A Comparison of Postoperative Delirium in Children Undergoing Elective Herniorrhaphy Following General Anesthesia with Sevoflurane and Isoflurane

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Abstract

Introduction: Postoperative delirium and agitation is a distressing event that occurs in most children. This study aimed to compare of postoperative delirium in children undergoing elective herniorrhaphy following general anesthesia by sevoflurane and isoflurane.

Materials and Methods: In this double-blind randomized clinical trial, 50 children aged 2 to 6 years; candidates for inguinal herniorrhaphy were divided into two groups of general anesthesia induced by sevoflurane and isoflurane. Anesthesia was induced by administering 5-7 mg / kg sodium thiopental and 0.5 mg / kg atracurium. They were monitored every 10 minutes to 30 minutes for postoperative delirium (POD) using Pediatric Anesthesia Emergence Delirium (PAED) scale.

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Results: The POD frequency was in the isoflurane and sevoflurane groups 1 (4%) and 18 (72%), respectively and this difference was significant between two groups (P=0.001). According to PAED, the POD severity in isoflurane group was less than sevoflurane group at minute 10 (P = 0.001). Also, there was a significant difference between the two groups in terms of POD severity at minute 20 (P= 0.001). The highest POD severity was seen in the isoflurane group at minute 30 (P =0.001).

Conclusion: The results of the present study showed that the use of sevoflurane in the anesthesia maintenance phase for children less than 6 years of age leads to higher POD incidence as compared to isoflurane.

Keywords

- Sevoflurane
- Isoflurane
- Agitation
- Delirium
- Herniorrhaphy
- General anesthesia

Introduction

Postoperative delirium(POD) and agitation is a distressing event that occurs in most children in the pre-school age group immediately after anesthesia and its incidence is between 10 and 80% and is reported as a major clinical problem by 42% of pediatric.[1] Although these events are short-lived, they increase the likelihood of self-harm and delay patients' discharge and increase treatment costs.[2] The prevalence of POD increases when sevoflurane and isoflurane are administrated as less soluble anesthetics. These two compounds cause early analgesia after anesthesia and increase agitation. [3] Several factors should be considered in the occurrence of this agitation, including physiological and pharmacological factors, type of procedure and type of anesthetic, the degree of painful stimulation, and patient-related factors.[4] Recent studies have investigated the relationship between this agitation and pain, although in some cases, this relationship is not seen. The persistant sevoflurane-induced agitation during anesthesia has led many researchers to carry out studies to compare this agent with other anesthesia techniques in terms of their involvement in this agitation.[5] Various studies have shown that the risk of postoperative agitation is lower with propofol than sevoflurane administration.[6,7]

Postoperative agitation was first reported by Acken Hoff (1961) as a post-anesthetic event and refers to a state of confusion and impaired positioning accompanied by restlessness, involuntary movements, and instability[8], which is usually self-limiting and short-lived. This condition usually occurs in the first 30 minutes after anesthesia and usually lasts for a few minutes to a few hours and sometimes two days.[9,10] The incidence of postoperative agitation is reported to be between 5-15% and up to 80% in some studies.[11,12] Although self-limiting, it can be dangerous for the child and make the parents feel uneasy. A restless child removes his or her drains and can injure the caregiver. This restlessness also increases the likelihood of bleeding from the operation site, increases the incidence of postoperative behavioral disorders in the child (including anxiety, aggression, sleep disorders and eating disorders) and delays hospital discharge.[13]

Postoperative agitation risk factors include pre-school age, male patients, failure to prescribe inhaled anesthetics as premedications, type of surgery (ear, nose, throat and eye surgeries), failure to prescribe adequate analgesia to poorly adapted patients and children.[13] The main cause of postoperative agitation has not been known exactly. However, some possible causes include hypoxia, hypercarbia, hypoglycemia, pain, airway obstruction, increased intracranial pressure, medications, fear, anxiety, and the child's inherent mood.[10, 14] Isoflurane is a non-flammable liquid that is used as a vapor to create and maintain general anesthesia. Isoflurane activates the calcium-dependent ATPase in the sarcoplasmic reticulum. On the other hand, by acting on the receptors of glutamate, glycine and GABA, it creates the necessary conditions for anesthesia induction and continuation. This drug induces muscle relaxation and reduces pain sensitivity.[15] On the other hand; it changes the activity of the channels and the cell interactions, which affects the action potential of the cell. In general, these processes cause general anesthesia. The drug is used by inhalation and has a rapid onset of action (7-10 minutes). The duration of action of the drug is also short and depends on the amount of tissue blood flow. Isoflurane has a low hepatic metabolism and the metabolized drug is excreted in the urine.[16-18] Isoflurane may reduce mental function, which resolves within 2 to 3 days after taking the drug. Like other anesthetics, there are slight changes in the patient's mood that may continue for up to 6 days after taking the drug. Sevoflurane is a fragrant and non-flammable volatile anesthetic.[20]

Sevoflurane is used as an inhalation anesthetic to induce and maintain general anesthesia. Sevoflurane alters the activity of neural ion channels, especially synaptic neurotransmitter receptors such as nicotinic acetylcholine, GABA, and glutamate receptors. Sevoflurane is less blood soluble than isoflurane or halothane, but not desflurane. Its onset of action is 2 to 3 minutes and depends on the blood concentration. Its metabolism is hepatic (3-5%) via CYP2E1 to hexafluoroisopropanol and it is mainly excreted by respiratory exhalation and only 3.5% is excreted through the urine.[21, 22] Considering the extensive use of inhaled anesthetics in pediatric anesthesia, we decided to investigate this agitation in the use of sevoflurane and isoflurane and compare them with each other in order to achieve the best one with the least amount of postoperative agitation. The aim of the present study was to determine and compare the incidence of POD in children undergoing elective herniorrhaphy under general anesthesia with sevoflurane and isoflurane.

Materials and Methods

Study design

This randomized double-blind clinical trial study was performed on 50 children aged 2 to 6 years who were candidates for inguinal herniorrhaphy. Exclusion criteria including a history of mental and behavioral disorders at birth time, emergency surgery, surgeries lasting more than one hour, presence of active respiratory system disease, history of sleep apnea, febrile seizures, developmental disorders and heart disorders. According to the mean and standard deviation of PAED Scale at minute 10th in a previous study (15) (3.5 ±93.12 in the sevoflurane group and 9.46 ± 3.29 in the isoflurane group) with power=90% and 95% confidence interval and 20% drop out rate, the sample size was calculated 25 subjects in each group.

Procedure

After obtaining the permission and coordinating with the hospital officials, the research objectives were explained to the parents and their consent was obtained. Patients were divided into two groups; i.e. general anesthesia with sevoflurane and isoflurane. Patients were randomly assigned numbers 1 to 50 using random number tables. After initial monitoring including heart rate, pulse oximetry and ECG in the operating room, all patients received intravenous fentanyl (2 µg / kg) as a preoperative premedication. Midazolam was avoided as a drug that may inhibit postoperative agitation and delirium. Anesthesia was induced by prescribing 5-7 mg / kg sodium thiopental and 0.5 mg / kg atracurium. After intubation with endotracheal tube of appropriate size and ensuring proper ventilation and symmetry of both lungs' ventilation, the endotracheal tube was fixed. Anesthesia maintenance was performed using minimum alveolar concentration (MAC) of sevoflurane of 1.2 MAC (n = 25, group = S) and 1.2 MAC of isoflurane (n = 25, group = I) with 50% nitrous oxide and 50% oxygen. To double-blind the study, the observer anesthesiologist and the parents of the patients in each group did not know about the content of study groups. Also, the volatile anesthetics of sevoflurane and isoflurane were covered with a cloth during surgery so that the type of anesthetic could not be detected during the operation. Prior to surgical incision, patients were prescribed 25-50 mg diclofenac suppositories for analgesia. If the patient's intraoperative heart rate fluctuations were more than 20%, analgesia seemed to be insufficient and fentanyl was re-administered at a dose of 2 µg / kg. Intraoperative heart rate, pulse oximetry and capnography were monitored. Ondansetron was prescribed as an anti-nausea drug at a dose of 0.1 mg / kg, and the last prescribed atracurium was administrated 15 minutes before the end of surgery. Inhalation anesthetic was also discontinued at the end of the last surgical stimulation.

At the end of the operation and when observing the return of spontaneous respiration, patients were reversed with 0.02 mg / kg atropine and 0.04 mg / kg neostagmine and were extubated when observing regular breathing, targeted movements and opened eyes. After this stage, patients were transferred to the recovery room and monitored for postoperative agitation and delirium every

10 minutes to 30 minutes using PAED (19) by an anesthesiologist who was unaware of the study content. The maximum score of this table is 20. The PAED score >12 was considered as postoperative agitation and delirium. If the POD was severe which was resulted in hemodynamic disturbances or physical self-injury in the child, intravenous midazolam 0.015 mg / kg was administered.

Data Analysis

Continuous variables were reported as mean ± standard deviation (SD) and categorical data were reported as frequency and percentage. Chi-square test was used to compare the frequency of variables between the two groups. Independent t-test was used to compare the mean POD severity between two groups. Data analysis was performed using SPSS 17 software and P<0.05 was considered as the significance level.

Result

In this study 50 patients were analyzed (25 subjects in each group). In isoflurane group, 22 (88%) were boy and 3 (12%) were girl, and in the sevoflurane group, 18 (72%) were boy and 7 (28%) were girl. The mean age of children in the isoflurane and sevoflurane groups was 3.28 ± 1.36 and 3.54 ± 1.54 years, respectively. There was no statistically significant difference in age and sex between two groups (p>0.05) **(Table 1).**

Table1: Demographic characteristics of the participants

Variable		Group		p-value
		Isoflurane	Sevoflurane	
Age (years), mean±SD		3.28±1.36	3.54±1.54	0.53¶
Sex	Girl	3(12)	18(72)	
	Boy	22(88)	7(28)	0.15¥

¶: independent t-test. ¥: Chi-square test.

The frequency of POD in the isoflurane and sevoflurane groups was 1 (4%) and 18 (72%), respectively, there was a significant difference between two groups in terms of POD frequency (p = 0.001). The results showed that POD frequency had a significant difference between two groups by sex sub analysis. Among both boys and girls, the highest POD rate was observed in sevoflurane group (boys: 72.2%, girls: 71.4 %) and this difference was statistically significant between two groups (P = 0.001) **(Table 2).**

Table 2: Comparison of POD frequency between two groups by sex

		POD, n (%)		P-value¶
		Yes	No	
Total	Isoflurane Sevoflurane	1 (4) 18 (72)	24 (96) 7 (28)	0.001
Boys	Isoflurane Sevoflurane	1 (4.5) 13 (72.2)	21 (95.5) 5 (27.8)	0.001
Girls	Isoflurane Sevoflurane	0 5 (71.4)	2 (100) 2 (28.6)	0.03

¶: Chi-square test.

In both subjects with age <3 years and 3-6 years, the POD frequency was higher in Sevoflurane group than isoflurane group (P <0.05) **(Table 3).**

Table 3: Comparison of POD frequency between two groups by age groups

Age groups	Group	POD, n (%)		P-value¶
		Yes	No	
<3	Isoflurane Sevoflurane	0 7 (77.8)	10 (100) 2 (22.2)	0.001
3-6	Isoflurane Sevoflurane	1 (7.1) 11 (68.8)	14 (93.3) 5 (31.2)	0.001

¶: Chi-square test.

According to PAED, the POD severity in the isoflurane group was significantly less than the sevoflurane group at minute 10 (P = 0.001). Also, there was a statistically significant difference between two groups at minute 20 (P = 0.001). The highest POD severity was observed in the isoflurane group at minute 30, which was statistically significant (P = 0.001) **(Table 4, Figure 1).**

Table 4: Comparison of POD severity at minutes 10, 20, and 30 between two groups

Variable	Isoflurane	Sevoflurane	P-value¶
Minute 10	5.96±3.03	12.12±4.68	0.001
Minute 20	4.96±1.69	9.56±4.35	0.001
Minute 30	5.28±4.01	9.72±4.37	0.001

¶: independent t-test.

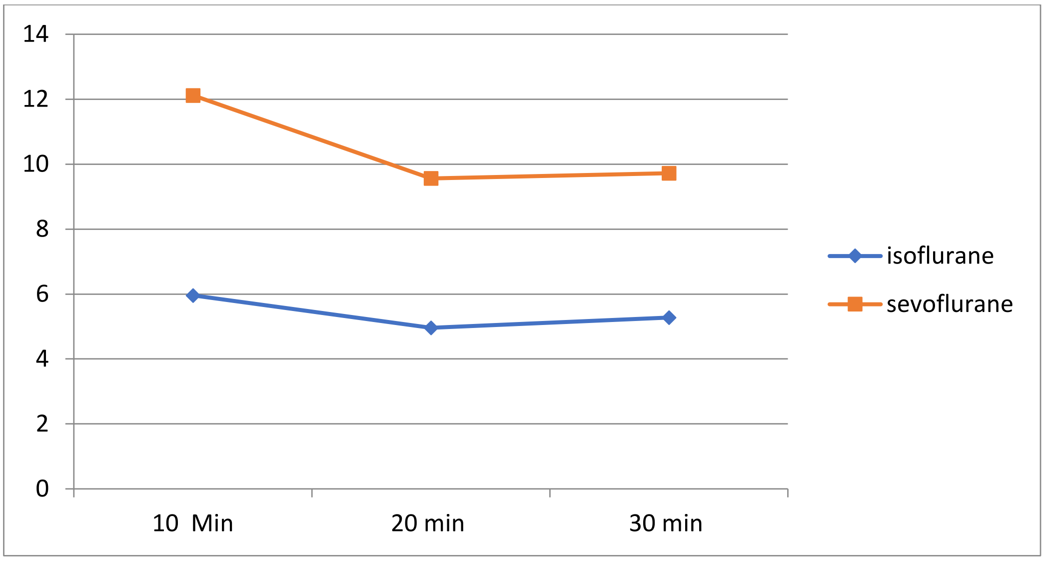

Figure 1: The POD severity rates in the two groups at minutes 10, 20, and 30

Discussion

Sevoflurane is the most common volatile anesthetic for anesthesia induction in children. However, the rate of awakening from sevoflurane anesthesia is directly related to POD in this group of patients.[22] Studies have shown higher POD incidence in pre-school age group, i.e. 2-6 years, and this complication is also seen in adults, especially older adults.[23] However, the high-risk group includes children aged less than 5 years.[24]

In our study, the POD incidence in the patients 3-6 years old was higher in sevoflurane recipients and, therefore, there is a correlation between these two variables, which can be due to emotional excitement in children, mental fatigue due to separation from parents, spending recovery period in an unfamiliar environment for the child. Some studies suggest that POD is more common in short-term surgeries due to the patient's quickly wake up before analgesics reach their peak effect.[13] In our study, the anesthesia duration was almost the same in all patients and, therefore, this variable was not investigated in the present study, and if the surgery was prolonged for any reason, those patients were excluded from the study. The preoperative anxiety had directly effect on postoperative behavioral problems.[25]

Results of a study of 791 children showed that a 10% increase in preoperative anxiety scores increased the POD risk by 10%, in order to reduce the POD incidence, various drugs have been recommended in addition to general anesthesia. These drugs include protocol, midazolam, ketamine, narcotics, and alpha 2 agonists including clonidine and dexmedetomidine.[26-30] These agents are prescribed before induction of anesthesia or at the end of surgery and clearly reduce the POD incidence. Another method is caudal analgesia, which reduces the POD severity and duration but has no effect on its incidence. However, this finding has been proven when comparing sevoflurane with halothane. In our study, the POD prevalence in the sevoflurane group is clearly higher than in the isoflurane group. To justify this finding, it can be stated that there is a direct relationship between the preoperative anxiety score and the POD incidence. Therefore, it is recommended to adopt strategies in this regard.

It is important to note that the type of surgery can also be effective as a confounding factor in causing POD. It can be stated that there are usually several risk factors for POD. There is no information regarding the reasons for elevated POD incidence rate in sevoflurane-induced anesthesia, but sevoflurane can stimulate the central nervous system because seizure-like activity on electroencephalography has been reported in some sevoflurane recipients who had no previous history of seizures.[31,32] The mechanism of sevoflurane-caused cortical seizures is unknown.[33] Some studies have suggested that low-solubility inhalation anesthetics normally increase the POD incidence, which may be due to the faster waking up from anesthesia induced by these inhalation anesthetics. However, this justification for faster wakening from general anesthesia drugs such as propofol does not apply to POD.[34] Therefore, it cannot be stated with certainty that the cause of POD depends on rapid wakening from anesthesia, although it has been stated in various studies that the administration of sedatives as a pre-medication before anesthesia can reduce anxiety and therefore reduce POD incidence.[35] Although routine benzodiazepines administration before anesthesia is useful, but in this study we did not administered because it could be as a confounding factor on POD evaluation. The data from our study showed that sevoflurane increases POD in children, and pediatric anesthesiologists should be aware of this risk. Stressful recovery periods after anesthesia alone cannot be harmful. However, it may cause the patient to commit self-injury or to remove clothing and vascular catheters. Parents will become doubly anxious when this POD occurs and they see their crying child, although this POD is self-limiting and resolves within 15 minutes. However, prescribing additional drugs to eliminate this condition can delay the patient's discharge from the recovery room and consequently, impose additional costs on the patient. The pediatric anesthesiologist should adopt methods to reduce the risk of POD following sevoflurane-induced anesthesia. Prescribing various drugs such as opioids, benzodiazepines, and alpha 2 agonists is helpful.[36, 38] another suggestion is propofol administration as an intravenous anesthetic.[34, 39] Also, and the effect of changing the maintenance phase of anesthesia using sevoflurane instead isoflurane has also been proven.[40-42]

Prior to the use of the PAED Scale to assess POD in children, there has been no reliable scale.[13] For example, the PAED Scale ≥ 10 was set as a point to define the presence or absence of POD in a study by Sikich et al.[13] Recent studies have stated that PAED Scale ≥ 12 has a higher degree of sensitivity and specificity for POD.[17, 43] Although this difference was not significant in the present study, we found that the highest PAED score was found in sevoflurane recipients 10 minutes after transfer to the recovery room. At this period, the number of patients with PAED≥ 12 was about 12.12% and was 5.96% in the isoflurane group. Although we used diclofenac supp as an analgesic, but one of the limitations of the present study was the presence of postoperative pain that could interfere with POD, which needs to be investigated and differentiated in future studies. It seems that in order to evaluate the POD incidence rate in both sexes, further studies with larger sample size should be designed.

Conclusion

The results of the present study showed that the use of sevoflurane in the anesthesia maintenance phase for children less than 6 years of age leads to higher POD incidence as compared to isoflurane. It is recommended to use sevoflurane in the maintenance phase of anesthesia be limited only for short-term surgery, and other inhalations or intravenous anesthetics such as total intravenous anesthesia (TIVA) are suggested to be used for anesthesia maintenance phase in long-term surgery.

Ethical Consideration

The present study has been approved by the Ethics Committee of Urmia University of Medical Sciences under the Ethics Code IR.UMSU.REC.1397.200. The study protocol has been registered in Iranian Registry of Clinical Trials under the number IRCT20170515033986N2. Consent form was received from the parents of all participants .

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Conflict of interests

There is no conflict of interest

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