

Comparison of remifentanil versus ketamine for paediatric day case adenoidectomy

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Summary : Few studies exist of using remifentanil and intravenous ketamine for anaesthetic induction in paediatric day case anaesthesia. Therefore, we studied 75 unpremedicated ASA I-II children (age 1-7 years) who were randomly assigned in a double-blind fashion to receive either remifentanil (1 µg/kg), ketamine (0.7 mg/kg) or placebo before the anaesthetic induction. Anaesthesia was induced with propofol and maintained with O₂-N₂O-sevoflurane. Induction characteristics, recovery times and the need for postoperative analgesia were evaluated. The required induction dose of propofol was lower in the groups receiving remifentanil and ketamine compared with the group receiving placebo. After tracheal intubation heart rate and blood pressure were better attenuated with remifentanil than with ketamine or placebo. In the recovery room children in the placebo group required more doses of oxycodone than the other two groups but this did not reach statistical significance. There were no differences between the groups in achieving predetermined recovery end-points, attaining full points on the Steward score or in the well being at home. In conclusion, remifentanil provides haemodynamically more stable induction of anaesthesia compared with ketamine or placebo. Ketamine with its' longer duration of action does not prolong recovery but does not have a clear opioid-sparing effect either in the immediate postoperative period.

Key words : Anaesthesia : paediatric ; Surgery : day case ; Anaesthetics : intravenous, ketamine, remifentanil.

INTRODUCTION

The anaesthetics used in paediatric day case surgery should enable quick recovery and good pain relief without compromising the child's safe return home (26). Remifentanil, a potent µ agonist (3), could be suitable for paediatric outpatient surgery because of its short duration of action (6). It has been found to attenuate haemodynamic responses to tracheal intubation as well as alfentanil in children (22). On the other hand, DAVIS *et al.* found that postoperative pain/discomfort scores were higher with remifentanil compared to fentanyl after

adenotonsillectomy and suggest that postoperative pain should be effectively taken care of with intra-operative prophylactic analgesics (6).

Ketamine in smaller doses has been reintroduced into the anaesthetic practice mainly to improve postoperative analgesia (18). A small dose (0.1-0.5 mg/kg) of ketamine, while minimizing unwanted psychotomimetic reactions, has a noticeable analgesic effect (14). This has been found to be particularly useful in supplementing regional or local anaesthesia (14). When given orally as a premedication, it has been found to prolong recovery (1) and has therefore not gained popularity in day case anaesthesia.

There are few studies of remifentanil in paediatric patients and to our knowledge none exists of ketamine when used in small doses. Therefore, our aim was to compare both drugs in the same setting to investigate their induction characteristics and recovery profiles after a short-lasting procedure such as adenoidectomy. We tested the hypothesis that small-dose ketamine, with its longer duration of action, could provide better immediate postoperative analgesia after surgery but would not delay recovery compared with remifentanil or placebo.

METHODS

After institutional ethics committee approval and written, informed parental consent 75 children

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(ASA physical status I or II, aged 1-7 yr) scheduled for day case adenoidectomy (with or without myringotomy) were included in the study.

A randomized, double-blind, placebo-controlled study design was used. The unpremedicated children were randomly allocated (sealed envelope method) to receive either remifentanyl, ketamine or placebo. After arrival in the operating room, routine monitoring was applied and an intravenous (i.v.) cannula was inserted (facilitated by EMLA® cream; Astra, Sweden). Atropine 0.01 mg/kg i.v. was administered before induction of anaesthesia. Children received 0.1 ml/kg of the study drug which consisted of either remifentanyl 10 µg/ml, ketamine 7 mg/ml or 0.9% saline (placebo) injected over 15 s. Thus, the remifentanyl dose was 1 µg/kg and the ketamine dose 0.7 mg/kg. The study drugs were prepared by a nurse not otherwise participating in the care of the children. We waited thirty seconds after administration of the study drugs. Anaesthesia was then induced with propofol, given manually 10 mg/sec, until the eyelash reflex disappeared after which suxamethonium 1.5 mg/kg was given to facilitate tracheal intubation. Pain on injection of propofol was assessed using a four-point scale, where 0 = none, 1 = mild (grimacing), 3 = moderate (crying), 4 = withdraws hand (19). All observers, as well as the children and their parents, were unaware of the study drug used. The child was ventilated with 100% oxygen and after intubation anaesthesia was continued with sevoflurane in N₂O 67% in O₂. Adenoidectomy was started immediately (in 2-5 min) after the intubation, because the ear-nose surgeon was ready in the theatre to start the procedure after the induction of anaesthesia. The inspired sevoflurane concentration was adjusted to maintain mean arterial blood pressure (MAP) within ± 20% of initial readings which was 3-4% of inhaled sevoflurane. A semi-closed circle system was used throughout anaesthesia and ventilation was controlled to maintain normocapnia. Immediately after intubation a suppository of acetaminophen 20 mg/kg was administered for postoperative analgesia. Oxygen saturation (SpO₂), end-tidal carbon dioxide values (Capnomac Ultima™; Datex, Finland) and heart rate (HR) were monitored continuously. Blood pressure (BP) was recorded automatically before intubation, after intubation and every 5 min during surgery. At the end of surgery, all anaesthetics were discontinued and extubation performed when spontaneous breathing was regarded as adequate. All children were extubated while still unconscious. Surgical conditions were scored by the surgeon as

easy, moderate or difficult on the basis of bleeding, ease of inserting the mouth gag or patient reaction. In the recovery room, vital signs (HR, BP, SpO₂) were monitored until the child was fully awake. Parents of the children were allowed to enter the recovery room once the child had woken up. A trained nurse who was blinded to the anaesthetic induction protocol evaluated every patient during the recovery period. Early recovery was assessed using the Steward score (27). The child was evaluated every 15 min for the first hour then every 30 min until discharge. The following recovery times (from discontinuation of sevoflurane and nitrous oxide) were also recorded: (1) time to opening eyes spontaneously (emergence); (2) time to responding to the nurse or parent (interaction); (3) time to be able to ambulate according to age; and (4) time to achieving discharge criteria. The discharge criteria were: fully awake, stable vital signs for at least 30 min, no bleeding, no signs of excessive pain, no vomiting, and able to ambulate according to age.

The quality of recovery was also evaluated. If the child was crying inconsolably, thrashing or was severely agitated he or she was regarded as suffering from post-anaesthetic excitement evaluated by the same and experienced recovery room nurse. Intravenous Oxanest® (Oxycodone; Orion Pharmaceuticals, Finland) 0.05 mg/kg was given for postoperative pain relief at the discretion of the recovery nurse; the time to administration of the first dose and the total amount of analgesic needed were recorded.

Upon discharge the parents were asked to fill in a postoperative questionnaire of the well being (pain, vomiting, tiredness, sleep) of the child at home until 24 hr after anaesthesia. They were advised to give acetaminophen, 20 mg/kg, per rectum at home whenever the child was in pain.

A power analysis demonstrated that a minimum of 17 patients would be required in each group to detect a 20 min difference in discharge times with an estimated discharge time of 90 min (SD 20) in the placebo group. This would give the study an 80% power (1-β) at a significance level of 5%. Results are presented as mean ± SD or number (%) where appropriate. Demographic data were analyzed using one-way ANOVA with Bonferroni's correction. Continuous non-parametric data were analyzed with the Kruskal-Wallis and Mann-Whitney U tests. Differences in categorical data were compared with χ²-test and the Fishers' exact test, where appropriate. A p value of < 0.05 was considered significant.

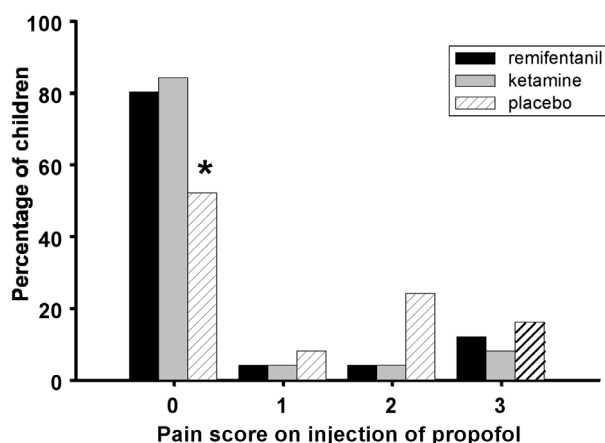


Fig. 1. — Pain scores on injection of propofol in the different study groups. 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = withdraws hand. * p = 0.02 placebo group vs remifentanil and ketamine groups.

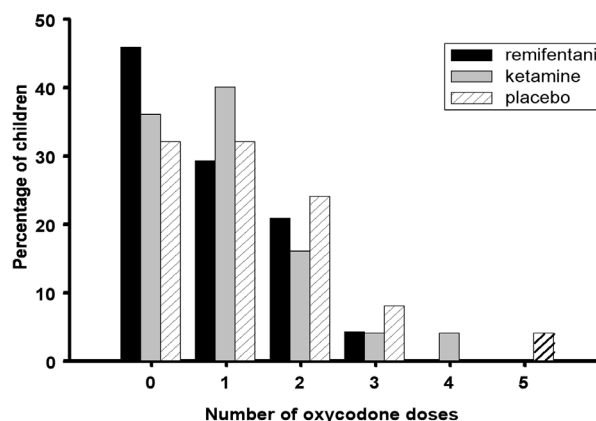


Fig. 2. — Number of oxycodone doses given to the children in the different study groups. No statistically significant differences between groups.

Table I

Demographics and anaesthetic data of the patients

	Remifentanil (n = 25)	Ketamine (n = 25)	Placebo (n = 25)
Age (mo)	46 (25)*	31 (21)	35 (22)
Weight (kg)	17 (5)	14 (5)	15 (6)
Duration of anaesthesia (min)	26 (12)	24 (9)	23 (7)
Propofol (mg/kg)	2.7 (0.5)**	2.6 (0.4)***	3.0 (0.5)

Data are mean (SD). * p = 0.018 vs ketamine, ** p = 0.03 vs placebo, *** p = 0.017 vs placebo.

RESULTS

Apart from the children in the remifentanil group being older than the children in the ketamine group, the three study groups were demographically comparable (Table I). The required induction dose of propofol was lower in the groups receiving remifentanil and ketamine compared with the group receiving placebo (Table I). More children experienced no pain on injection of propofol in the remifentanil and ketamine groups than in the placebo group (p = 0.02) (Fig. 1). There were no differences between the groups in the surgical conditions assessed by the operator. Remifentanil attenuated the haemodynamic response to tracheal intubation better than ketamine and placebo (Tables II and III). Three (12%) of the children receiving ketamine experienced laryngospasm at extubation (p = 0.08 vs the two other groups).

Eleven (45.8%), 9 (36%) and 8 (32%) children in the remifentanil, ketamine and placebo groups, respectively, did not need rescue analgesia after surgery (ns). The time to the first dose of oxycodone did not differ between groups. The children in the placebo group received more doses of oxy-

codone than the children in the remifentanil and ketamine groups but this did not reach statistical significance (Fig. 2).

There were no differences between the groups in achieving predetermined recovery end-points in the recovery room (Table IV) or attaining full points on the Steward score. Ten (41.7%), 4 (16.7%) and 6 (24%) children suffered from post-anaesthetic excitement upon awakening after anaesthesia in the remifentanil, ketamine and placebo groups, respectively (p = 0.13). Vomiting occurred in 1 (4%) child in the remifentanil and placebo groups each and 4 (16%) children in the ketamine group (p = 0.1). The only child with vomiting in the remifentanil group was treated with droperidol 0.2 mg i.v. because of repeated vomiting. No other serious adverse events were recorded.

The postoperative questionnaire was returned by 72 (96%) parents. Recovery at home did not differ between the groups. Five (21.7%), 3 (12.5%) and 4 (16%) children vomited at home in the remifentanil, ketamine and placebo groups respectively (ns). Eleven (47.8%), 11 (52.4%) and 7 (29.2%) children in the remifentanil, ketamine and placebo groups respectively did not need a rescue analgesic

Table II

Systolic blood pressure (mmHg) before (BI) and after (AI) tracheal intubation in the three study groups

	BI	AI	% increase
Remifentanyl (<i>n</i> = 25)	122 (21)	125 (21)	2.9%
Ketamine (<i>n</i> = 25)	131 (24)	140 (17)	6.6%
Placebo (<i>n</i> = 25)	126 (19)	138 (16)*	9.0% **

* *p* = 0.007 compared with the situation before intubation, ** *p* = 0.07 vs remifentanyl.

Table III

Heart rate (beats/min) before (BI) and after (AI) tracheal intubation in the three study groups

	BI	AI	% increase
Remifentanyl (<i>n</i> = 25)	116 (21)	119 (21)	2.8%
Ketamine (<i>n</i> = 25)	130 (24)	141 (18)*	7.9%
Placebo (<i>n</i> = 25)	132 (29)	140 (17)	6.3%

* *p* = 0.03 compared with heart rate before intubation.

at home (ns). None of the children reported nightmares during the night following surgery.

DISCUSSION

Our study shows that remifentanyl attenuates haemodynamic responses to intubation better than small-dose ketamine or placebo although the placebo group was given more propofol compared to the other groups. Ketamine did not prolong early recovery or discharge time compared with remifentanyl or placebo. However, it did not seem to have a clear opioid-sparing effect either. Recovery at home was similar in all groups.

The induction dose of remifentanyl was chosen according to previous studies (7, 20, 22), although doses of 2 to 4 µg/kg have also been given when muscle relaxants were not used (2, 13). According to the study of Ross *et al.* (23) the pharmacokinetics of remifentanyl in children aged 2-12 yr is very similar to those reported in adults. Similarly to ROBINSON *et al.* we found remifentanyl to provide haemodynamically stable induction of anaesthesia without any side-effects (22). We did not use a continuous infusion of remifentanyl after the induction dose as we aimed to provide similar inhalational anaesthesia with sevoflurane to all groups in order to compare recovery after the same maintenance agent. On the other hand, based on the study by DAVIS and colleagues, remifentanyl is such a short-acting drug, which, although administered as an infusion during anaesthesia, could not prevent

postoperative pain (6). On the contrary, in their study postoperative pain scores were higher compared to a bolus dose of fentanyl (6).

Because no studies exist on small-dose ketamine in paediatric day case anaesthesia, the dose of ketamine 0.7 mg/kg used in our study was based on studies evaluating the analgesic (9, 18, 24) and adverse effects of ketamine (2, 14, 25, 28). Ketamine is a potent analgesic at subanaesthetic plasma concentrations, probably due to its interaction with central and spinal opioid and NMDA receptors (21). CLEMENTS AND NIMMO showed that the analgesic effect of ketamine occurs at much lower plasma concentrations (100 ng/ml) than the anaesthetic effects (700 ng/ml) (5). When used with another i.v. agent, in this study propofol, doses can be reduced remarkably, in order to produce only the analgesic effect. In addition, with smaller doses unwanted psychotomimetic reactions can be reduced (14). SEKERCİ and colleagues found that no psychic reactions were recorded when the oral dose of ketamine was < 3 mg/kg (25). With small doses of i.v. ketamine (0.15 mg/kg – 1 mg/kg) psychotomimetic reactions did not occur (9, 18, 24, 29). Furthermore, bad dreams and hallucinations seem less frequent in children (28). In our study, neither hallucinations in the recovery room nor bad dreams occurred at home, although the dose of 0.7 mg/kg is higher than average amongst the studies using small-dose ketamine (9, 18, 24).

Ketamine is a cardiovascular stimulant and it increases plasma catecholamine concentrations (12). In our study with the dose of 0.7 mg/kg, intubation increased systolic blood pressure (SAP) by only 6.6%, which was less than that found in the placebo group (9%). On the other hand, HR increased by 7.9%, which was more than in the placebo group (6.3%). Similar results were found in the study by LEDOWSKI and colleagues with the dose of 0.5 mg/kg in adults (16). However, in their study after intubation both HR and MAP increased more in the placebo group than in the ketamine group. In our study in children, the placebo group was given more propofol for induction of anaesthesia, which may explain why HR and SAP did not increase to a larger extent. LEVY *et al.* found significant haemodynamic differences during anaesthetic induction with 1.5 mg/kg ketamine compared with alfentanil and placebo (17). Ketamine increased MAP by 13.8% and decreased HR by 2.5% when given after propofol induction and before intubation (17). We did not take blood pressures before the beginning of anaesthetic induction to provide less disturbance for the children. On the other hand,

Table IV

Recovery details (min) in the different study groups

	Remifentanil (n = 25)	Ketamine (n = 25)	Placebo (n = 25)
Time to first analgesia	15 (10)	19 (14)	20 (12)
Eyes open	11 (6)	10 (4)	12 (7)
Interaction	17 (10)	21 (15)	19 (8)
Ambulation	56 (27)	72 (28)	66 (27)
Home readiness	104 (30)	103 (31)	89 (24)

Data are mean (SD). No differences between groups.

we used atropine at induction of anaesthesia, which increases HR and may diminish the reliability of the haemodynamic responses of the i.v. agent *per se*.

Three patients in the ketamine group produced laryngospasm compared with none in the other groups. Similar results have been published earlier with ketamine (8, 11). ZSIGMOND and colleagues compared different doses of ketamine (6 mg/kg, 3.5 mg/kg and 2.5 mg/kg) and found that high dose caused proneness to laryngospasm (30). The difference in the occurrence of laryngospasm in this study did not reach statistical significance, which may have been due to our small sample size. Furthermore, we used atropine, which should in theory diminish the number of children suffering from laryngospasm because it reduces ketamine-induced excessive salivation (14).

We hypothesized that used in subanaesthetic doses ketamine would not prolong recovery after an anaesthesia of approximately 30 minutes of duration. Our results support this hypothesis. Earlier studies have shown that recovery time with ketamine is dose-dependent (14, 4). With oral ketamine (5 mg/kg) ALDERSON *et al.* found delayed recovery compared with midazolam 0.5 mg/kg (1). Furthermore, when used i.v. for cardiac catheterization, ketamine 2 mg/kg was found to delay recovery compared to propofol and was not recommended for this purpose (15). In our study, the dose of ketamine was optimal in that it did not delay recovery. On the other hand we could not detect any clear pre-emptive effect on postoperative pain found in earlier studies in adults (18, 24, 9). It is possible that paediatric patients need higher doses for a noticeable analgesic effect. GRANT *et al.* have previously discovered greater dose requirements of ketamine in children (10).

In conclusion, both remifentanil and small-dose ketamine are suitable for day case anaesthesia in children. Remifentanil attenuated the haemodynamic response to tracheal intubation better than

ketamine or placebo. Recovery characteristics did not differ between these drugs. No clear reduction in postoperative opioid consumption was discovered with ketamine.

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