Remifentanil versus fentanyl for propofol-based anaesthesia in ambulatory surgery in children

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Abstract

Aim: To test whether remifentanil results in significantly more rapid emergence in children anaesthesia.

Methods: In forty children, age 1-6 yrs, general anaesthesia was induced and maintained with propofol. The patients were randomized to receive either fentanyl 2 µg/kg at start and then 1 µg /kg as needed or remifentanil 1 µg /kg bolus followed by infusion of 0.5 µg /kg/min.

Results: The remifentanil patients had significantly less signs of minor movement at start of surgery, lower heart rate, lower systolic blood-pressure, less total dose of propofol during the procedure and higher need of postoperative opioid pain rescue.

Conclusions: Remifentanil, as dosed in this study, did not result in clinical significant benefits.

Keywords: General Anaesthesia, Remifentanil, Fentanyl, Children, Ambulatory Surgery.

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Introduction

Propofol and opioid anaesthesia in children are preferred by many anaesthesiologists in Norway due to the lower incidence of post-operative agitation, pain and nausea when compared with inhalational techniques [1,2]. However, the traditional opioid anaesthetics such as sufentanil or fentanyl have been associated with side-effects due to prolonged opioid effect; such as delayed emergence, delay in spontaneous breathing and respiratory control as well as cases of opioid induced nausea or vomiting [1,3]. Remifentanil, being a very short acting opioid, should potentially result in fewer of these side effects while also allowing for higher opioid dosing and better control of stress response and haemodynamics during the surgical procedure. In a review of different opioids for adult general anaesthesia in 85 trials and 13,057 patients, the remifentanil patients had clinical signs of deeper anaesthesia, i.e. less occurrence of haemodynamic stress response during surgery but also more episodes of hypotension and bradycardia [4]. Postoperatively, remifentanil was associated with more rapid emergence and less respiratory events, but more need of supplemental analgesics, whereas nausea or vomiting occurred with similar frequency as with the other opioids [4].

In children there is less documentation on the potential clinical outcomes of using remifentanil instead of fentanyl as a supplement during propofol based anaesthesia, although a meta-analysis in 2006 concluded on remifentanil as a safe and effective alternative in children [5].

The purpose of our study was to compare remifentanil with fentanyl for emergence as well as perioperative haemodynamic variables and side-effects during elective ambulatory surgery in children given propofol infusion anaesthetic with a non-opioid multimodal analgesic regimen.

Methods

The protocol of this randomized, double blind study was reviewed and approved by the Regional Committee for Medical Research Ethics in Eastern Norway.

ASA I children (1–6 years) scheduled for elective surgery of hernia, testicular retention or hydrocoele were included after written informed consent had been obtained from the parents.

Exclusion criteria were regular use of any drugs or known contraindication to any planned medication or anaesthesia method.

All patients received local anaesthetic pads (EMLA®, Astra-Zeneca, Sweden) on dorsum of both hands or feet at least 60 min before start of anaesthesia and oral premedication with midazolam 0.5 mg/kg 30–60 min before start of anaesthesia.

All patients received an IV cannula before start of anaesthesia, while sitting on parent's knee. Then propofol 3 mg/kg was given, immediately followed by opioid per their randomized allocation (see below, Group allocation). A facemask or a laryngeal mask airway (LMA) was inserted and the patients were normoventilated with 30% oxygen in air throughout the procedure. Intravenously paracetamol (Perfalgan ®) 20 mg/kg was given in a separate cannula immediately after induction of anaesthesia. Propofol 15 mg/kg/hr infusion was given initially for maintenance of anaesthesia, and then adjusted to maintain BIS values between 45 and 55. Opioid was given as either fentanyl in repeated bolus dosing or remifentanil by infusion (see below).

At start of final wound closure, propofol infusion and opioid infusion or supplements were stopped. Bupivacaine, 0.5 ml/kg of 2.5 mg/ml was infiltrated locally in the surgical wound by end of surgery. Patients with testicular retention received a sacral block with bupivacaine 1.67 mg/ml, 1 ml per kg weight, maximum 20 ml. For postoperative pain relief paracetamol 20 mg/kg was given rectally every 6 hr if needed, and while in the unit with IV ketobemidone 0.05 mg/kg.

Subjects were randomized to receive per-operative opioid supplement with either fentanyl (Group F) or remifentanil (Group R)

based on computer-generated code stored in sequentially numbered, sealed envelopes which were opened immediately before start of anaesthesia. The nurses who registered postoperative data were blinded as to group allocation of the patients.

In Group F a starting dose of fentanyl 2 µg/kg was given IV as part of anaesthetic induction. Additional supplements of fentanyl 1 µg/kg were given by start of surgery and additionally throughout surgery, upon any sign of movement or heart rate or systolic blood pressure above 130% of resting value.

In Group R, remifentanil was given as continuous IV infusion, starting during induction with a bolus of 1 µg/kg, then 0.5 µg/kg/min initially. The infusion rate was adjusted up upon any sign of movement, or heart rate or systolic blood pressure above 130% of resting value, and adjusted down by signs of hypotension or bradycardia. During induction, time to loss of eyelash reflex was registered, as well as reactions to LMA insertion, any signs of movements, tears or abnormal vital signs (i.e. BP, heart rate, pulse oxymeter reading). Any reaction upon start of surgery was noted as well as regular recordings of vital signs and BIS through the procedure. After end of surgery the time to spontaneous breathing, removal of laryngeal mask, emergence and discharge from the OR were noted, as well as any signs of physical or emotional distress. In the postoperative care unit, times to sit and eating ice cream were noted, as well as regular evaluation of pain, agitation and retching/vomiting using a 4-point verbal scale: none-little-medium-much-very much. As judged by the trained postoperative nurse, ketobemidone 0.05 mg/kg was given iv when needed for clinical signs of pain. Time to home discharge readiness and actual discharge were noted.

Statistics: Time from end of surgery until eyes opening during emergence was the primary efficacy variable. We wanted to show with significance of 0.05 if any group had a mean reduction in this variable by 50%, with a standard deviation of mean in both groups of 50%. With 20 patients per group a power of 90% was calculated for revealing such a difference. The data set was analyzed using independent samples T-test for continuous variables with nearly normal distribution; otherwise the Mann-Whitney U-test was used. The Chi-square test was used for categorical data. Repeated measures ANOVA was used for VAS scores and sedations scores. Data were analyzed in SPSS 16.0. The significance level was set to 0.05.

Table 1 Demographic and preoperative data (mean ± SD) or n.

	Group F (n=20)	Group R (n=20)	
Age (yr)	3.1 ± 1.6	4.3 ± 2.0	(P=0.08)
Weight (kg)	15 ± 5.1	18 ± 6.0	
Gender (boy/girl) (n)	15 / 1	14 / 1	
Tired before induction (n: yes/no)*	18 / 2	19 / 1	
Paracetamol dose (mg)	295 ± 92	355 ± 117	
Preop heart rate (beats/min)	106 ± 21	96 ± 23	(P=0.12)

*The anaesthesist should evaluate if the child appeared normal or tired.

Results

Forty patients were studied per protocol for the planned peroperative and postoperative period (Fig. 1). Demographic and preoperative data were similar in the two groups (Table 1). Dose of local anaesthetic as well as type and duration of surgery were also similar (Table 2). The doses of propofol were lower in Group R.

The remifentanil patients had significantly less movements at start of surgery, and lower values of blood pressure and heart rate during the procedure (Table 2). There was wide variability in the time to resume spontaneous ventilation. Postoperatively, the time to emergence, transport out of OR, time to sit and time to discharge and discharge readiness were similar in the 2 groups (Table 3). Postoperative pain and incidence of vomiting were also similar, but significantly more patients in the remifentanil group needed rescue opioid before discharge (25% versus 55%) None of the patients needed more than 2 doses of iv rescue opioid (Table 3). Time to eat ice cream in the remifentanil group was significantly shorter than for fentanyl (91±37 vs 120±42, mean±SD, P=0.03).

There were no serious side-effects in any patient.

Discussion

There were no serious problems or complications in any of the children studied.

Our study showed that remifentanil allowed for deeper and stronger general anaesthetic effect during surgery with few differences between the groups postoperatively. More remifentanil subjects needed rescue analgesia postoperatively but had significantly shorter time to eat ice-cream. There were no serious problems or complications in any of the children studied.

As both remifentanil and fentanyl are considered to be pure µ-agonists [5] , there should be no difference in quality of effect or side-effects at strictly equipotent doses. Thus, with a higher dose of fentanyl it would most probably not be any problem to match the abscense of movements and the low values of blood-pressure and heart rate seen with remifentanil in our patients. In a study of intubation in children, less stress response was shown with remifentanil [6] whereas a study on cardiac children surgery showed similar heamodynamics with remifentanil when compared to fentanyl [7]. Our study may thus be criticised for not having used equipotent per-operative dosing, in order to visualize the potential benefits of rapid elimination of remifentanil. Still, the fentanyl dosing used in our study seemed to be adequate, there were only one child (as with remifentanil) with a medium reaction to start of surgery, and only two cases with episodes of moderate hypertension or tachycardia (ns).

The equipotent doses of remifentanil versus fentanyl is hard to calculate, as remifentanil has a more rapid onset and a very much more rapid offset and elimination than fentanyl. In a study of equiananaesthetic doses of fentanyl vs remifentanil in adults, Vuyk found a dose relationship of 3:1 during induction, but 1:8–10 during maintenance for 30 min [8]). In our study the induction dose rate was 2:1 and the maintenance 1:15, thus the opioid effect of remifentanil should be expected to be stronger. Then, the question will be if we should have reduced the remifentanil dose. We had two cases of hypotention or bradycardia in the remifentanil patients (ns), but an almost significant prolongation of apnoe after end of surgery (3.6 min vs 0.9 min after fentanyl, P=0.07) suggesting that the opoid effect from remifentanil dosing certainly were stronger at that point. There were no indications of severe residual opioid respiratory or haemodynamic effects with remifentanil, as the LMA removal and discharge from OR were similar in both groups. In a study of

Table 2 Peri- operative data (mean ± SD) or n.

	Group F (n=20)	Group R (n=20)	
Time to loss of eyelash reflex (sec)	11 ± 5.9	17 ± 2.7	
Movements at start of surgery (none/small/medium/strong)	6 / 13 / 1 / 0	17 / 2 / 1 / 0	P=0.002
Type of surgery (n) Inguinal hernia Testicular retention Testicular hydrocoele Umbilical hernia	 9 8 2 1	 11 8 1 0	
Duration of surgery (min)	28 ± 11	24 ± 5.7	
Caudal anaesthesia (yes/no)	7 / 12	7 /13	
Highest heart rate (beats/min)	119 ± 22	97 ± 21	(P=0.003)
Lowest heart rate	95 ± 16	75 ± 14	(P=0.001)
Average heart rate	105 ± 17	85 ± 91	(P=0.003)
Bradycardia (< 60/min, n)	0	1	
Tachycardia (>150/min, n)	2	0	
Highest systolic BP (mmHg)	95 ± 8.1	83 ± 7.9	(P=0.001)
Lowest syst BP	79 ± 8.9	69 ± 8.4	(P=0.01)
Average syst BP	87 ± 6.5	76 ± 5.4	(P=0.001)
Hypertension (>110, n)	1	0	
Hypotension (<60, n)	0	2	
Lowest oxygen saturation (%)	97± 4.3	97 ± 4.1	
Patients with sat <90% (n)	1	1	
Total propofol dose (mg)	206 ± 64	206 ± 64	
Propofol dose; mg/kg	14 ± 5	10 ± 6	
Total time in OR (min)	50 ± 14	47 ± 9.3	

Table 3 Post- operative data (mean ± SD) or n:.

	Group F (n=20)	Group R (n=20)	
Time to spontaneous breathing (min*)	0.94 ± 3.9	3.6 ± 4.6	(P=0.06)
Time to LMA removal	4.1 ± 3.7	5.1 ± 5.1	
Out of OR (min*)	7.9 ± 4.0	9.7 ± 4.6	
Awake (min *)	63 ± 27	50 ± 27	(P=0.09)
Able to sit (min *)	113 ± 44	108 ± 28	
Able to eat ice-cream (min *)	119 ± 42	91 ± 37	(P=0.03)
Pain (no/minor/medium/much) Need of rescue opioid (n) 1 dose / 2 doses	5 / 8 / 1 / 4 5 3/2	4 / 6 / 7 / 2 11 6/5	(P=0.05)
Restless (no/minor/medium/much)	8 / 4 / 3 / 4	8 / 4 / 3 / 4	
Vomiting (n)	0	2	
Home ready (min *)	207 ± 53	207 ± 53	(P=0.09)
Sent home (min *)	227 ± 51	213 ± 66	

* Min after end of surgery.

tonsillectomy in ENT children, Davis et al were able to show more rapid extubation after remifentanil when compared to fentanyl, but also at the cost of more postoperative pain [9].

The mean time to emergence of 4–5 minutes in both our groups may seem long, but may be a result of the standardized research setting where propofol was running until end of surgery. In a clinical situation most anaesthesiologist will taper down the infusion rate towards end of surgery and eventually stop the pump before the last suture is done.

In terms of post-operative characteristics of remifentanil as a shortacting opioid, we confirmed previous studies showing that the need of rescue analgesia was higher than with fentanyl, in 11 vs 5 patients (P=0.5). This was in spite of multimodal non-opioid pain prophylaxis with iv paracetamol, local anaesthesia wound infiltration or many cases with caudal analgesia. The incidence of vomiting was negligible, only 2 patients among the 40 studied, both in the remifentanil group. Recording nausea is a more sensitive variable than vomiting, but as nausea is a subjective experience expressed verbally, it is hard to study in young children. After procedures with a high incidence of vomiting, such as strabismus surgery in children, Eltzsig et al showed less episodes of vomiting when fentanyl was replaced by remifentanil [10]. An indication of low incidence of nausea in our study was that all children were able to eat ice-cream within 2–3 hrs postoperatively. Although significantly sooner in the remifentanil group, this may be a coincidental finding as the p-value of significance was only 0.03.

In terms of home readiness, there were no significant differences between the groups, all children being sent home within 4–5 hours after the procedure. This long mean time before discharge is due to the children usually being accompanied by one parent in the recovery unit, and usually allowed to stay there until one more parent or relative arrives in the afternoon for assistance during home travel.

Fentanyl is cheap, ready for use and was given by simple bolus dosing due to a more smoth and slow onset and offset. Remifentanil is a little more demanding, it has to be prepared from powder and preferably given by a syringe pump. A fentanyl ampoule of 100 µg costs about 1.2 euro, whereas the smallest glass of 1000 µg remifentanil costs about 9 euro. As the remifentanil vial may be divided into 4–5 patients and fentanyl into 2 patients, the minor cost level and difference between these drugs become rather negligible in the context of all other direct and indirect costs associated with a surgical case in a child.

In conclusion, with our dosing schedule of remifentanil or fentanyl, the clinical characteristics came out quite similar. Still, remifentanil may allow for better control of haemodynamics and stress response during surgery, but may be associated with more need of postoperative opioid rescue.

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References

1. Lerman J, Johr M. Inhalational anesthesia vs total intravenous anesthesia (TIVA) for pediatric anesthesia. ***Paediatr Anaesth*** 2009;***19***:521–34.
2. Glaisyer HR, Sury MR. Recovery after anesthesia for short pediatric oncology procedures: propofol and remifentanil compared with propofol, nitrous oxide, and sevoflurane. ***Anesth Analg*** 2005;***100***:959–63.
3. Hofer CK, Zollinger A, Buchi S, et al. Patient well-being after general anaesthesia: a prospective, randomized, controlled multi-centre trial comparing intravenous and inhalation anaesthesia. ***Br J Anaesth*** 2003;**91**:631–7.
4. Komatsu R, Turan AM, Orhan-Sungur M, et al. Remifentanil for general anaesthesia: a systematic review. ***Anaesthesia*** 2007;**62**:1266–80.
5. Welzing L, Roth B. Experience with remifentanil in neonates and infants. ***Drugs*** 2006;**66**:1339–50.
6. Yang QY, Xue FS, Liao X, et al. Comparison of bolus remifentanil versus bolus fentanyl for blunting cardiovascular intubation responses in children: a randomized, double-blind study. ***Chin Med J*** (Engl) 2009;**122**:44–50.
7. Akpek EA, Erkaya C, Donmez A, et al. Remifentanil use in children undergoing congenital heart surgery for left-to-right shunt lesions. ***J Cardiothorac Vasc Anesth*** 2005;**19**:60–6.
8. Vuyk J, Mertens MJ, Olofsen E, et al. Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. ***Anesthesiology*** 1997;**87**:1549–62.
9. Davis PJ, Finkel JC, Orr RJ, et al. A randomized, double-blinded study of remifentanil versus fentanyl for tonsillectomy and adenoidectomy surgery in pediatric ambulatory surgical patients. ***Anesth Analg*** 2000;**90**:863–71.
10. Eltzschig HK, Schroeder TH, Eissler BJ, et al. The effect of remifentanil or fentanyl on postoperative vomiting and pain in children undergoing strabismus surgery. ***Anesth Analg*** 2002;**94**:1173-7, table.