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Ketamine for co-induction of anaesthesia in oral surgery

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Abstract

Ketamine has additive interaction with propofol and analgesic properties. The aim was to determine if ketamine co-induction reduced propofol induction doses, improved pain relief and produced any adverse effects. Forty ASA I and II patients scheduled for extraction of third molars were enrolled in a randomised, double blind study. Group ketamine patients ($n = 20$) received ketamine 0.3 mg/kg prior to induction with propofol running at 300 ml/h. Group control patients ($n = 20$) received a corresponding volume of normal saline. All patients were intubated and maintained on N_2O:O_2 admixture and isoflurane. Post-operatively, patients were given i.v. fentanyl boluses, oral Panadeine Forte or Oxycodone as rescue medication for pain. Data collected consisted of propofol induction doses, blood pressure and heart rate readings at 1 min intervals, visual analogue score (VAS) pain scores at various intervals and fentanyl requirements in recovery. Duration of surgery and time to discharge were also recorded. Possible side effects of nausea, dreams and hallucinations were noted. There was no significant difference in propofol induction doses, pain requirements and pain scores between the two groups. However, there was significant increase in the blood pressure ($P < 0.006$) and heart rate ($P < 0.009$) at induction. The discharge time in the ketamine group was not prolonged and no adverse side-effects like bad dreams or emergence delirium were noted. We conclude that low-dose ketamine at 0.3 mg/kg does not reduce the induction dose of propofol or improve the post-operative pain of oral surgery. However, this dose does not affect recovery or produce unpleasant side-effects, making it a possibility for use in day surgery.

Keywords: Co-induction; Ketamine; Additive interaction; Analgesia

1. Introduction

Co-induction of anaesthesia has been receiving wider acceptance recently as it offers advantages of improved effect profile, a more balanced ratio of desired versus adverse effects, simpler treatment requirements and lower costs [1]. Hitherto, the combination of midazolam and propofol has been most popular as the synergism between the two has reduced required doses of propofol by up to 40% [2].

Ketamine is an intravenous anaesthetic that has shown additive interaction with propofol when used for induction in female patients [3]. Furthermore, low dose ketamine has been shown to reduce post-operative pain [4] and by blocking *N*-methyl-D-aspartate (NMDA) receptors, may even possess a pre-emptive effect [5]. In the day surgery setting, co-induction with midazolam has not affected discharge times. However, ketamine has not been widely used as a co-induction agent as there have been concerns of delayed discharge and visual disturbances with confusion [6]. It was the aim of this study to determine if co-induction with ketamine in the day-surgery setting reduced propofol induction requirements, improved post-operative pain relief and affected recovery profiles of patients.

2. Methods

The study was approved by the Hospital Ethics Committee and all patients gave written informed consent to participate in a randomised, double-blinded study. Forty ASA I and II patients aged 17–50-years old admitted for extraction of wisdom teeth were ran-

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Table 1
Scoring for surgical difficulty of third molar extractions

Score	Description
(*A*) *Pre-surgical assessment*	
1	Periodontally involved with weak bone attachment
2	Vertical unimpacted (exposed)
3	Vertical soft tissue impactation
4	Mesioangular superficial
5	Mesioangular deep or distoangular superficial
6	Distoangular deep or horizontal superficial
7	Horizontal deep
(*B*) *Post-surgical assessment*	
a	Unfavourable root formation
b	Nerve involvement
c	Surgical access
d	Operative success including time taken

Pre-surgical assessment score (1–7) is strictly applied and then (i) left unchanged, (ii) increased by 1–3 or (iii) decreased by 1–3 according to a post-surgical assessment that includes a–d.

domly allocated into two groups by drawing encoded cards from an envelope. Patients received either a ketamine bolus of 0.3 mg/kg diluted in 10 mg/ml dilution (group ketamine) or a corresponding volume of normal saline (group control) prior to induction. The drawing of the cards and administration of the pre-induction drug was performed by a member of the team not involved in the anaesthetic.

A 22 gauge cannula was inserted in a suitable vein in the arm and baseline measurements of non-invasive blood pressure, arterial oxygen saturation (SaO_2) and heart rate were made. The patient was pre-oxygenated with oxygen 4 l/min by face-mask. After the initial injection of ketamine or normal saline, fentanyl at 1.5 μg/kg was injected 60 s later, followed by iv lignocaine 20 mg. After 20 s, anaesthesia was induced with a 1% propofol infusion running at 300 ml/h using a Graseby 3200 pump. The end-point of induction was reached when the anaesthetist lost verbal contact with the patient and there was no response to eyelash reflex, both of which were repeated in 5 s intervals. Thereafter, an appropriate dose of vecuronium was given and the patient was bagged on 4 l N_2O:2 l O_2 admixture with isoflurane at an end-tidal concentration of 1% for 2 min before nasal intubation. All patients were given local infiltration of lignocaine 2% with adrenaline 1:80 000 before surgery commenced.

The hemodynamic measurements were taken at 1 min intervals from administration of ketamine or normal saline till 5 min thereafter. The time to reach the end-point and the dose of propofol required were noted. The duration of surgery, degree of surgical difficulty and number of wisdom teeth extracted were recorded. The degree of surgical difficulty was scored by the surgeon performing the surgery based on a scoring system used by Rudkin et al. [7] (Table 1).

In the recovery, besides blood pressure, heart rate and SaO_2 measurements, time to discharge from phase II recovery were also recorded. Pain scores were taken by recovery staff who were blinded to the anaesthetic technique. We used a visual analogue score (VAS) with 0, no pain; and 10, worst pain ever which were taken at various intervals in the recovery. These were namely on arrival, 1 h after admission and upon discharge from the recovery ward. Rescue medication was given in the form of i.v. fentanyl boluses of 25 μg, oral Panadeine Forte 1 g and Oxycodone 10 mg. Vomiting requiring anti-emetic treatment with maxolon was also noted.

The next day, all patients were interviewed by telephone during which the analgesic requirements, possible post-operative effects of drowsiness, vomiting, hallucination, vivid dreaming or nightmares were asked. Global satisfaction was scored by patients at this time using a verbal rating scale (0, not satisfied; 1, neutral; 2, satisfied; 3, very satisfied).

Nominal data was analysed using student's *t*-test and non-parametric data was analysed using Mann–Whitney test. The χ^2-test was used to compare the number of patients requiring analgesics, anti-emetics and the incidence of dreaming and post-operative vomiting after discharge. Data are presented as mean ± S.D. $P < 0.05$ indicated a statistically significant difference between groups.

3. Results

Forty patients, 20 in each group were enrolled into the study. The two groups were comparable with respect to demographics, duration of surgery (Table 2) and in degree of difficulty of surgery (Fig. 1). The induction doses of propofol in total and per kg body weight were not significantly different (Table 2).

Although the number of patients requiring fentanyl rescue in the control group was almost twice the num-

Table 2
Demographics, duration of surgery and propofol induction doses of patients receiving ketamine or normal saline (control) prior to induction

Group	Age (years)	Weight (kg)	Duration of surgery (min)	Propofol dose (mg)	Propofol (mg/kg)
Ketamine ($n = 20$)	24.1 ± 5.3	68.4 ± 15.3	25.4 ± 13.9	95.2 ± 33.9	1.42 ± 0.47
Control ($n = 20$)	24.1 ± 6.6	68.1 ± 16.6	26.1 ± 14.9	111.5 ± 31.5	1.68 ± 0.49

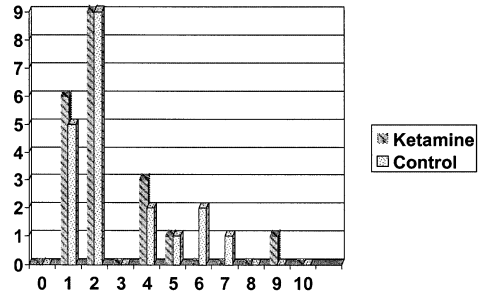

Fig. 1. Distribution of surgical difficulty by scoring.

ber in the ketamine group (nine vs. five, respectively), this was found to be not significant. Likewise, the mean dose of fentanyl given in the two groups was not significantly different (60 ± 37.9 vs. 86.1 ± 89.3 μg).

The time to first request for fentanyl was significantly longer in the ketamine group as compared with the control group (Table 3). When comparing pain scores, there were no significant differences in the pain scores between the groups taken on first admission, at 1 h and upon discharge from the recovery (Table 4).

Blood pressure and heart rate variables taken 2 min before induction and 5 min after induction did not show significant differences except for the readings at induction which corresponds to 2 min after the study drug was given (Tables 5 and 6). The blood pressure ($P < 0.006$) and heart rate ($P < 0.009$) values at this juncture were significantly higher in the ketamine group.

Discharge times of patients from phase II recovery and the number of patients requiring anti-emetics in recovery were not significantly different (Table 7).

The number of patients requiring Panadeine Forte 1 g and Oxycodone 10 mg in the recovery were as follows, 13 and 4, respectively, for ketamine group, 12 and 3, respectively, for the control group. Fifteen patients in the ketamine group required Panadeine Forte 1 g 4 h on the first post-operative day as compared with 16 patients in the control group. The number of patients who reported dreaming post-operatively were similar in both groups. Verbal satisfaction scores were not significantly different (Tables 7 and 8).

Table 5
Changes in MAP between the ketamine and control group over 7 min after test drug administered

Time at record of MAP	Ketamine group (mmHg)	Control group (mmHg)
On injection of ketamine/saline (0 min)	94.9 ± 9.4	94.9 ± 10.7
After 1 min	93.9 ± 9.4	92.8 ± 8.8
After 2 min	98.6 ± 10.8[a]	89.2 ± 9.5
After 3 min	97.0 ± 13.1	91.9 ± 15.9
After 4 min	96.3 ± 15.8	90.9 ± 11.9
After 5 min	94.3 ± 13.1	90.7 ± 19.1
After 6 min	95.5 ± 15.2	89.2 ± 19.1

[a] Significant group difference with $P < 0.05$.

Table 6
Changes in heart rate between the ketamine and control group over 7 min after test drug administered

Time at record of heart rate	Ketamine group (beats per min)	Control group (beats per min)
On injection of ketamine or saline (0 min)	79.5 ± 11.6	75.6 ± 13.8
After 1 min	81.4 ± 17.6	74.3 ± 15.6
After 2min	84.1 ± 18.1[a]	70.4 ± 12.6
After 3 min	83.8 ± 16.2	70.2 ± 13.1
After 4 min	81.6 ± 16.6	74.5 ± 10.9
After 5 min	80.5 ± 13.8	76.6 ± 16.3
After 6 min	82.5 ± 14.7	77.7 ± 15.5

[a] Significant group difference with $P < 0.05$.

4. Discussion

Propofol and ketamine have been shown to have an additive effect even though their mode of action is

Table 3
Number of patients requesting fentanyl, time to first request for fentanyl and mean doses of fentanyl for ketamine group and control group

Group	Number of patients requesting fentanyl	Time to first request (min)	Mean fentanyl dose (μg)
Ketamine	5/20	42.8 ± 46.9[a]	60 ± 37.9
Control	9/20	27.9 ± 14.6	86.1 ± 89.3

[a] Significant group difference with $P < 0.05$.

Table 4
Pain scores on arrival to recovery, 1 h after arrival and upon discharge from recovery for ketamine group and control group

Group	Pain score on arrival	Pain score 1 h after	Pain score on discharge
Ketamine	1.23 ± 3.45	2.63 ± 2.63	2.1 ± 2.05
Control	1.42 ± 3.63	2.35 ± 1.63	3.1 ± 2.19

mediated by different receptors [3]. In the study by Hui et al., the ED_{50}s to achieve hypnotic end-point as denoted by failure to open the eyes on verbal command were 0.97 mg/kg propofol and 0.33 mg/kg ketamine. Sakai et al. [8] showed similar additive interaction between the two for achieving hypnotic endpoints, however, only ketamine bolus more than 0.5 mg/kg iv followed by an adjunctive ketamine infusion, resulted in reduction of propofol doses for achieving hypnosis. In our study, we found that ketamine 0.3 mg/kg given at induction did not reduce the induction doses of propofol significantly. This could be due to two reasons. Unlike the previous two studies where the patients were mainly Asian in origin, our patient population comprised mainly of Caucasians and by nature of the surgery that was performed, our patients were young and likely to be anxious. Baseline anxiety has been shown to increase anaesthetic requirements [9] and Kindler et al. have demonstrated a high degree of anxiety in young patients [10]. Thus the study dose of ketamine although effective in the previous study [3] for co-induction, may not have been sufficient for our study population to cause an appreciable difference in propofol induction doses. Secondly, the patients who received ketamine showed a significantly higher blood pressure and heart rate compared with the control group. This would result in a reciprocal increase in the cardiac index which has been demonstrated with ketamine before [11,12]. Cardiac output on brain concentration of propofol has been demonstrated in the sheep model and this has been found to be inversely proportional [13]. We postulate that with this increase in cardiac output by ketamine, the distribution of propofol to the brain is reduced and although previous studies have shown additive effect between the two drugs, this effect of ketamine on propofol brain concentration may cancel out its effectiveness as a co-induction agent.

Previous studies have shown low dose ketamine to reduce post-operative pain [5,14,15] and Suzuki et al. [16] had even showed the analgesic effect of ketamine to last for three to five plasma half-lives of ketamine. Our study failed to demonstrate a reduced need for analgesia in the form of intravenous fentanyl, oral Panadeine Forte or Oxycodone in the immediate post-operative period up to discharge time in the ketamine group. Although the time to first request for fentanyl was longer in the ketamine group as compared with the control group ($P < 0.05$), this beneficial effect was not delayed sufficiently to reduce overall analgesic demands while in the recovery.

This lack of difference in analgesic needs between the two groups could be due to the local infiltration of lignocaine at the start of the surgery which would have masked the subtle effect of ketamine on analgesia as evidenced by the mean fentanyl requirements in phase I recovery.

We had deliberately chosen not to omit the local anaesthetic as it was intended to assess if ketamine further augmented the standard pain relief methods that were in use.

Since none of the patients received ketamine after the surgical procedure coupled with iv fentanyl and local infiltration prior to incision, we are unable to comment on the efficacy of pre-emptive administration of ketamine. Some previous studies [4,5,16] have shown the analgesic effect of low-dose ketamine to be long-lasting and may even decrease analgesic requirements for up to 2 days post-operatively, far outlasting the duration of action of ketamine. In our study, we were unable to demonstrate this reduction in Panadeine Forte requirements in the ketamine group on the first post-operative day, by which time the local anaesthetic had worn off. Ketamine is said to mediate analgesia via various mechanisms of which one is the synergistic or additive interaction among opioids, which elicits activation of the NMDA receptors [17] and NMDA antagonists. Unlike the previous studies which used morphine for post-operative analgesia, our patients were given Panadeine Forte and this interaction was not evident.

Table 7
Discharge time, number of patients requesting anti-emetics and pain relief in ketamine group and control group

Group	Discharge time (min)	Number of patients given anti-emetic	Number of patients given Panadeine Forte 1 g	Number of patients given Oxycodone 10 mg
Ketamine	121.8 ± 26.8	1/20	13/20	4/20
Control	143.6 ± 56.8	1/20	12/20	3/20

Table 8
Number of patients with Panadeine Forte 4 h requirements, vomiting, dreaming and verbal satisfaction scores

Group	Number of patients needing Panadeine Forte 1 g 4 h	Number of patients with dreaming	Number of patients with post-operative vomiting	Satisfaction score
Ketamine	15/20	4/20	7/20	1.38 ± 0.7
Control	16/20	4/20	7/20	1.65 ± 0.49

The discharge times were not prolonged in the ketamine group. This may reflect the minimal effect of recovery problems such as drowsiness, nausea and vomiting which are the main factors which delay discharge after day surgery [18]. A bolus of (*S*)-ketamine 50–200 μg/kg has been shown to produce drowsiness resembling that of ethanol ingestion [19] and in the study by Suzuki et al., patients receiving ketamine 100 μg/kg and morphine had higher drowsiness scores which affected the duration of phase I recovery. We had not scored the level of drowsiness in our patients as our aim was to determine if the overall discharge time from the day surgery unit was affected by ketamine, which was felt to be of more clinical significance.

Ketamine has been said to increase nausea and vomiting. In a study by Badrinth et al. [20] where ketamine was used in combination with propofol for monitored anaesthetic care, there was a dose-dependent rise in the incidence of nausea and vomiting in the groups receiving ketamine. Our patients did not show a difference in the need for anti-emetics or post-operative vomiting after discharge and this was probably related to the low dose of ketamine used.

Ketamine at doses of 100–500 μg/kg have produced dose-related impairment of sensory perception and altered mood states [21,22] whilst higher doses at 1–3 mg/kg are associated with unpleasant dreams and acute psychosis-like symptoms on emergence [23]. In our study, we could not detect a significant difference in the incidence of post-operative dreaming although one patient in the ketamine group complained of frightening nightmares whilst in the recovery. A study by Hejja and Galloon found that patients who dreamed after ketamine were those who normally dreamed at home [24] and this is a point to bear in mind before administering ketamine.

Our findings show that low dose ketamine, although unsatisfactory as a co-induction agent in reducing the induction dose of propofol has no adverse effect on the patient, even in the day surgery setting. It does not enhance non-opioid analgesia and in the day surgery where analgesics other than opioids are preferably used, ketamine does not appear to offer an advantage of enhancing pain relief. At this dose, ketamine can be used in the day surgery without ill effects. In order to enjoy the effects of reduction of propofol dosage and analgesia, future studies may need to employ higher doses of ketamine for induction. However, one will have to consider the possibility of increased incidence of nausea, vomiting and drowsiness which may affect discharge after day surgery.

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