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PREVENTION OF SEVOFLURANE RELATED EMERGENCE AGITATION IN CHILDREN UNDERGOING COCHLEAR IMPLANT: A COMPARISON OF NALBUPHINE AND PROPOFOL

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ABSTRACT

Background: Aim of present study was to compare the effect of single dose of propofol or nalbuphine prior to termination of sevoflurane based anesthesia on incidence and severity of EA in children. **Methods:** Thirty children, ASA I-II, 18 months to 8 years old undergoing cochlear implant surgery under sevoflurane based anesthesia were enrolled in the study. Children were randomly allocated to one of three equal groups: Group C received 10 ml saline 0.9%, Group P received propofol 1 mg/kg and group N received nalbuphine 0.1 mg/kg^{-1}. Study drugs were administered 5 min before the end of surgery. In post anesthesia care unit (PACU), incidence of EA was assessed with Aonos four point scale and severity of EA was assessed with pediatric anesthesia emergence delirium scale upon admission (T0), after 5 min (T5), 15 min (T15) and 30 min (T30). Extubation time, emergence time and duration of PACU stay were assessed. **Results:** Incidence and severity of EA were lower in group P and group N compared to group C at T0, T5 and T15 . Incidence and severity of EA in group P were higher than group N at same times. Incidence and severity of EA decreased significantly over time in all groups. The modified Children's Hospital of Eastern Ontario Pain Scale was lower in group N compared to group P and group C. **Conclusions:** Although statistically not significant but Nalbuphine $0.1mg/kg^{1}$ was more effective than propofol 1 mg/kg in decreasing incidence and severity of EA, when administered 5 min before end of surgery in children undergoing cochlear implant surgery under sevoflurane anesthesia.

KEYWORDS: Children, nalbuphine, emergence agitation, propofol, sevoflurane

INTRODUCTION

Sevoflurane is widely used as an anesthetic agent for childrenbecause of its less pungent nature and also as it has a lowersolubility and greater hemodynamic stability than the otherpotent inhaled anesthetics.[1] The occurrence of emergence agitation (EA) in children after sevoflurane anesthesia is common, with a reported incidence up to 80%.[2] EA is characterized by a period of restlessness, agitation, inconsolable crying, disorientation, delusion, hallucination and cognitive changes plus memory impairment.[3] EA in children is generally short-lived with no after-effect, however, it is a troublesome phenomenon, because it can result in injury to the patient or damage to the surgical site, leads to dissatisfaction and anxiety for the parents, and requires extra nursing care with associated costs.[4] Different drugs such as propofol, α2-adrenoreceptor agonists, midazolam, nalbuphine and ketamine have been used to allow a smooth emergence from sevoflurane anesthesia.[5] Generally, propofol is used in children for its sedative action as well as for induction and maintenance of general anesthesia.[6] Based on previous studies,[7,8] propofol seems to be effective in preventing EA and is dependent on the timing of administration.[5]

Nalbuphine is an agonist-antagonist opioid that has analgesic and sedative effects. Nalbuphine exhibits a ceiling effect; in other words, once its maximum plasma concentration has been reached, incremental doses do not potentiate its analgesic effects or increase the risk of respiratory failure.[9] Nalbuphine is primarily a kappa agonist/ mu antagonist analgesic. Nalbuphine in a dose of 0.1 mg kg-1 administered at the end of anaesthesia has been shown to decrease the incidence of excitation and anxiety after anaesthesia more effectively than ketamine without prolonging the awakening time.[10]

This double-blinded randomized prospective study was conducted to compare the effect of administration of a single dose of propofol or nalbuphine prior to the termination of sevoflurane-based anesthesia on the incidence and severity of EA as well as emergence and discharge time in children undergoing cochlear implant surgery.

METHODS

After obtaining the approval of the institutional review board and informed written consent from the parents, 30 children, aged between 18 month and 8 years, with American Society of Anesthesiologists physical status I-II, who scheduled to undergo elective cochlear implant surgery under general anesthesia with the expected duration of 90-180 min were enrolled in this prospective, randomized, double-blinded, placebo-controlled study. The patients were then randomized to one of three equal groups using a computer generated randomization table, the control group (Group C), propofol group (Group P) and nalbuphine group (Group N). Exclusion criteria included congenital diseases, genetic syndromes, facial and airway abnormalities, history of sleep apnoea ,mental disease, neurologic or cardiac disease,recent illness, upper respiratory tract infections and treatment with sedatives.

Children fasted for 8 h for solid food but received clear fluids untill 4h preoperatively. All were premedicatedwith 0.4 mg/kg^1 oral midazolam approximately 30 min before separation from the parents. The number of children who were agitated during induction of anesthesia despite premedication with midazolam was recorded in each group. An electrocardiogram, pulse oximeter and noninvasive arterial blood pressure monitor were attached. General anesthesia was induced with 8% sevoflurane in 70% nitrous oxide in oxygen, via a facemask. After establishing a venous access, rocuronium 0.9 mg/kg^1 was given. Orotracheal intubation was performed and anesthesia was maintained with 60% nitrous oxide in oxygen, supplemented by an end-tidal concentration of 1.5-2% sevoflurane with controlled ventilation, to maintain an end-tidal CO_2 of 35±4 mmHg. All patients received 15 mg/kg^1i.v.paracetamol for the control of postoperative pain and 1 mg/kg^1i.v. dexamethasone (maximum 16 mg) for the control of postoperative laryngeal edema, pain, nausea, and vomiting. About 5 min before the end of surgery, patients in Group C received 10 ml NaCI 0.9%, patients in Group P received propofol 1 mg/kg^1 and patients in Group N received nalbuphine 0.1 mg/kg^1 diluted in 10 ml NaCI 0.9%. Experimental drugs were administered intravenously over 5 min. At the conclusion of the procedure, following the discontinuation of sevoflurane and nitrous oxide, residual muscle relaxation was reversed with neostigmine 0.05 mg/kg^1 and glycopyrollate 0.01 mg/kg^1i.v.Extubation was performed when the patient's gag reflex was restored and they showed facial grimaces or purposeful appearing motor movements and adequate spontaneous respiration. Children were transferred to the post anesthesia care unit (PACU). Upon arrival to the PACU, all children were received by one of their parents, who stayed with them until discharge.

Aonos four point scale;[11] 1=calm; 2= The incidence of EA was evaluated using not calm but could be easily consoled; 3=moderately agitated or restless and not easily calmed; 4=combative, excited, or disoriented, thrashing around. Scores of one and two were considered as absence of EA, and scores of three and four were analyzed as presence of EA. The severity of EA was evaluated using pediatric anesthesia emergence delirium (PAED) scale devised by Sikich*et al*.[3] [Table1], a five-point rating scale with five grades for each item. The incidence and severity of EA were measured upon admission to the PACU (T0) and in the PACU at 5 min (T5), at 15 min (T15) and at 30 min (T30). Children were considered severely agitated if they had a PAED scale of 15/20 or higher.

Table 1Pediatric anesthesia emergence delirium scale

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
Make eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surrounding	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

Postoperative pain was assessed using the modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) in the PACU at (T0), (T5), (T15) and (T30). Vomiting was treated with ondansetron 0.15 mg/kg^1i.v. and the incidence of vomiting was recorded. Nausea was not recorded as it was difficult to assess in children. The incidence of adverse events such as hypotension, bradycardia, laryngospasm, bronchospasm and oxygen desaturation, were noted.

The following time intervals were recorded: The duration of surgery (from the time of local infiltration to the completion of the procedure), duration of sevoflurane anesthesia (from mask induction to the discontinuation of the inhaled anesthetic), duration of extubation (from the discontinuation of sevoflurane to the removal of endotracheal tube), time of emergence (from discontinuation of sevoflurane to return spontaneous respiration, voluntary swallowing and normal conciousness), and duration of PACU stay (from arrival to the PACU until discharge). Discharge criteria included being fully awake, stable vital signs for 30 min, no bleeding, no pain, no nausea or vomiting and able to ambulate according to age and children were considered ready for discharge from the PACU to ward when the modified Aldrete post-anesthesia score was ≥9.[26] All above i.v. agents were prepared and hidden behind drapes and administered by the one anesthesiologist

according to the group to which the patient was randomized. The recordings of all variables were collected by the another anesthesiologist who was blinded to the group to which the patient was assigned.

STATISTICAL ANALYSIS

Tests applied were chi square and ANOVA tests. The incidence of emergence agitation in children after sevoflurane anaesthesia was assumed to be 40% based on the results of Aono et al.[11] and a 50% reduction in emergence agitation was considered to be clinically significant. By using statistical programme for social science (SPSS) software for Windows version 11(SPSS Inc, Chicago, IL, USA), arithmetic mean and standard deviation values for different variables were calculated and statistical analyses were performedfor each group. P< .05 was considered statistically significant.

RESULTS

30 patients were allocated to participate in this study (10 in each of the study group). All groups were comparable as regards to demographic data as well as duration of anesthesia and duration of surgery (*P*>0.05) [Table 2].

Table 2 Patients' criteria and anesthetic details

	Grp. C (n=10)	Grp. P (n=10)	Grp. N (n=10)
Age (years)(mean±SD)	3.3 ± 1.05	3.0 ± 0.66	3.8 ± 1.22
Weight(kg)(mean±SD)	11.8 ± 1.75	13.2 ± 1.13	12.4 ± 1.42
Sex (M:F) (n)	7/3	8/2	7/3
Duration of surgery (min.) (mean±SD)	110.8 ± 5.39	115.1 ± 9.17	112.8 ± 6.01
Duration of Anaesthesia (min.) (mean±SD)	118.4 ± 5.30	124.1 ± 8.19	121.3 ± 5.88

The incidence and severity of EA were significantly lower in group P and group N compared to group C at T0, T5 but not at T15 and T30. Compared to group N, the incidence and severity of EA in group P was higher at T0, T5, and T15 but not at T30. The number of patients who developed severe EA (PAED >15) was least in group N and lower in group P compared to group C but the difference was not statistically significant. Modified CHEOPS was lower in group N compared to group P and group C at T0, T5 andT15 but not at T30. There was no significant difference between group P and group C at any time of measurement. Aonos four point scale, PAED scale and modified CHEOPS decreased significantly over time in each group. Regarding the incidence of vomiting, there was no difference among the studied groups. Times to emergence and extubation in group P were longer compared to group C and group N but not statistically significant. Time to discharge from the PACU was same among the studied groups [Table 3].

Table 3 Incidence of emergence agitation, pediatric anesthesia emergence delirium scale, modified children's hospital of eastern ontario pain scale and recovery characteristics

Incidence of emergence agitation (n)	Grp. C (n=10)	Grp. P (n=10)	Grp. N (n=10)
To	7	3	1
T5	5	2	0
T15	3	1	0
T30	0	0	0

PAED (mean±SD)			
T0	14.2 ± 4.8	12.1 ± 3.5	10.2 ± 2.58
T5	8.8 ± 4.2	6.3 ± 3.2	4.8 ± 3.0
T15	5.3 ± 3.5	4.8 ± 2.1	4.1 ± 1.8
T30	4.4 ± 1.7	4.1 ± 2.4	3.2 ± 1.8

Patients with PAED score > 15	2	1	0

Modified CHEOPS (mean±SD)			
T0	5.7 ± 1.7	5.3 ± 1.5	4.4 ± 1.3
T5	4.5 ± 1.3	4.3 ± 1.5	3.5 ± 1.2
T15	3.5 ± 1.9	3.5 ± 2.0	2.7 ± 1.5
T30	2.2 ± 1.4	2.3 ± 1.6	2.1 ± 1.2
Duration of extubation (min)	7.4 ± 1.45	8.8 ± 1.52	7.8 ± 1.48
Time of emergence (min)	6.8 ±1.05	8.0 ± 1.35	7.4 ±1.20
Duration of PACU stay (min)	45	45	45
Vomiting in PACU	0	0	0

No adverse events such as laryngospasm, bronchospasm, hypotension, bradycardia and oxygen desaturation episodes were recorded in any of the children.

DISCUSSION

The etiology of EA in children is not fully understood but possible risk factors are intrinsic characteristics of an anesthetic, rapid emergence from anesthesia, postoperative pain, preschool age, otolaryngologic surgical procedures, preoperative anxiety, and child temperament.[2] Meta-analysis of 23 randomized controlled trials revealed that EA occurred more frequently with sevoflurane than halothane.[12] Rapid awakening after sevoflurane anesthesia has been assumed to be a cause for the phenomenon. However, it is currently thought that rapid emergence is not the only cause of EA, because recovery from propofol anesthesia, which also has rapid emergence properties, is associated with low incidence of EA.[13] No single factor in isolation could be identified as causing postoperative agitation, and the condition should be considered to be a syndrome with biological, pharmacological, psychological and social components.

In our study, the incidence and severity of EA were significantly lower in group N compared to group P and group C. Considering its ability to induce moderate sedation and potent analgesic effects, nalbuphine is one of the drugs that is recommended for postoperative pain management in children above the age of 18 months.[14] Hyun-Jung Kim et *al*.[15] reported nalbuphine 0.1 mg/kg at the end of strabismus surgery under sevoflurane anesthesia effectively reduced emergence agitation in children without delaying recovery,butpropofol did not. In another study, comparing nalbuphine (0.1 mg/kg^{-1}) with ketamine (0.25 mg/kg^{-1}), administered at the end of inhaled sevoflurane anesthesia to children aged 6 months to 8 years before cerebral magnetic resonance imaging, a lower incidence of post-emergence agitation was detected in the group of patients given nalbuphine. Agitation occurred more frequently in the control group.[16]

Recovery from propofol anesthesia is smooth and delayed, so propofol anesthesia is associated with a lower incidence of EA compared to sevoflurane.[17] The decreased incidence of EA could be accounted for the residual sedative effect of propofol in the early recovery period.[18] Abu-Shahwan's study[20] showed that the administration of sub-hypnotic doses of propofol at the end of sevoflurane general anesthesia was effective in decreasing the incidence and severity of EA in children undergoing magnetic resonance imaging (MRI). Aouad*et al*.[21] reported that the administration of a single dose of propofol 1 mg/kg^{1} after discontinuation of sevoflurane at the end of surgery in children undergoing strabismus surgery significantly decreased the incidence of EA and improved patient satisfaction.

The presence of pain is thought to be one of the major causes of EA, but painless treatment does not guarantee calm emergence from sevoflurane anesthesia.[2] Isik*et al*.[22] reported that EA was seen in 48% of pediatric patients after sevoflurane anesthesia for MRI. A recent meta-analysis shows no correlation of the efficacy of ketamine, α2-agonists, or fentanyl in postoperative pain relief and EA reduction.[19] These results suggest that the analgesic properties alone of these compounds are unlikely to be involved in their preventive effects for EA. Nevertheless, the properties to induce emergence sedation could explain their preventive effect.

The modified CHEOPS was lower in group N compared to group P and group C at T0 and T5. Modified CHEOPS in each group decreased significantly over time. Modified CHEOPS was not influenced by propofol because propofol is not an analgesic agent. Kim *et al*.[15] reported that propofol 1 mg/kg^{1} at the strabismus surgery under sevoflurane anesthesia did not reduce EA in children, and they emphasized the importance of pain control.

Many studies have shown that EA is self-limited and is resolved without pharmacologic intervention over time.[2,23] Our data also demonstrated that the incidence and severity of EA and pain intensity are improved over time without analgesic or sedative drugs. Our study allowed children to stay with one of parents in the PACU and this seemed to help them to acclimatize themselves to a strange and naive environment.

Time of extubation and emergence time were significantly longer in group P compared to group C. This is consistent with previous studies[20,21] showing that the time to awakening correlates negatively with EA scores. The difference between group P and group N is of small magnitude and is not clinically significant. The delayed extubation time and emergence from anesthesia in group P did not delay discharge; children in all groups had comparable durations of PACU stay.

The incidence of vomiting in our study is low.[24] This finding may be explained by the following facts: Only paracetamol, a nonopioid analgesic was administered, in addition to dexamethasone that possesses both analgesic[25] and antiemetic properties. Also, children stayed for approximately half an hour in the PACU. Discharge from the PACU coincided with the end of the study period. Therefore, the occurrence of delayed vomiting may have not been recorded by the investigators.

CONCLUSION

In our study although statistically not significant, nalbuphine 0.1mg/kg^{1} was more effective than propofol 1 mg/kg^{1} in decreasing the incidence and severity of EA, when they administered 5 min. before the end of surgery in children undergoing cochlear implant surgery under sevoflurane anesthesia. Nalbuphine decreased

postoperative pain, extubation time and emergence time compared to propofol without affecting the length of stay in PACU.

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