[4]on children undergoing magnetic resonance imaging (MRI) reported that propofol was effective in reducing EA. Incidence of EA at T5 was found to be 9% in group M and 19.6% in group P. However, both the groups were comparable at T30.

In our study, PAED scores were significantly lower in group M than in group P. This is similar to the study conducted by Kim YH *et al.*[7] He reported that propofol 1mg/kg administered during strabismus surgery under sevoflurane anaesthesia did not reduce EA in children.

Duration of PACU stay was significantly delayed in group P than in group M.

Nausea and vomiting was found in both groups but the incidence was significantly lower in group M. When compared to number of children treated with fentanyl, results were insignificant among the two groups.

One of the limitations of our study was the absence of a placebo group. This idea was rejected as administering no premedication could lead to severe EA. Secondly, parental presence had to be allowed during recovery at PACU. Another major limitation was the difficulty in differentiating between pain and delirium.

There is a need to further investigate the effects of different doses and methods of administration to examine the effects of propofol and midazolam on emergence agitation in children receving sevoflurane based general anaesthesia.

Conclusion

Administration of midazolam (0.1 mg/kg i.v) prevents incidence and severity of emergence agitation much more effectively than propofol (1 mg/kg) when administered 5 minutes before the end of surgery in children undergoing abdominal

or urogenital surgeries under sevoflurane anaesthesia. It also reduces the duration of PACU stay without producing any appreciable side effects.

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Conflicts of Interest: There are no conflicts of interest.

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