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RESEARCH ARTICLE

AWAKENING PROPERTIES OF SEVOFLURANE AND ISOFLURANE IN PAEDIATRIC PATIENTS UNDERGOING SURGERY FOR SPINAL DYSRAPHISM

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ABSTRACT

Background: Isoflurane had always been known to have neuroprotective properties. Sevoflurane by virtue of its low solubility provides rapid onset and offset of an aesthesia, thus facilitating early postoperative evaluation of the patients especially in the neurosurgical procedures. However superior role of sevoflurane to isoflurane in pediatric patients requiring intermediate lasting anaesthesia remains controversial. Therefore the aim of this prospective comparative randomized study was to compare inhaled anesthetics sevoflurane and isoflurane in paediatric patients undergoing surgery for spinal dysraphism on the basis of early post recovery outcomes, pain, intraoperative and postoperative hemodynamics, and postoperative side effects of both the agents. **Materials and Methods**: 60 patients scheduled for spinal dysraphism surgery of ASA physical status I & II, of either sexes, aged between 6 months - 6 years, were divided into two groups. After I.V. induction maintenance anesthesia was given on low-flow with inhalational agent as isoflurane for Group I (n=30), and sevoflurane for Group II (n=30). The primary end points being post-anaestheisa recovery, extubation time, discharge readiness in PACU and emergence agitation, While the secondary end points included intraoperative and postoperative Heat Rate, noninvasive blood pressure and SpO_2 and postoperative complications such as nausea, vomiting, shivering, and desaturation episodes (SpO_2<95%). **Results:** While faster times to awakening and extubation were observed with sevoflurane compared with isoflurane ($p< 0.001$), no difference in discharge readiness in recovery room was seen. Moreover, emergence agitation was almost absent in both the groups and no complications were observed in PACU during our observation period. **Conclusion:** Both isoflurane and sevoflurane can be used safely in maintenance of anaesthesia in pediatric patients undergoing spinal dysraphism surgery. Since isoflurane is a cheaper alternative, so in developing countries it could be preferred over sevoflurane on the basis of risk benefit ratio.

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INTRODUCTION

Early postoperative neurological evaluation and prompt management of surgical complications, rapid recovery is the mainstay of neuroanaesthesia (Cohen, 2002). Inhalational anesthetics are the agents of choice for maintenance of general anesthesia in neurosurgical operations due to various reasons such as their ease of administration, the availability of end-tidal agent monitoring and predictable postoperative characteristics and early recovery. Isoflurane, formerly considered as the most appropriate Inhalational anaesthetic agent for intracranial surgeries due to its property of causing vigorous suppression of cerebral metabolism (Newberg, 1983) and has minimal effects on cerebral blood flow and intracranial pressure (ICP) in hypocapnic patients (Campkin, 1989) as well as the lowered cost compared with the other inhalational anaesthetic agents. Sevoflurane being a fluorinated ether with low blood/gas partition coefficient (0.69) having low solubility, provides rapid onset and offset of anaesthesia, thus facilitating early postoperative evaluation of the patients especially in the neurosurgical cases[4] .Hence, a new dimension has been added to recovery from anaesthetics especially after the introduction of sevoflurane. The effects of sevoflurane on cerebral hemodynamics are similar to that of isoflurane (Duffy, 2000). Many studies have also revealed that sevoflurane produce less vasodialation as compared with isoflurane. However; the probable toxicity from sevoflurane resulting from the relatively high rate of its metabolism as well as its reaction with carbon dioxide (CO2) absorbents had been a source of considerable concern (Ghoneim, 2015). In Paediatric patients requiring intermediate lasting anaesthesia, sevoflurane doesn't seem superior to isoflurane for maintenance since the recovery and discharge parameters were found to be similar when isoflurane and sevoflurane were compared (Le Berre, 2001). This prospective, comparative randomized study was designed to study the awakening characteristics of isoflurane and sevoflurane in paediatric patients undergoing surgery for spinal dysraphism.

MATERIALS AND METHODS

The prospective randomized double blinded trial was completed in the operation theatres and PACU after ethical committee approval of the university. An informed written consent was taken from the parents/guardian of the patients. Inclusion criteria: Study was carried out in ASA physical status I & II patients of either sex, aged 6 months - 6 years, undergoing surgery for spinal dysraphism. Exclusion criteria were: parental refusal, patients with cardiac, renal, hepatic and respiratory dysfunction, associated hydrocephalus and Arnold chiari malformation, and history of seizures.

Randomization and blinding: The patients were randomized according to a computer generated random number table. Subjects were allocated into two groups of 30 each. The designated intervention was carried out by anesthesiologist not involved in the study. Another anaesthesiologist blinded to the identity of study intervention monitored and managed the patients and collected data.

Anaesthetic intervention: On the day of surgery, EMLA cream was applied at the site of IV cannula insertion half an hour before surgery and an intravenous access was secured. No sedative premedication was given in the preoperative room. Routine monitors including pulseoximetery, electrocardiogram (ECG) and noninvasive blood pressure (NIBP) were attached and baseline vitals were recorded. Patient was induced according to thestandard protocol of the institution using propofol (3mg/kg) and fentanyl (2μg/kg), followed by atracurium (1mg/kg) to facilitate endotracheal intubation. Anaesthesia was maintained with 60% nitrous oxide in oxygen and sevoflurane or isoflurane (according to the study group) at fresh gas flow of 2 L/min and lungs were mechanically ventilated to maintain an end-tidal carbon dioxide ($EtCO_2$) of 35 to 40 mmHg.

Group I Sevoflurane was started at 2 volume % initially.

Group II isoflurane started at 1.5 volume % initially and subsequently agents were adjusted to maintain the hemodynamics. Fentanyl (1μg/kg) was repeated at the time of dural incision and thereafter at persistent relative increase in SBP or HR lasting for more than 3 min (defined as 20% increase in SBP or HR) not responding to maximal allowable anesthetic concentration of inhalational anesthetic. Atracurium(0.1mg/kg)was given to maintain neuromuscular blockade using capnograph monitoring. Ringer's lactate was given for intraoperative fluid replacement according to the formula of Holliday and Segar (Holliday, 1957). The hemodynamic parameters (HR,NIBPand Spo2)were continuously monitored and observations were recorded just after induction of anesthesia, at skin incision, during dural incision and stretching, skin closure and at the time of discontinuation of anaesthetic agents. Episodes of hypotension (decrease in SBP>20% from baseline) not responding to intraoperative fluid replacement (sustained for 3 min) was managed with mephentermine sulphate. Bradycardia (HR <20% of baseline) lasting more than 1 min was treated with atropine sulphate 0.02mg/kg IV. These episodes of hemodynamic changes were recorded and also notified to the operating surgeon. Intraoperatively normothermia was maintained with the use of warm IV and irrigation fluids and was monitored with nasopharyngeal temperature probe. I.V paracetamol (10mg/kg) was given intraoperatively as additional analgesic to all the patients and bupivacaine (0.125%) was infiltrated at the site of skin incision at the time of skin closure as a part of multimodal analgesia. Inhalational agent and nitrous oxide was simultaneously turned off once the patient is positioned supine .Residual neuromuscular blockade was reversed with neostigmine (50μg/kg) and glycopyrrolate (20μg/kg). Tracheal extubation was done when patient met appropriate criteria such as resumption of regular respiratory pattern, adequate minute ventilation, oxygen saturation more than 95% and recovery of airway reflexes. Patients were then transferred to Post Anesthesia Care Unit (PACU). The primary end point of this study were : the post-anaestheisa recovery which was assessed by emergence time; defined as the time elapsing from end of anesthesia until the patients were able to open their eyes (spontaneously), extubation time; defined as the time elapsing from discontinuation of inhalational anesthetic to extubation after adequate spontaneous ventilation was established, discharge readiness in PACU which was measured by the time interval required to reach Modified Aldrete score ≥ 9 (Table 1) (Aldrete, 1995). Postoperative pain was evaluated using a modified objective pain score by Hannallah et al (Table 2) (Hannallah, 1987) at different time interval. The emergence agitation (EA) was assessed by using 5 point Cole's agitation score (Table 3) (Cole, 2002) at similar intervals. The secondary end points included intraoperative and postoperative HR, noninvasive blood pressure and SpO_2 and postoperative complication such as nausea, vomiting, shivering, and desaturation episodes(SpO_2<95%).

Statistical analysis: The results are presented in frequencies, percentages and mean ± SD. The Chi-square test was used to compare categorical/dichotomous variables between groups. The Unpaired t-test was used to compare the continuous variables between the groups. The p value <0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

Sample size calculation: The emergence time for sevoflurane was taken from the study by Singh et al (2009) for calculating sample size for two groups, anticipating 20% change with isoflurane with 5% level of significance and 85% power the sample size of 30 patients in each group was calculated.

RESULTS

Table 1 depicts, the groups were comparable with respect to age, sex, duration of surgery and duration of an aesthesia. Table 2 shows various recovery characteristics measured between Group I and Group II. Variation in Extubation time and emergence time were statistically significant among both the groups (p-value<.01). The extubation time was significantly (p=0.0001) higher among patients of Group I (8.55±0.87) compared to Group II (4.76±1.43). Similarly higher emergence time was (p=0.0001) observed among patients of Group I (11.26±2.02) as compared to Group II (8.13±1.30). The comparison of cole score >3 between the groups was done and was found to be statistically insignificant (p-value>.05). Cole score E3 was found only in Group I (3.3%). The time to attain MAS>9 was insignificantly (p>0.05) higher among patients of Group I (75.50±17.38) than Group II (71.50±20.34). Hanallah Pain score ≥4 was achieved only in Group I which was found to be statistically insignificant. A score of 3.3% was attained in Group I and none in Group II. Figure 2 and 3 shows the values of heart rate and systolic blood pressure between all the three groups at various time intervals, which was found to be statistically insignificant.

Table 1. Modified Aldrete Scoring System

Observation	Criteria	Score
Activity	Four extremities	2
(Able to move voluntarily or on command)	Two extremities	1
	No extremities	0
Respiration	Able to breathe deeply and cough freely.	2
	dyspnoe, shallow/limited breathing .	1
	Apnea	0
Circulation	B.P. within 20mmHg of preoperative level	2
	B.P. within 20-50 mmHg of preoperative level	1
	B.P. within +/- 50 mmHg of preoperative level	0
Conciousness	Fully awake	2
	Arousable on calling	1
	Unresponsive	0
Oxygen Saturation	SPO_2>92%	2
	Needs O_2 to maintain SPO_2>90%	1
	SPO_2 <90% with O_2	0

Note:- 9 or more points are required for recovery to be confirmed

Table 2. HANNALLAH Pain Scale

No.	Observation	Criteria	Score
1	Blood Pressure	+ 10 % Preoperative	0
		>20 % Preoperative	1
		> 30 % Preoperative	2
2	Crying	No crying	0
		Crying responds to tender loving care	1
		Crying not responding to tender loving care.	2
3	Movement	None	0
		Restless	1
		Thrashing	2
4	Agitation	Asleep/Calm	0
		Mild	1
		Hysterical	2
5	Posture	No special posture	0
		Flexing leg and thigh	1
		Holding groin	2
6	Complain of Pain	Asleep/States no pain	0
		Cannot localise	1
		Can localise	2

Note: Score≥4 is considered significant and i.v Tramadol 1mg/kg were given when patient scored ≥4.

Table 3. Cole score >3 Emergence Agitation Score

Score	Behaviour
1	Sleeping
2	Awake, Calm
3	Irritable, Crying
4	Inconsolable Crying
5	Severe restlessness, Disorientation

Note- 1, 2, 3 Score = Absence of agitation 4, 5 Score = Presence of agitation

DISCUSSION

In our study the two groups did not differ significantly with respect to demographics, duration of surgery and anesthesia and intraoperative or postoperative hemodynamic changes. We observed faster times to awakening and extubation with sevoflurane compared with isoflurane. This is expected as sevoflurane is less soluble compared with isoflurane and is washed out more rapidly (Singh, 2009; Ghouri, 1991; Smiley, 1991; Smith, 1992). However, we did not observe any difference in discharge readiness from recovery room between sevoflurane and isoflurane. The extubation time was significantly (p=0.0001) higher among patients of isoflurane group (8.55±0.87 min) compared to sevoflurane group (4.76±1.43min).The emergence time was significantly (p=0.0001) higher among patients of isoflurane group (11.26±2.02min) compared to sevoflurane group (8.13±1.30 min).

Our findings are in accordance with the study done by Singh et al. (2009). They also compared recovery characteristics of sevoflurane and isoflurane in pediatric patients undergoing spinal surgery and found that extubation (6.4±3.3 vs. 10.7±4.6 min) and emergence times (7.8±3.4 vs. 12.8±5.6 min) were significantly shorter with sevoflurane (P<0.001). However, rapid awakening with sevoflurane didn't translate to early discharge from recovery room in our study. The time to attain Modified Aldrete Score >9 was statistically insignificant (p>0.05) among patients of isoflurane group (75.50±17.38 min) and sevoflurane group (71.50±20.34 min). Moreover, emergence agitation was almost absent in both the groups. According to Cole's five point score, a score of >3 was seen Only in one patient of isoflurane group while none in sevoflurane group and the findings are in accordance with a previous study by Meyer et al. (2007). The incidence of emergence agitation was significantly higher in sevoflurane group when compared with propofol.[42] Many authors have also observed a higher incidence of EA with sevoflurane compared with isoflurane (Voepel-Lewis, 2003; Bortone, 2006) while, higher incidence of EA was observed with isoflurane as compared to sevoflurane in an another study by Valley et al. (1999). Our findings may be due to use of propofol and fentanyl as induction agent and also due to short follow up period (only up to 2 hours postoperatively). EA generally occurs within the first 30 min after anaesthesia is over and generally self-limiting, with a mean duration of 5-15 min.[36, 42, 45] however, agitation and regressive behaviour lasting up to 2 days have also been reported (Bortone, 2006). We found no difference in the occurrence of emergence agitation between children according to their age. However, contradictory literature is available on this issue. Some studies showed no association of EA with age (Davis, 1999), while even in those studies where a positive correlation was observed, the range of "at risk age" varied considerably (Aono, 1997; Eckenhoff, 1961; Breschan et al., 2007). Studies examining the effects of duration of anaesthesia on incidence of EA have yielded contradictory results (Vittanen et al., 1999; Aouad, 2005; Lepouse et al., 2006). Higher incidence has been observed in short duration surgeries (Davis, 1999; Gupta et al., 2004) and long duration surgeries (Valley et al., 1999; Lepouse, 2006) while some noted no effect of duration on incidence of EA (Voepel-Lewis et al., 2003).

We observed no correlation between EA and duration of anaesthesia. Pain has been the most important confounding variable while assessing a child's behavior upon emergence because of the overlapping clinical picture with EA, especially in pre-verbal children who cannot vocalize.[50]A reliable, valid and simple scoring scale to measure postoperative pain and EA is very important in PACU. Unfortunately, none of the scale has been tested to differentiate EA from pain. Many studies have demonstrated a 3-4 fold decline in EA with preemptive analgesia, suggesting that pain maybe it's major source (Davis, 1999; Bortone et al., 2006). Therefore, in our study pain was adequately taken care of with multimodal analgesia. However, EA has also been reported in patients undergoing painless procedures (Uezono, 2000). It can be postulated that pain during emergence may cause EA in some patients but it may not be the sole etiological factor. In a previous study by Singh et al (2009), time (min) taken to achieve full Aldrete (modified) scores was less with sevoflurane (13.9+/-5.3 min) than isoflurane (20.3±6.5 min) ($P<0.001$) but no statistical significance was found. Moreover, the time taken to achieve discharge criteria from PACU (140.7+/-49.3 vs. 146±43.3) was similar to our study ($p>0.05$). We didn't observe any complications in PACU like PONV, apnoeic spells and desaturation episodes (SPO_2, <95%) during our observation period (i.e 2 hours). However, in a previous study (Ghoneim, 2015) out of 60 patients, 3 patients (15 %) in Isoflurane group, 2 (10%) in Sevoflurane group and 1 (5%) in Desflurane group developed postoperative vomiting on recovery that required rescue medication (p=0. 57).

Conclusion

In summary, isoflurane and sevoflurane can be used safely in maintenance of anaesthesia in pediatric patients undergoing spinal dysraphism surgery. Difference in emergence time, discharge readiness from PACU and incidence of emergence agitation were clinically insignificant with the use of either isoflurane or sevoflurane.

The cost is a major constraint in government organization of developing countries like ours. Therefore, it is recommended that the cost benefit ratio should be weighed for the rapid recovery and short duration of stay in recovery room against the increased cost associated with the use of sevoflurane. Therefore, we suggest the use of propofol-fentanyl combination along with cheaper inhalational agents i.e. isoflurane in the pediatric surgical settings in developing nations to achieve cost-effective anesthesia and better recovery profile.

Limitations of the study

Small sample size

- Multiple observers have recorded the findings which could have a subjective bias. It was important that only one blinded observer should have graded all scores employed in the study.
- Hemodynamic variable were used to indicate depth of anaesthesia intraoperatively, although these variables are not reliable for monitoring the depth of anaesthesia.
- Sedative property of propofol and analgesic effect of fentanyl may have influenced the incidence of emergence agitation and probably the recovery characteristics of the inhalational agents used.

- As we all know Emergence agitation; a major variable of the recovery characteristics with maintenance of anesthesia using newer inhalational agents, is a multifactorial syndrome. We recommend more randomized double blind studies using large sample size with appropriate definition, validation scales and standardized protocols to understand this phenomenon in terms of its incidence, risk factors in the perioperative period and its correlation with the age of the patients and duration of surgery.

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