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Haemodynamic effects of propofol and desflurane during remifentanil-based anaesthesia with controlled hypotension for paediatric otorhinolaryngeal surgery

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Summary

Introduction. The aim of the study was to compare haemodynamic effects of propofol with desflurane during remifentanil-based anaesthesia for paediatric otorhinolaryngeal surgery. ***Material and methods.*** Forty-one ASA I-II children, aged 7 – 18 years, were randomly assigned to two groups to receive remifentanil and propofol (PRO) or remifentanil and desflurane (DES). After standardised premedication and induction, anaesthesia was maintained with 3-4 mg/kg/h propofol (PRO) or 3-4% desflurane in the oxygen/air mixture. Analgesia was provided in both groups with continuous infusion of 0.75 μg/kg/min remifentanil. MAP was maintained within the range of 50 to 65 mmHg to reduce bleeding in the surgical field. Bradycardia and hypotension were treated with rescue atropine or/and fluid replacement or/and decrease of the remifentanil infusion rate. Surgical conditions were assessed by an attending surgeon who used a bleeding score classification. ***Results.*** The targeted MAP was achieved in most cases in both groups (ns). MAP < 50 mmHg occurred more frequently in DES group ($p<0.05$), MAP > 65 mmHg was more frequently observed in PRO group ($p<0.05$). Mean intraoperative HR and MAP were higher in PRO group ($p<0.05$). HR after the extubation was higher in DES group ($p<0.05$). The incidence of severe hypotensive and bradycardic episodes were higher in DES group (ns), as well as the need for atropine administration (ns) and remifentanil infusion rate decrease (ns). Intravenous fluid resuscitation was more frequently required in DES group ($p<0.05$). In both groups intraoperative bleeding was assessed as minimal and the surgical field was rated satisfactory. ***Conclusions.*** Both methods were equally effective in inducing and maintaining controlled hypotension and both provided satisfactory surgical conditions. The circulation was less stable when desflurane and remifentanil were used. Therefore, the protocol based on propofol-remifentanil seems to be preferable for paediatric ENT surgery which requires minimal bleeding. *Anestezjologia i Ratownictwo 2010; 4: 301-306*

Keywords: remifentanil, propofol, desflurane, haemodynamics, controlled hypotension, paediatric anaesthesia

Introduction

Controlled hypotension during general anaesthesia has been recommended for selected otorhinolaryngeal (ENT) surgery to reduce bleeding and improve visibility in the operative field [1,2]. Remifentanil (Ultiva, GlaxoSmithKline, GB), an ultrashort-acting μ-opioid receptor agonist, was found to be useful for anaesthesia requiring controlled hypotension. Remifentanil alone, by reducing the mucosal blood flow in the middle

ear, may secure the bloodless operative field both in adults and children undergoing tympanoplasty [3,4]. It is, however, is not sufficient for general anaesthesia and it has to be combined with hypnotic agents, intravenous or inhaled, and the choice of the latter may affect quality of anaesthesia. Propofol, diisopropyl phenol, and desflurane, a halogenated volatile agent, have favourable recovery characteristics, which make them particularly useful in paediatric anaesthesia for ENT procedures.

There have been no studies in which effects of propofol/remifentanil vs. desflurane/remifentanil on the cardiovascular system in paediatric ENT surgery have been compared.

Aim

We aimed to compare haemodynamic effects of propofol vs. desflurane during remifentanil-based controlled hypotension in children scheduled for elective ENT surgery.

Material and methods

The study was approved by the local institutional Ethics Committee. After obtaining written informed consent from parents and children older than 16 years, 41 ASA I and II class patients, aged 7-18 years, scheduled for elective otorhinolaryngeal surgery (septoplasty, endoscopic sinus surgery - ESS or antromastoidectomy) were enrolled to this prospective, randomized study. Patients were excluded from the study if they had a history of clinically relevant preoperative cardiac, pulmonary, hepatic or renal diseases, morbid obesity and if there were any contraindications for the drugs used in the study. Patients were randomly assigned to receive remifentanil/propofol (group PRO) or remifentanil/desflurane (group DES) based anaesthesia.

All children were premedicated orally with 0.3 mg/kg (up to 7.5 mg) midazolam one hour before the surgery. After arrival to the operating room the standard monitoring (ECG, pulse oximetry and NIBP) was affixed and infusion of Ringer's lactate was started at a rate of 4 ml/kg/h (patients aged 6-10 years) or 2 ml/kg/h (patients older than 10 years). Anaesthesia was induced using the same sequence in all patients. After the bolus dose of 0.5 μg/kg remifentanil (Ultiva, GlaxoSmithKline, UK), injected over 30 to 60 seconds, and injection of propofol (Propofol 1% MCT/LCT, Fresenius Kabi, Germany) in a dose 2 to 3 mg/kg titrated to hypnotic effect, 0.1 mg/kg vecuronium (Norcuron, MSD, USA) was given to facilitate tracheal intubation. During anaesthesia the patients were mechanically ventilated with oxygen/air mixture (FiO_2 0.35-0.45) to maintain normocapnia ($ETCO_2$ 35-45 mmHg) and SpO_2 between 96% and 100%. Analgesia was provided with 0.75 μg/kg/min continuous infusion of remifentanil. In PRO group 3 to 4 mg/kg/h propofol infusion was given for maintenance; patients in DES group received 3-4% ET desflurane (Suprane, Baxter, USA). Vecuronium was repeated in 0.03 to 0.05 mg/kg increments when required.

We aimed to maintain MAP within 50 - 65 mmHg range to minimize bleeding in the surgical field. HR, SBP, DBP and MAP were recorded in anaesthetic chart at 5 minute intervals. HR and MAP were noted at six time points: at T1 – before induction, T2 – 5 min after intubation, T3 – start of surgery, T4 – intraoperative period, T5 – end of surgery, T6 – after extubation.

Adverse haemodynamic incidents during anaesthesia were noted and defined as "inadequate hypotension" (MAP > 65 mmHg), "excessive hypotension" (MAP < 50 mmHg), "tachycardia" (HR above the upper limit of age-adjusted range values at rest), "bradycardia" (HR < 40/min). Episodes of inadequate anaesthesia were defined as an increase in MAP above 65 mmHg or a tachycardia episode and were treated in both groups, firstly by increasing the doses of respective anaesthetics by 25%, and, if not sufficient, by additional 0.5 μg/kg bolus doses of remifentanil.

Cardiovascular compromise (MAP below 50 mmHg) was initially treated with bolus of 10 ml/kg Ringer's lactate solution and, if insufficient, by infusion of 10 ml/kg 6% HES 130,000/04 (Voluven, Fresenius Kabi, Germany). If the volume replacement therapy was not effective, the infusion rate of remifentanil was decreased by 25%. Bradycardia was treated with atropine if required.

All patients received analgesia with 0.1 mg/kg subcutaneous morphine and 20 mg/kg iv paracetamol (Perfalgan, Bristol-Myers Squibb, USA) 30 minutes before the end of surgery.

The intraoperative bleeding and adequacy of a surgical field was done by an attending surgeon according to the bleeding score classification (Table 1) [5].

Table 1. The six-grade intraoperative bleeding scale [5]

0	No bleeding
1	Slight bleeding – no suctioning of blood required
2	Slight bleeding – occasional suctioning required. Surgical field not threatened
3	Slight bleeding – frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed
4	Moderate bleeding – frequent suctioning required. Bleeding threatens surgical field directly after suction is removed
5	Severe bleeding – constant suctioning required. Bleeding appears faster than can be removed by suction. Surgical field severely threatened and surgery impossible

Results

There were no significant differences in patient demographics among the groups (Table 2).

Table 2. Patient demographics, type and duration of surgery

	PRO N=21	DES N=20
Male / Female	13 / 8	12 / 8
Age (years)	12 ± 3	13 ± 3
Weight (kg)	41 ± 11	45 ± 16
Height (cm)	150.1 ± 14.5	147.5 ± 17.2
Duration of operation (min)	59.2 ± 24.6	69.2 ± 25.3
Duration of anaesthesia (min)	71.3 ± 28.1	80.4 ± 24.4

Values are presented as means ± SD. No statistically significant differences were observed between the groups.

There were no significant differences in baseline values (T1) of HR and MAP between the groups (Figures: 1 and 2). Although HR and MAP decreased significantly in each group after induction of anaesthesia (T2), there were no differences in HR and MAP between the groups at T2. During the further stages of surgery (T3-T5) the mean HR and MAP values were decreased in both groups. However, mean intraoperative (T4) HR and MAP values were significantly higher in PRO group. After extubation (T6) HR was significantly higher in DES group.

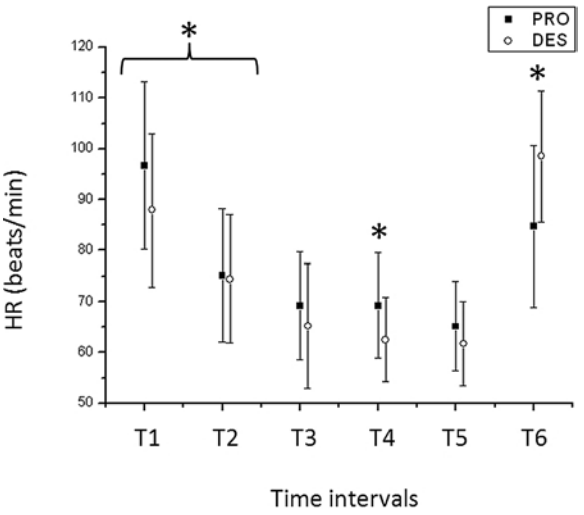

Figure 1. Heart rate during anesthesia in PRO and DES groups; time intervals: T1 – before induction, T2 – 5 min after intubation, T3 – start of surgery, T4 – intraoperative period, T5 – end of surgery, T6 – after extubation, * $p < 0.05$

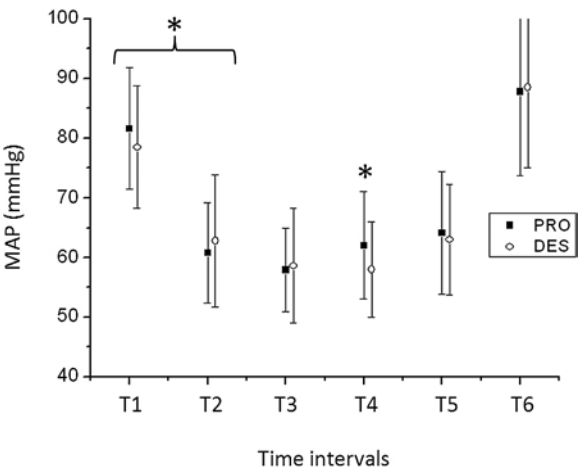

Figure 2. Mean arterial pressure during anaesthesia in PRO and DES groups; time intervals: T1 – before induction, T2 – 5 min after intubation, T3 – start of surgery, T4 – intraoperative period, T5 – end of surgery, T6 – after extubation, * $p < 0.05$

The targeted MAP range of 50 to 65 mmHg was reached in both groups (77% vs. 75%, p=ns) (Figure 3). Hypotensive episodes (MAP < 50 mmHg) were observed more frequently in DES group (1% vs. 10%, p<0.05)

(Figure 3). The median MAP values were 61 and 58 mmHg, in PRO and DES groups, respectively ($p<0.05$). Fifty percent of the observed MAP values were within 57-65 mmHg limits (PRO group) and 54-62 mm Hg limits (DES group). We observed a higher incidence of hypertensive episodes (MAP > 65 mmHg) in PRO group (22% vs. 15%, $p<0.05$) (Figure 3). The median HR value in PRO group was 65 bpm, in DES group 60 bpm; Fifty percent of recorded values were in range of 60-74 bpm in PRO group and 55-66 bpm in DES group. Adverse haemodynamic responses and therapeutic interventions were rare in both groups (Table 3) – however, occurred more frequently in DES group, where number of rescue volume replacement interventions was significantly higher.

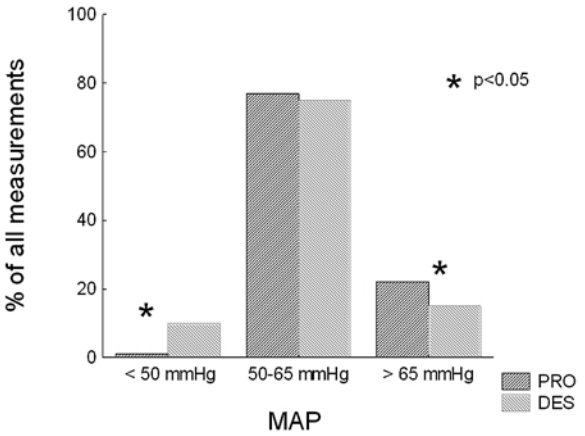

Figure 3. Distribution of mean arterial pressures in PRO and DES groups, * $p < 0.05$

Table 3. Adverse haemodynamic responses and therapeutic interventions

	PRO n=21	DES n=20
Adverse haemodynamic responses		
Severe hypotension	1 (5%)	3 (15%)
Bradycardia	1 (5%)	3 (15%)
Therapeutic interventions		
Rescue iv fluids	1 (5%)	5 (25%) *
Atropine	1 (5%)	2 (10%)
Decrease in remifentanil delivery rate	1 (5%)	4 (20%)

Values represent number of episodes (%), * $p < 0.05$

Bradycardia occurred in three patients of DES group and in one patient of PRO group and resolved promptly after iv atropine administration. The lowest noted HR values were: 36 bpm in PRO group, and 26 bpm - in DES group. The lowest noted MAP were: 48 mm Hg in PRO group, and 46 mmHg, 43 mmHg and 36 mmHg in DES group. All hypotension episodes responded to the volume replacement therapy and reduction of the remifentanil infusion rate. In both groups intraoperative bleeding was assessed as slight, suctioning was required occasionally and the quality of surgical field was not impaired.

Discussion

Remifentanil administered together with propofol or desflurane provided: a) similar degree of hypotension with MAP of 50-65 mmHg; b) good intraoperative conditions. It was also associated with low incidence of adverse cardiovascular effects. Propofol seemed to offer better haemodynamic stability than desflurane when combined with remifentanil.

The efficacy of remifentanil as a primary agent for controlled hypotension has been previously demonstrated by other authors, comparing remifentanil with nitroprusside sodium or esmolol. In adults undergoing tympanoplasty remifentanil was given in concentrations 0.25 to 0.5 μg/kg/min with parallel propofol infusion at the rate of 6 mg/kg/h, and the target level of hypotension was SBP of 80 mmHg [3]. In another study, conducted in children undergoing middle ear surgery, remifentanil 0.2-0.5 μg/kg/min was used with 2% sevoflurane, and the target MAP was 50 mmHg [4]. In both cases, regardless if it was combined with propofol or sevoflurane, remifentanil provided adequate hypotension and good surgical conditions. We could not find, however, any studies directly comparing effects of different anaesthetic agents on haemodynamic, when used with remifentanil as a primary hypotensive agent.

Propofol and desflurane, due to their favourable recovery characteristics [6], are widely used in paediatric settings [7]. Both drugs are known to compromise the cardiovascular system [8,9]. In this aspect, it was particularly interesting to investigate if propofol or desflurane can be useful during remifentanil-based controlled hypotension.

In this study we used anaesthetic methods and drugs routinely used in our department for the middle ear surgery, ESS and septoplasty - remifentanil in the induction dose of 0.5 μg/kg and infusion rate of 0.75 μg/kg/min with propofol 3-4 mg/kg/h or desflurane at the end-tidal concentration of 3-4%. It is worth

to mention that we used higher remifentanil infusion rates than recommended by Degoute et al. for several reasons. First, it has been shown that children require almost double remifentanil infusion rates than adults to block somatic response to skin incision during both propofol-TIVA and balanced anaesthesia with sevoflurane [10,11]. Second, some synergistic drug interaction between propofol and volatile agents and opioids have been described and clinically used [12,13]. The target mean propofol blood concentrations required to provide adequate anaesthesia are reduced when used with remifentanil, and they were assessed to be 4.96 μg/ml and 3.01 μg/ml, with remifentanil target blood concentration 2 ng/ml and 8 ng/ml, respectively [14]. Similarly, adding remifentanil to desflurane/60% nitrous oxide/oxygen mixture resulted in dose-dependent decrease of ED_{50} (concentration required to block the cardiovascular responses to skin incision in 50% of patients) 6.2–3–2.3% with remifentanil target-controlled concentrations 0–1–3 ng/ml, respectively) [15]. In most of these studies remifentanil and propofol were administered by target-controlled infusion (TCI) pumps, whereas in our study a conventional, non-modelled, TIVA was used. Also, the problem of equipotent anaesthetic doses arises when iv and volatile anaesthetics are compared. To assess depth of anaesthesia we relied on clinical signs. Although no somatic reactions were observed, children in the PRO group had higher incidence of tachycardic/hypertensive episodes and required more often the increase of propofol infusion rate (47.6% vs. 20%, $p<0.05$) and injection of remifentanil boluses (23.8% vs. 10%, p=ns).

Both anaesthetic methods were equally effective in inducing and maintaining MAP at 50-65 mmHg and providing good operative conditions. It is worth to mention, however, that mean intraoperative HR and MAP values were lower in DES group. The incidence of hypotensive and bradycardic episodes and the rate of therapeutic interventions to restore normal values were higher in patients anaesthetized with desflurane.

During induction and maintenance of anaesthesia propofol and desflurane present similar cardiovascular profile: they produce decrease in SBP, DBP, MAP, stroke volume and systemic vascular resistance [16,17]. HR does not change significantly after injection of propofol [8], whereas rapid increase in desflurane concentrations exceeding 1 MAC may result in sympathetic stimulation and tachycardia [9]. We observed, however, that the protocol based on high-dose remifentanil infusion and desflurane at concentration lower than 1 MAC decreased the risk of desflurane-related tachycardia. We must stress, that relatively low doses of propofol and desflurane concentrations used in this study are unlikely to be solely responsible for hypotensive episodes and bradycardia that occurred in our patients. The lowest heart rate was observed in DES group – 26 beats/min; this patient successfully responded to atropine. Observed bradycardia was probably caused by remifentanil - its depressive effects on cardiovascular system have been reported in clinical observations [18,19]. The mechanisms of opioid-induced hemodynamic changes remain unclear. In animal studies remifentanil decreased HR and MAP by its central vagotonic effect and by stimulation of the peripheral μ-opioid receptors [20]. In children, during echocardiographic study, remifentanil decreased blood pressure and cardiac index, mainly as a result of decreased heart rate [21]. Although in this study atropine was able to minimize bradycardic effects, it did not completely prevent the compromise of cardiac index, which may suggest the direct negative chronotropic effect of remifentanil.

In experimental studies on isolated human atria remifentanil had no direct effect on the contractility of myocardium [22]. It produced, however, "concentration-dependent" relaxation in human saphenous vein strips. The venous dilatation, observed in this study, was independent from the venous endothelium, which was removed prior to the exposure to remifentanil from one part of vein strips, and left intact in the other. This proved that the endothelium or mediators from the endothelium such as nitric oxide or prostaglandins were probably not involved in the mechanism of the relaxation, which, in turn, suggested direct vascular effect of remifentanil [22].

Unique pharmacokinetic properties of remifentanil - extremely short context-sensitive half-time and its quick metabolism by plasma esterases allow easy titration of this drug and are responsible for rapid offset of its actions after infusion stop. Remifentanil, used by a skilful and experienced anaesthesiologist working with modern monitoring techniques seems to be a logic choice for described settings.

Conclusions

1. Both methods of anaesthesia described in the study provided good operating conditions for an ENT surgeon.

2. Remifentanil-propofol anaesthesia provided better haemodynamic stability than the one based on remifentanil-desflurane.
3. Propofol seems to be preferable adjunct to remifentanil-based controlled hypotension in paediatric ENT procedures. However, in each case a great vigilance of the anaesthesiologist is required because of possible haemodynamic side effects.

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