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Comparison of Remifentanil-Propofol and Sevoflurane for Preventing Cardiovascular Response and Quality of Recovery in Paediatric Otolaryngologic Surgery

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Abstract: As the practice of outpatient paediatric surgery advances, the search continues for anaesthesia that provides rapid smooth induction, stable patient haemodynamics, rapid emergence and minimal unpleasant side effects.

Therefore, this study was designed to compare the haemodynamic changes, emergence and recovery characteristics of remifentanil-propofol (TIVA) and sevoflurane anaesthesia for adenoidectomy with bilateral myringotomy and insertion of tubes and/or tonsillectomy (ENT surgery) in children.

Children aged 6.3±1.6 years, undergoing elective ENT surgery, were randomly assigned to receive TIVA (n=15) and sevoflurane (n=15).

In both groups, anaesthesia was induced with propofol and remifentanil and maintained either with infusion of propofol-remifentanil or sevoflurane with 50% N_2O in oxygen. End-tidal CO_2 concentration ($ETCO_2$) and oxygen saturation (SaO_2) were monitored and ventilation was controlled to maintain normocapnia. Heart rate and systolic-diastolic blood pressures were measured before and after induction, after tracheal intubation, at the beginning of the incision and at the end of the surgery. The time intervals from discontinuation of the anaesthetic, early emergence and recovery and the incidence of side effects were assessed.

There were no differences in patients' demographics among the groups. Both of the anaesthesia methods could not provide stable haemodynamics at the time of intubation or at the start of surgery, but heart rates and blood pressures were significantly higher with sevoflurane ($p<0.05$).

Times to restoration of spontaneous ventilation and extubation were significantly faster and mean scores of the quality of emergence scale were higher in the sevoflurane group than in the TIVA group ($p<0.05$). There was a significantly greater incidence of postoperative agitation in patients who received sevoflurane (100%) compared with those who received TIVA (46.7%) ($p<0.05$).

It was concluded that TIVA provided less postoperative agitation and lower peroperative heart rates and blood pressures than sevoflurane-based anaesthesia.

Key Words: Remifentanil, propofol, sevoflurane, emergency quality, cardiovascular response

Introduction

Fast emergence and short recovery with a low incidence of postoperative side effects are two important goals of anaesthesia for paediatric outpatient surgery (1,2). Both sevoflurane and propofol possess qualities that are desirable for infants and children who require ambulatory surgery under general anaesthesia. Studies in children have confirmed the excellent induction characteristics, haemodynamic stability and rapid emergence and recovery qualities for both anaesthetics (3-5).

The esterase-metabolized opioid, remifentanil hydrochloride, has pharmacokinetic properties that may translate into benefits for ambulatory anaesthesia and recovery. The pharmacokinetics of remifentanil allows easy titration of changing intraoperative conditions and smooth emergence from anaesthesia and it may be a useful anaesthetic for paediatric outpatient surgery (2,6). A total IV anaesthesia (TIVA) regimen with remifentanil and propofol is a useful anaesthetic technique for controlling responses to tracheal intubation and intense surgical stimulation, but little data is available in paediatric patients (2,7,8).

We undertook this study to examine the haemodynamic response and the recovery profile of remifentanil-propofol combination (TIVA) and to compare this total intravenous anaesthesia with an inhalation anaesthesia technique based on sevoflurane.

Materials and Methods

After obtaining the approval of the hospital Ethics Committee, 30 children, aged 6.3±1.6 (ASA I or II) undergoing adenoidectomy with bilateral myringotomy and insertion of tubes and/or tonsillectomy (ENT surgery), were included in the study (Table 1).

A eutectic mixture of local anaesthetics (EMLA) cream was applied on both hands of the children 1 hour before surgery. After an i.v. catheter was inserted, all children were premedicated with midazolam 0.03-0.05mg/kg intravenously.

In both groups, anaesthesia was induced with remifentanil 1µg/kg and propofol 2mg/kg. Cisatracurium (0.01mg/kg) was given to facilitate orotracheal intubation. After induction of anaesthesia, paracetamol suppositories were administered rectally in all children. For maintenance of anaesthesia, children were randomized to receive either TIVA (group I) or inhalation anaesthesia based on sevoflurane (group II).

In group I, separate infusions of propofol (3mg/kg/h) and remifentanil (0.5µg/kg/min) were started immediately after the anaesthesia induction and the patients' lungs were ventilated with 100% O_2 and 50% oxygen in oxygen/air after tracheal intubation. No N_2O was given.

In patients assigned to group II, anaesthesia was continued with 2.5-3% sevoflurane in 100% O_2 until tracheal intubation and N_2O was added to obtain an end-tidal concentration of 50% N_2O. Throughout the procedure, end-tidal CO_2 ($ETCO_2$) and oxygen saturation (SaO_2) were monitored and ventilation was adjusted to maintain $ETCO_2$ between 35 and 45 mm/Hg (Cicero EM, Drager).

Heart rate and arterial blood pressures were recorded regularly after induction, after tracheal intubation, at the beginning of incision, 5 min after incision, 10 min after incision, 20 min after incision and at the end of the surgery. Atropine sulphate (0.01 mg/kg) was given for bradycardia. Bradycardia was defined as heart rates less than 80 bpm for children less than 8 years old and 60 bpm in children 8 and over.

For all patients, signs of inadequate anaesthesia (increase in blood pressure or heart rate more than 20% from baseline and responses such as movement or sweating) were treated with an additional bolus dose (0.5µg/kg) of remifentanil. In group II, increasing concentrations of sevoflurane up to end-tidal concentration of 3% were also used.

At the end of surgery, after inhaled gases and intravenous anaesthetics were terminated, any residual neuromuscular block was antagonized with neostigmine and atropine sulphate.

For 10 minutes after the discontinuation of anaesthesia, no physical stimulation (e.g., suctioning of the oropharynx or jaw thrust) was performed. If the patient did not respond after 10 minutes, then stimulation was allowed. Time to return of spontaneous ventilation, time to extubation and time to eye opening were recorded by the same experienced anaesthesiologist.

A trained postanaesthesia care unit (PACU) nurse, blinded to the anaesthetic technique used, assessed the

Table 1. Preoperative classification of patients according to the American Society of Anaesthesiologists

Status	Disease state
ASA Class 1	No organic, physiologic, biochemical or psychiatric disturbance
ASA Class 2	Mild to moderate systemic disturbance that may or may not be related to the reason for surgery
ASA Class 3	Severe systemic disturbances that may or may not be related to the reason for surgery
ASA Class 4	Severe systemic disturbances that is life threatening with or without surgery
ASA Class 5	Moribund patient who has little chance of survival but is submitted to surgery as a last resort (resuscitative effort)
Emergency Operation (E)	Any patient in whom an emergency operation is required

quality of emergence and postoperative agitation. The standard scoring scale was used for evaluating quality of emergence (Table 2) (6). The scale measured four dimensions of quality of emergence: facial expression, posture, crying and hangover. The scores on each dimension of the scale were summed to provide a single measure of quality of emergence for each patient. Scores could range from 0 (smooth, problem-free emergence) to 8 (uncomfortable, problematic emergence).

Table 2. Scoring System for Quality of Emergence from Anaesthesia

Facial Expression	0 = relaxed, neutral expression, calm 1 = frowning 2 = eyes closed, open mouthed grimace
Posture	0 = relaxed, neutral, inactive 1 = active, unsteady, poor balance 2 = very active, unsteady, requiring protective restraint
Crying	0 = none 1 = intermittent or persistent whimpering or weeping 2 = persistent, marked loud crying or screaming
Hangover	0 = calm, sleepy, quiet 1 = displeased, unhappy, anxious, fretful 2 = dysphoric, disoriented, frantic

Postoperative agitation was assessed according to Davis et al. (4) by a 3-point score: 1=asleep or calm, 2=mildly agitated, crying but consolable, restless; 3=hysterical, crying inconsolably.

The Mann-Whitney U test was used to determine the statistical significance between group differences. Frequencies in the two groups were analyzed using Wilcoxon's ranked sum test. Results were expressed as means ± S.D., and statistical results were considered significant when the P value found in each test was lower than 0.05.

Results

The demographic data is shown in Table 2. No significant differences were found between two groups in terms of age, weight, sex ratio and ASA physical status. Duration of anaesthesia and surgical procedures were similar in both groups (Table 3). The induction was calm and easy without excitation. None of the children showed a rigidity of extremities or thoracic muscles after administration of remifentanil.

Three children of both groups received additional bolus doses of 0.5µg/kg remifentanil (i.v) once to compensate for light anaesthesia.

No complications of the airway were recorded throughout the procedure but four children in the sevoflurane group had breathholding and laryngospasm after extubation.

Cardiovascular responses

There was no statistical difference between the two groups in terms of baseline values of systolic and diastolic arterial blood pressures (SAP and DAP) and heart rates (HR). In both groups, arterial blood pressure levels decreased after the induction of anaesthesia and increased to baseline values following tracheal intubation.

After intubation and at the start of the operation there was a slight increase in arterial pressure in both groups and it tended to remain high throughout the procedure. This increase was more evident in the sevoflurane group and it was found to be statistically significant ($p<0.05$).

Heart rates decreased in both groups after induction of anaesthesia; none of the children in the sevoflurane group and three children in the TIVA group had received atropine sulphate for bradycardia.

Following tracheal intubation and at the start of the operation, heart rates increased significantly in both

Table 3. Demographic data, surgical and anaesthetic times. Values are means ±SD

	Group I (remifentanil/propofol)	Group II (sevoflurane/nitrous oxide)
Number of patients	15	15
Sex (% M/F)	40/60	53.3/46.7
Age (year)	6.3±1.6	7±2
Weight (kg)	22.4±4.6	24.6±8.9
Duration of surgery (min)	37.3±7.9	36.6±8.9
Duration of anaesthesia (min)	42.3±8.4	42±8.6

groups and remained significantly increased compared to baseline values until the end of the surgery. Increases in heart rates at these intervals were more evident in group II (p<0.05) (Table 4).

Recovery data

Times to restoration of spontaneous ventilation and extubation were significantly shorter in the sevoflurane group and time to eye opening was shorter in the TIVA group (Table 5). None of the children in the sevoflurane group (100%), and ten children in the TIVA group (46.7%) showed postoperative agitation score<2. This difference was statistically significant (p<0.05) (Table 5).

Mean scores on the quality of emergence scale at the time of awakening were 1.9±1.7 for the TIVA group, and 4.8±1.06 for the sevoflurane group. These differences were found to be statistically significant (p<0.05) (Table 5).

Discussion

New potent inhaled anaesthetics with low blood-gas solubility coefficients and i.v. anaesthetics of ultrashort duration can provide optimum anaesthetic qualities (2,10). Remifentanil is a new, ultra-short acting, synthetic opioid (8). Because of its unique pathway for opioid metabolism and propofol's ideal anaesthetic characteristics of smooth - rapid recovery and the low blood-gas and tissue coefficients of sevoflurane, this study was performed to compare the haemodynamic response and emergency profile of remifentanil and propofol (TIVA) with sevoflurane.

One of the difficulties in designing a study in which an inhaled anaesthetic is compared with an intravenous agent is ensuring that the depth of anaesthesia for the two anaesthetics remains similar. In this study, however, where one anaesthetic is an inhaled agent and the other is an intravenous agent, there is no common clinical mea-

Table 4. Haemodynamic data at selected time points.

	Group I (remifentanil/propofol)			Group II (sevoflurane/nitrous oxide)		
	HR (beats per min)	SAP (mm/Hg)	DAP (mm/Hg)	HR (beats per min)	SAP (mm/Hg)	DAP (mm/Hg)
Baseline	96.9±14.0	98.4±10.6	62.7±8.1	105.2±11.9	107.2±11.7	65.3±6.0
After induction	86.1±11.1	86.1±13.6	50.8±8.1	92.3±12.0	91.1±8.2	51.7±7.5
After intubation	100.1±12.1*	96.4±14.0*	61.5±11.6	111.5±14.0	109.1±14.3	6.9±12.8
Incision	105.1±11.9*	103.2±16.0*	67.4±11.5	123.3±11.7	116.7±13.2	70.8±11.7
10 min after incision	111.1±13.9	106.0±14.2	70.5±19.3	119.2±10.5	112.4±15.0	69.6±11.8
20 min after incision	104.0±8.9	102.4±13.0	70.6±17.4	117.6±11.6	107.9±12.3	65.4±7.7
End of anaesthesia	101.4±9.7	98.8±14.7	68.1±15.6	113.0±9.7	106.1±10.2	64.9±6.8

*p<0.05 between groups at the indicated times
HR (heart rate), SAP (systolic arterial pressure), DAP (diastolic arterial pressure)

Table 5. Recovery times (mean ± SD min), agitation and quality of emergence scores of groups I and II.

	Spontaneous Ventilation (min)	Extubation (min)	Eye opening (min)	Agitation score	Emergency score
Group I	7.9 ± 0.8	7.9 ± 0.8	7.9 ± 0.8	1.8 ± 1.0	1.9 ± 1.7
Group II	4.6 ± 0.8 *	6.8 ± 0.8	9.2 ± 2.1	4.8 ± 1.0*	4.8 ± 1.0*

* p<0.05 between groups

sure or instrument to gauge comparable depths of anaesthesia in children. In this study, all anaesthesia was provided by the same experienced anaesthesiologists and the doses of anaesthetics applied were comparable to those used in other studies to achieve a state of surgical anaesthesia as judged clinically (2,7,11).

Like other opioids, remifentanil causes a dose-dependent reduction in blood pressure and a decrease in heart rate (12). Thompson and colleagues have found that a bolus dose of remifentanil 1µg/kg given over 30 s, followed by an infusion of 0.5µg/kg^{-1}/min^{-1} at induction of anaesthesia decreased HR and mean arterial pressure (MAP) significantly. Occasionally, greater decreases have occurred in the presence of other drugs like propofol (12,13). Propofol has many cardiovascular effects including bradycardia and hypotension. In several studies in which propofol was used, HR decreased after induction and it remained low during the maintenance of anaesthesia (3,14,15). In our study, heart rates were lower in the TIVA group than in the sevoflurane group. This response may result from the cardiovascular properties of remifentanil-propofol infusion.

A rapid increase in heart rates and blood pressures has been reported following endotracheal intubation and at the start of surgery. The tendency of this sympathetic activation was higher in the sevoflurane group. This may be in part explained by the fact that additional bolus doses of remifentanil were only applied when an increase in inspired concentration of sevoflurane did not control haemodynamic changes by painful stimulations and once the stress response is activated and catecholamines are released, opioids are much less effective in maintaining heart rate and blood pressure (7).

Remifentanil and propofol, at the infusion rates used in this study, offer a clinically important advantage with respect to a good quality of emergence in the immediate recovery period compared with sevoflurane. Even though times to restoration of spontaneous ventilation and extubation were longer, children in the TIVA group were much less sedated, more alert and oriented and could be transferred from the operating room to the postanaesthesia recovery room earlier.

Faster awakening in the TIVA group was most probably caused by a more rapid elimination of remifentanil compared with that of sevoflurane (2). Previous studies have indicated that early recovery from propofol anaesthesia results in longer but calmer recovery (12,16,17). Remifentanil-based anaesthesia might even be accelerated by combining remifentanil with an inhaled anaesthetic in a small concentration instead of propofol because of faster and more predictable elimination of the inhaled anaesthetic when compared with propofol (12). A similar effect should be achieved for total intravenous anaesthesia by reducing the propofol and increasing the remifentanil concentration as in the present study. Dershwitz et al. (11) reported that the ED_{50} for remifentanil to abolish all surgical responses in adults was 0.52 µg/kg^{-1}/min^{-1} and a similar rate in children. However, because remifentanil alone cannot reliably ensure the loss of awareness, a minimal propofol infusion (80 µg/kg^{-1}/min^{-1}) or volatile anaesthetic concentration (0.3 MAC) must always be administered in conjunction with remifentanil (12).

The rapid emergence and recovery from anaesthesia were associated with a high incidence of agitation in both groups. The agitation incidence after sevoflurane anaesthesia (100%) was significantly higher than that after TIVA (46.7%). In previous investigations, high emergence agitation was reported for sevoflurane compared with propofol and other inhalation anaesthetics (16,18,19). Naito et al. (20) compared emergence after sevoflurane and halothane anaesthesia in children and described a greater incidence of restlessness and agitation in children anaesthetized with sevoflurane. The reason for this remains unclear. A central nervous system excitatory effect and epileptiform activity with sevoflurane has been previously reported, but the cases observed were during induction of anaesthesia (21,22).

The high incidence of agitation in both groups may be directly related to the speed of emergence. It is possible that the rapid transition from anaesthesia to consciousness in an unfamiliar area with unfamiliar people taking care of the child results in fear and apprehension (18).

One of the most frequently reported causes of emergence agitation is pain. Postoperative pain can be difficult to qualify in children and may mimic the signs of emergence agitation (23). In this study, although the children were treated with rectal paracetamol, pain relief may have been inadequate. The average duration of anaesthesia was 42.3±8.4 min in the TIVA group and 42.0±8.6 min in the sevoflurane group, but the mean time to peak analgesia after rectal paracetamol administration has been reported to be 60-180 minutes and the dose used in this study may have been subtherapeutic (8,24).

Finally, complete awakening and orientation immediately after termination of surgery is highly desirable, especially in these challenging procedures (2). Data from this study suggests that this goal can most likely be achieved by remifentanil-propofol-based anaesthesia. However, the high incidence of agitation after both anaesthesia methods is an unresolved problem.

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Anesteziyoloji ve Reanimasyon ABD

Mersin - TÜRKİYE

References

1. Pickard V, Dumont L, Pellegrini M. Quality of recovery in children: sevoflurane versus propofol. Acta Anaesthesiol Scand, 44: 307-10, 2000.
2. Larsen B, Seitz A, Larsen R. Recovery of cognitive function after remifentanil-propofol anaesthesia: a comparison with desflurane and sevoflurane anaesthesia. Anesth Analg, 90: 168-74, 2000.
3. Guard B, Sikich N, Lerman J, Levine M. Maintenance and recovery characteristics after sevoflurane or propofol during ambulatory surgery in children with epidural blockade. Can J Anaesth, 45: 1072-78, 1998.
4. Hannaallah RS, Britton JT, Schafer PG, Patel RJ et al. Propofol anaesthesia in paediatric ambulatory patients: a comparison with thiopentane and halothane. Can J Anaesth, 41: 12-8, 1994.
5. Lerman J, Davis J, Welborn LG et al. Induction, recovery and safety characteristics of sevoflurane in children undergoing ambulatory surgery. Anesthesiology, 84: 1332-40, 1996 .
6. Peacock JE, Philip BK. Ambulatory anaesthesia experience with remifentanil. Anesth Analg, 89: 22-7, 1999.
7. Grundmann U, Uth M, Eichner A, Wilhelm W, Larsen R. Total intravenous anaesthesia with propofol and remifentanil in paediatric patients: a comparison with a desflurane-nitrous oxide inhalation anaesthesia. Acta Anaesthesiol Scand, 42: 845-50, 1998.
8. Davis PJ, Lerman J, Suresh S, McGowan F, Cote C et al. A randomized multicenter study of remifentanil compared with alfentanil, isoflurane or propofol in anesthetized pediatric patients undergoing elective strabismus surgery. Anesth Analg, 84: 982-9, 1997.
9. Craig PM, Carroll NV. Quality of emergence from anesthesia and incidence of vomiting with remifentanil in pediatric population. Anesth Analg, 89: 71-4, 1999.
10. Davis PJ, Finkel JC, Orr RJ, Fazi L et al. A randomized double-blinded study of remifentanil versus fentanyl for tonsillectomy and adenoidectomy surgery in pediatric ambulatory surgical patients. Anesth Analg, 90: 863-71, 2000.
11. Dershwitz M, Randel GI, Rosow CE, Fragen RJ et al. Initial clinical experience with remifentanil, a new opioid metabolized by esterases. Anesth Analg, 81: 619-23, 1995.
12. Glass PS, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg, 89: 4S; 9-22
13. Thompson JP, Hall AP, Russel J, Cagney B, Rowbothem DJ. Effect of remifentanil on the haemodynamic response to orotracheal intubation. Br J Anaesth, 80: 467-69, 1998.
14. Doyle E, Mcfadzeon W, Morton NS. IV anaesthesia with propofol using a target controlled infusion system: comparison with inhalation anaesthesia for general surgical procedure in children. Br J Anaesth, 70: 542-5, 1993.
15. Murray DJ, Oyos TL, Forbes RB, Disterhoft M et al. Haemodynamic depression during propofol infusions in children. Anesthesiology, 79: A1157, 1993.
16. Lopez Gil ML, Brimacombe J, Clar B. Sevoflurane versus propofol for induction and maintenance of anaesthesia with the laryngeal mask airway in children. Paediatr Anaesth, 9: 485-90, 1999.
17. Viitanen H, Tarkkila P, Mennander S, Viitanen M et al. Sevoflurane-maintained anesthesia induced with propofol or sevoflurane in small children: induction and recovery characteristics. Can J Anaesth, 46: 21-28, 1999.
18. Welborn LG, Hannallah RS, Norden JM, Ruttimann UE et al. Comparison of emergence and recovery characteristics of sevoflurane, desflurane and halothane in pediatric ambulatory patients. Anesth Analg, 83: 917-20, 1996.
19. Viitanen H, Baer G, Annila P. Recovery characteristics of sevoflurane or halothane for day-case anaesthesia in children aged 1-3 years. Acta Anaesthesiol Scand, 44: 101-4, 2000.
20. Naito Y, Tamai S, Shingu K, Fujimori R, Mori K. Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia. Br J Anaesth, 67: 387-89, 1991.
21. Eger EI. New inhaled anesthetics. Anesthesiology, 80: 906-22, 1994.
22. Adachi M, Ikemoto Y, Kubo K, Takuma C. Seizure-like movements during induction of anaesthesia with sevoflurane. Br J Anaesth, 68: 214-15, 1992.
23. Caumo W, Broenstrub JC, Fialho L, Petry MG et al. Risk factors for postoperative anxiety in children. Acta Anaesthesiol Scand, 44: 782-89, 2000
24. Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high dose (45mg/kg) rectal acetaminophen in children. Can J. Anaesth, 42: 982-6, 1995.