

# Effects of a propofol – ketamine admixture in human volunteers

Zac Morse\*  
 Kimito Sano\*\*  
 Tomio Kanri\*\*\*

\*Associate Professor, School of Oral Health, Fiji School of Medicine, Tel: 679 3311700. E-mail: z.morse@fsm.ac.fj;  
 \*\* Professor, Department of Anesthesiology, The Nippon Dental University at Niigata, Japan. \*\*\* Professor and Head, Department of Anesthesiology, The Nippon Dental University at Niigata, Japan.

**Abstract:** As the ideal sedative does not exist for all situations, particularly in settings with limited resources, the effect of a propofol-ketamine combination in human volunteers was examined. Eleven American Society of Anesthesiologists (ASA) physical status I volunteers were administered propofol at a loading dose of 1 mg/kg and two minutes later by 0.7 mg/kg of ketamine. This was followed by a propofol-ketamine combination of 5 mg/kg of propofol admixed with 0.7 mg/kg of ketamine that was infused over one hour via a 60 gtts/ml intravenous. Infusion set. Cardiorespiratory parameters were recorded and blood samples taken to measure plasma catecholamine levels prior to, during and for thirty minutes following the termination of the infusion. Rate of respiration and oxygen saturation levels did not alter significantly from baseline levels. When there was a cardiovascular decrease from base line levels it was on average 11% for systolic, 15% diastolic blood pressure and 14% for heart rate. Only plasma adrenaline and noradrenaline increased by 28 and 20%, 10 minutes following the bolus injections. No dysphoria was experienced. This combined sedoanalgesic technique in nonstimulated human volunteers maintains spontaneous ventilation and may be considered as abalanced alternative to traditional conscious sedation or general anesthesia.(PHD, 2003; 10 (1), Pages 51-54)

## Introduction

The ideal sedative is one that safely provides relief from pain, anxiety and unpleasant memories for a wide variety of procedures. In reality there are few such agents, hence the need for a combination of agents. The subhypnotic administration of intravenous anaesthetics during local or regional anesthesia is becoming more common particularly in fields such as oral health.

Propofol produces dose-dependant sedation, hypnosis, anxiolysis and amnesia as well as possessing antiemetic properties.<sup>1</sup> Unfortunately it is a weak analgesic and tends to depress haemodynamic parameters. Ketamine is a potent analgesic that minimizes the need for supplemental opioids and hence negating the further potentiation of respiratory depression.<sup>2</sup> Analgesics are often administered during sedation to improve comfort, supplement local anaesthesia and improve operating conditions. Ketamine also possesses sedative, hypnotic and amnesic properties and maintains protective airway reflexes in a manner superior to other sedatives. Unfortunately it tends to stimulate haemodynamic parameters and may cause vomiting and unpleasant psychic reactions.<sup>3</sup> When these two agents are combined, they attenuate the negative effects of each other and provide better sedation with less toxicity than either agent alone whilst decreasing the hypnotic requirement.<sup>4-6</sup>

The technique of combining propofol with ketamine has been termed dissociative sedation and may be considered as an alternative to other more traditional forms of conscious sedation or general anesthesia.<sup>7</sup>

The aim of this study was to determine the effects of a propofol- ketamine admixture on cardio respiratory dynamics and plasma catecholamines in young adult volunteers.

## Methods

Eleven American Society of Anesthesiologists physical status I volunteers without psychiatric and psychological

conditions that were not using any medicines were enrolled. Five males and six females were recruited. The study was approved by the Nippon Dental University's human investigation committee and written informed consent was obtained from all subjects.

The subjects fasted overnight and were seen in the morning. The study was conducted in the outpatient clinic of the dental hospital at the Nippon Dental University at Niigata. They were placed in the supine position and routine clinical monitoring that included automated, non-invasive arterial blood pressure, arterial oxygen saturation, tracheal auscultation and a three-lead ECG were applied throughout the entire study period. Following left forearm venipuncture with a 20- or 22-gauge cannula, an intravenous infusion of 0.9% saline was established. Venous blood sampling was taken from the antecubital fossa of the contralateral arm.

Propofol was administered over two minutes at a loading dose of 1 mg/kg, followed by 0.7 mg/kg of ketamine over a further two minutes. This was then followed by a propofol-ketamine combination of 5 mg/kg of propofol mixed with 0.7 mg/kg of ketamine to which saline was added to form a 60 ml solution that was infused over one hour via a 60 gtts/ml i.v. infusion set at a constant rate of 60 drops (gtts)/min. The subjects breathed spontaneously with supplemental oxygen administered via a nasal mask at 4-5 l/min.

The sedating propofol is required to be administered prior to the ketamine. Doses used are approximately half of those used in general anaesthesia and where selected to be somewhat liberal.<sup>8</sup> Baseline values for all the parameters were obtained prior to the administration of any medications. Measurements and blood samples were then taken immediately after the end of the loading doses and at ten minutes intervals until thirty minutes after the discontinuation of the infusion. Pain following the initial propofol injection was noted as either positive or negative.

Plasma catecholamine levels were detected using an automated catecholamine analyzer (HPLC)(High pressure liquid chromatography) HLC-725 CA (Tosoh – Tokyo, Japan). Two mg of EDTA·2Na were added to two ml of blood and centrifuged for ten minutes. 0.6 ml of plasma were removed and 0.3 ml of 4.8% perchloric acid added. After ten minutes of further centrifugation 0.6 ml of the supernatant was removed to determine catecholamine concentrations.

At the conclusion of the study the subjects were asked if they remembered having any dreams and if so if they were pleasant or unpleasant. Data were analyzed using an analysis of variance followed by a Bonferroni post-hoc t test, with  $P < 0.05$  being considered significant.

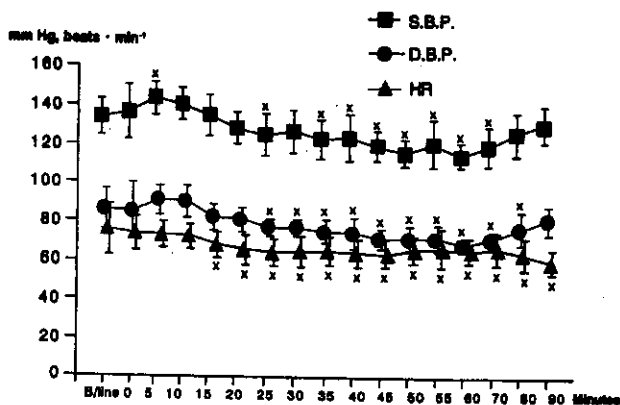
## Results

The average age of the subjects was 26 years (range 22 to 30 years) and weight was 62 kg (range 53 to 78 kg). Sixty-four percent of the subjects reported pain following the propofol bolus injection. Oxygen saturation levels did not alter significantly ( $P < 0.05$ ) and remained high at an average of approximately 99% (range 96-100%). Rate of respiration did not alter significantly from baseline levels ( $P < 0.05$ ) (range 8-24 breaths per minutes).

Average systolic blood pressure rose only at five minutes after the bolus administration of ketamine by seven percent. It then fell at the 25-minute mark (6%) and at the 35, 40, 45, 50, 55, 60 and 70 minute mark by 11, 8, 11, 13, 10, 14 and 11 percent respectively. This was an average decrease of approximately eleven percent from baseline levels.

Average diastolic blood pressure decreased from the 25 to the 80 minute marks by an average of fifteen percent. Average heart rate decreased from the fifteen-minute mark to the end of sampling by an average of fourteen percent (Figure 1). Plasma catecholamines levels remained stable with a transient increase in adrenaline (28%) and noradrenaline (20%) ten minutes following the bolus injections. Plasma dopamine levels remained unaltered from baseline levels.

**Figure 1: Time course of average systolic (S.B.P.) / diastolic (D.S.P) blood pressure and heart rate (HR). x (significantly different from baseline  $P < 0.05$ )**



Eighty-nine percent of the subjects reported experiencing dreams and from this group sixty-three percent stated that they were pleasant and the remainder stated that they

couldn't remember the content of their dreams. No subjects reported any dysphoria or unpleasant dreaming. Emergence type reactions were not experienced. There were no cases of nausea or vomiting. All subjects were alert and able to ambulate unassisted 30 minutes following the termination of the infusion.

## Discussion

For cases requiring sedation and analgesia to supplement regional anesthesia, an alternative to large doses of hypnotics is a sedoanalgesic combination. Both propofol and ketamine have a rapid onset and are not known to trigger malignant hyperthermia, hence avoiding the complexities associated with those agents. Narcotics for analgesia increase the risk of respiratory depression whereas ketamine at subanesthetic levels provides analgesia without respiratory depression.<sup>8, 9</sup> Ketamine poses the additional advantage of maintaining postoperative analgesia after sedative effects are no longer present and continues postoperatively.<sup>10</sup> Propofol has been shown to be an effective agent in reducing ketamine's adverse effects.<sup>11</sup> As has been observed by others Mortero et al the coadministration of propofol and ketamine did not depress ventilation.<sup>12</sup> Bradypnoea and respiratory depression with small doses of ketamine (<1 mg/kg i.v.) are minimal<sup>2</sup> and apnoea highly unlikely.<sup>5</sup> Ketamine has the ability to antagonize hypoventilation caused by respiratory depressants such as alfentanil in a dose-dependant manner. Although the carbon dioxide curve is shifted to the right, the slope of the curve remains unchanged.<sup>7, 13, 14</sup> The addition of ketamine will not protect against propofol induced apnoea, however smaller doses of propofol can be administered when in combination with ketamine and hence reducing the risk apnoea.<sup>5</sup> At sedative doses ketamine preserves spontaneous respiration and the ability to maintain an independent airway as protective reflexes remain intact and the muscular tone of the upper airway may be enhanced.<sup>17</sup> A further advantage of ketamine replacing opioids, is that nausea and vomiting can be totally eliminated.<sup>8, 15</sup> Nausea and vomiting associated with a ketamine or ketamine-propofol combination appears to be related to excessive dosing.<sup>2</sup>

Commonly recognized ketamine-induced hypertension and tachycardia were not witnessed in this propofol-ketamine combination and provides relatively good haemodynamic stability with only a mild decrease in cardiovascular parameters. The arterial pressure and heart rate effects usually seen with each agent are dose related and have been shown to offset each other,<sup>5</sup> hence the combination affords improved haemodynamic stability in comparison to utilizing each as a sole agent. Propofol-ketamine combinations have been used successfully at anaesthetic levels that do not affect mean arterial pressure or heart rate.<sup>16</sup> The admixture of propofol with ketamine has been demonstrated to be both physically and chemically compatible.<sup>17</sup>

The dysphoric effects of using ketamine as the sole agent make it infeasible in most situations and its use as the sole agent is not routinely recommended. At higher doses of ketamine symptoms are shown to resemble that of psychosis as in schizophrenia and are dysphoric.<sup>18</sup> The arousal and psychotomimetic activity that is seen with

ketamine are antagonized by the sedative effects of propofol.<sup>12</sup> There were no dysphoric or emergence type reactions in our study and propofol-ketamine combinations have actually been shown to increase postoperative mood and cognitive function recovery as well as decreasing analgesic requirements.<sup>12,19</sup> The mild euphoria associated with this technique is a phenomenon largely unrecognized in the literature and can be a source of patient satisfaction not to be underestimated.<sup>1</sup>

Although a high rate of dreaming was reported it was always experienced as being of a pleasant nature and has been observed by others using a propofol-ketamine technique.<sup>1</sup> Propofol only anaesthesia has been associated with dreaming with an incidence of approximately forty percent however patients emerge happier and feel less sick than with other agents.<sup>20</sup>

Ketamine is known to produce sympathomimetic effects via both central and peripheral mechanisms.<sup>13</sup> The increases in plasma catecholamines are caused by central sympathetic stimulation and not due to respiratory effects.<sup>21</sup> Ketamine inhibits the reuptake of catecholamines at the adrenergic nerve terminal, with the resultant sympathomimetic effects<sup>7</sup> but this phenomenon was not seen as the coadministered propofol diminished this effect. The transient increase in plasma catecholamines adrenaline and noradrenaline did not reflect haemodynamic changes.

It has been previously shown that when ketamine is infused as the sole agent it transiently increases plasma adrenaline and noradrenaline but the coadministration of hypnotics at sedative doses or inhalational anaesthesia oblates these increases.<sup>22,23</sup> Bolus doses are known to increase plasma adrenaline and noradrenaline significantly more so than micro-drip administration.<sup>24</sup> Plasma dopamine levels are usually not affected by ketamine administration.<sup>22,24</sup>

A possible side effect of this technique may be post sedation diplopia.<sup>21</sup> Although no problems were experienced in terminating the propofol and ketamine together, in clinical practice it may be wise to terminate the ketamine at least twenty minutes prior to the termination of the propofol to allow for the ketamine to redistribute out of the brain.<sup>1</sup>

In these non-stimulated subjects the lack of respiratory depression, slight fall in blood pressure and lower dose requirements with a combined technique would be clinically acceptable and compares favourably with other studies.<sup>25</sup> Few studies have examined the effect of a sedoanalgesic technique co administering propofol and ketamine. The effect of a propofol – ketamine combination on plasma catecholamines has not been studied previously. Spontaneous breathing is maintained hence avoiding the requirement of intubation together with

muscle relaxants. This combined technique may be considered as a balanced alternative to traditional conscious sedation or general anaesthesia particularly in settings with limited resources that would otherwise be unable to provide these services. In this regard further clinical investigations are required.

## Reference

1. Friedberg BL. Propofol-ketamine technique: dissociative anaesthesia for office based surgery (A 5-year review of 1264 cases). *Aesth Plast Surg* 1999; 23:70-75.
2. Badrinath S, Avramov MN, Shadrack M, et al. The use of a ketamine-propofol combination during monitored anaesthesia care. *Anesth Analg* 2000;90:858-62.
3. Kohrs R and Durieux ME. Ketamine: Teaching an old drug new tricks. *Anesth Analg* 1998; 87:1186-93.
4. Frey K, Sukhani R, Pawloski J, et al. Propofol versus propofol-ketamine sedation for retrobulbar nerve block: comparison of sedation quality, intraocular pressure changes and recovery profiles. *Anesth Analg* 1999; 89:317-21.
5. Hui TW, Short TG, Hong W, et al. Additive interactions between propofol and ketamine when used for anaesthesia induction in female patients. *Anesthesiology* 1995; 82(3):641-648.
6. Schuttler J, Schuttler M, Kloos S, et al. Optimal dosage strategies in total intravenous anaesthesia using propofol and ketamine. *Anesthesist* 1991; 40(4):199-204.
7. Giovannitti JA. Dental anaesthesia and pediatric dentistry *Anesth Prog* 1995; 42:95-99.
8. Guit JBM, Koning HM, Coster ML, et al. Ketamine as analgesic for total intravenous anaesthesia with propofol. *Anaesthesia* 1991; 46:24-27.
9. Blakely KR, Klein KW, White PF, et al. A total intravenous anaesthetic technique for outpatient facial laser resurfacing. *Anesth Analg* 1998; 87:827-9.
10. Mayer M, Ochman O, Doenicke A, et al. The effect of propofol-ketamine anaesthesia on hemodynamics and analgesia in comparison with propofol-fentanyl. *Anaesthesist* 1990; 39(12):609-16.
11. Rebozo MJA and Gonzales MF. Ketamine. *Rev Esp Anesthesiol Reanim* 1999; 46(3):111-22.
12. Mortero RF, Clark LD, Tolan MM, et al. The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. *Anesth Analg* 2001; 92(6):1465-9.

**Although a high rate of dreaming was reported it was always experienced as being of a pleasant nature and has been observed by others using a propofol-ketamine technique.**

13. Bregman SA Ketamine: Review of its pharmacology and its use in pediatric anesthesia. *Anesth Prog* 1999; 46:10-20.
14. Friezelle HP, Duranteau J and Samii K. A comparison of propofol with a propofol-ketamine combination for sedation during spinal anesthesia. *Anesth Analg* 1997; 84:1318-22.
15. Cheng KI, Tang CS, Chu KS, et al. Anesthesia for pediatric herniorrhaphy or hydrocelectomy: comparison of propofol/ketamine and thiopentone / halothane. *J Formos Med Assoc* 1998; 97:557-63.
16. Sakai K, Cho S, Fukusaki M, et al. The effects of propofol with and without ketamine on human cerebral blood flow velocity and CO(2) response. *Anesth Analg* 2000;90(2):377.
17. Trissel LA, Gilbert DL, Martinez JF. Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health Syst Pharm* 1997;54(11):1287-92.
18. Suzuki M, Tsueda K, Lansing PS, et al Midazolam attenuates ketamine-induced abnormal perception and thought process but not mood changes. 2000;47(9):866-874.
19. Fabbri LP, Batacchi S, Linden M, et al. Anaesthesia for urological endoscopic procedures in adult outpatients. *Eur J Anaesthesiol* 1995;12(3):319-24.
20. Brander B, Blagrove M, McCallum G et al. Dreams, images and emotions associated with propofol anaesthesia *Anesth* 1997;52:750-755.
21. Domio EF. Status of ketamine in anesthesiology. NPP books. *Ann Arbor MI* 1990.
22. Kobayashi S, Sano K, Kanri T. Effects of ketamine-midazolam micro-mini drip method as intravenous sedation on plasma catecholamine concentrations. *JJDSA* 1998;26(3):380-388.
23. Sugiyama N, Sano K, Kanri T. The influence of ketamine micro-mini drip on plasma concentration of catecholamines during general anesthesia. *Odontology* 1998;85(4).
24. Kaizu M, Sano K and Kanri T. Study of ketamine injection technique under general anesthesia: comparison between micro-mini drip and bolus injection, *JJDSA* 2001;29(1):24-33.
25. Gray C, Swinhoe CF, Myint Y, et al. Target controlled usion of ketamine as analgesia for TIVA with propofol. *Can J Anesth* 1999;46(10):957- 961.

**In these non-stimulated subjects the lack of respiratory depression, slight fall in blood pressure and lower dose requirements with a combined technique would be clinically acceptable and compares favourably with other studies.**

He that sleeps feels no toothache  
(William Shakespeare in *Cymbeline*)