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Research Article

A comparative study of total intravenous anesthesia with propofol/ketamine and propofol/tramadol combinations in orthopedic outpatient procedures

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ABSTRACT

Background: Propofol opioid/nonopioid combinations provide adequate analgesia during and after surgery. The aim of this study was to compare the effect of anesthesia with propofol/ketamine versus propofol/tramadol on the haemodynamic parameters and pain in patients undergoing orthopaedic outpatient surgical procedures.
Methods: Fifty patients with ASA status I-II between the age group of 20-50 years undergoing orthopaedic outpatient surgical procedures under general anesthesia were randomly assigned to propofol/ ketamine (n=25, group I) and propofol/ tramadol (n=25, group II) groups. Patients in group I were induced with propofol 150 µg/kg/min IV and ketamine 50 µg/kg/min IV and in group II induction was performed with propofol 150 µg/kg/min IV and tramadol 1 mg/kg/min. IV. The hemodynamic parameters, oxygen saturation (SpO2), respiration rate, sedation and pain were measured before and after induction at predefined time points and were compared between groups.
Results: There was significant difference between groups in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR). SBP, DBP and HR were stable in patients induced with propofol/ketamine. The SBP, DBP and HR decreased significantly after induction with propofol/tramadol compared to premedication, but tends to return to normal after 25 minutes. No significant changes in SpO2 found in both the groups at all-time points. Both groups are sedated and showed no difference in pain score with few episodes of unpleasant dreams or hallucinations or adverse complications.
Conclusions: Propofol/tramadol anesthesia in patients undergoing orthopaedic procedures provided stable hemodynamic and respiratory stability, sedation and pain reduction as effective as propofol/ketamine anesthesia.

Keywords: Ketamine, Propofol, Tramadol, Total intravenous anesthesia

INTRODUCTION

Total intravenous anesthesia (TIVA) gained widespread acceptance in human medicine after the development of computer controlled infusion devices that allow the depth of anesthesia to be altered as the same way it is altered during inhalation anesthesia.[1] Several intravenous anesthetic agents can be used in combination to execute an effective TIVA regimen.[2-4]

Propofol is regarded currently as the most suitable anaesthetic agent for TIVA. It allows rapid changes in anaesthetic depth and a rapid clear-headed recovery.[5,6] Other useful adjuncts for TIVA include fentanyl, ketamine, remifentanil, midazolam, dexmedetomidine.[7] Propofol produces dose dependent sedation, hypnosis, anxiolysis and amnesia as well as possessing antiemetic properties, but found to be weak analgesic and tends to depress haemodynamic parameters especially in patients with limited cardiovascular reserve and respiratory depression.

Studies have shown that infusion of opioids in conjunction with propofol improves cardiovascular function, and enhances the quality of anesthesia recovery. Anesthesia based on opioids and nonopioid analgesics offers many clinical benefits, such as optimum hemodynamic stability, blocking response to surgical

stress and capacity to reduce the required doses of other agents (either hypnotic or muscle relaxants).[8] Ketamine is an N-methyl-D-aspartate receptor antagonist that induces a "dissociative state" in which sensory input (sight, hearing, touch) normally perceived by the patient is blocked from reaching consciousness.[9] It is a unique anesthetic with profound analgesic, sedative, and amnestic properties and mostly used as an analgesic adjuvant to propofol in TIVA regimens.[2,3,10,11] But ketamine tends to stimulate haemodynamic parameters and may cause vomiting and unpleasant psychic reactions. In addition, Tramadol is a centrally acting analgesic which possesses opioid agonist properties and activates monoaminergic spinal inhibition of pain.[12-14] It also inhibits the reuptake of norepinephrine and promotes the release of serotonin. The synergy of monoaminergic and opioid activity of tramadol achieves analgesic effects. Tramadol rarely causes respiratory or cardiovascular depression, even in large doses and this sets it apart from all other opioid agonists. Bedirli et al. reported tramadol induced sedation as efficient as fentanyl with a better hemodynamic and respiratory stability and provided a superior safety and tolerance in propofol anesthetized younger children undergoing upper gastrointestinal endoscopy.[15] A dose of 100 mg tramadol added to 40 mL 1% mepivacaine improved the quality of the brachial plexus blockade in patients scheduled for surgery of the forearm and hand.[16] These drugs were selected because of their unique properties to achieve TIVA while providing cardiovascular stability and allowing rapid wake uptimes. Considering these drug contrasting haemodynamic properties, the present study was undertaken to evaluate the combination of propofol/ketamine and propofol/tramadol in providing satisfactory TIVA in orthopaedic outpatient procedures in terms of haemodynamic variables, analgesia, sedation and patient recovery.

METHODS

The present study was carried out in MGM Hospital, Warangal, Telangana, India. Eighty patients of either gender with ASA physical status I-II, aged 1–16 years who were undergoing surgery were included in this prospective, randomized, double blinded study. Patients with acute or chronic pulmonary infection, angina, congestive heart failure, aneurysm, or uncontrolled hypertension, brain injury associated with altered mental status, thyroid disorder, CNS mass lesion, hydrocephalus, history of behavioural problems and neurological impairment were excluded from the study. Pregnant and lactating women were also excluded. All subjects gave written informed consent prior to participation in the study. The protocol was approved by institutional ethical committee and the study was conducted in compliance with good clinical practice and with ethical standards for human experimentation established by declaration of Helsinki and in accordance with applicable regulatory requirements. No sedative premedication was administered, and the patients were fasted for at least 6 h. An intravenous line and standard anesthesia monitoring including cardiovascular and ventilation monitoring were maintained in all patients for the duration of sedation and recovery. Patients were randomly allocated to receive ketamine or tramadol for TIVA. In all the patients anaesthesia was induced and maintained with propofol 150µg/kg/min after initial bolus dose of 1mg/kg body wt. followed with ketamine 50µg/kg/min or tramadol 1mg/kg/min IV given slowly. Maintenance infusions varied according to patient condition and surgical stimuli. Glycopyrolate 0.2 mg IV was given exactly 5 minutes prior to induction of anesthesia in both the groups. Patients were ventilated with 100% oxygen via a facemask with the help of Bain's circuit. Baseline assessments included blood pressure, heart rate, ECG, respiratory rate, SpO2 and psychological evaluation by using visual analog scales for discomfort ("no discomfort"–"worst discomfort ever experienced"), nausea ("no nausea"–"worst nausea") and pain (no pain was graded as zero and the most excruciating pain as 10). The level of sedation was determined by using the Observer Assessment of Alertness/Sedation (OAA/S) scale (1 = awake, alert and 5 = unresponsive).[17] All the measurements were performed at premedication and were repeated at 3 minutes and 5 minutes following induction and at 5-minute intervals thereafter until the end of procedure. The preoperative HR and BP were first obtained when the patient entered the operating room. The propofol infusion and ketamine or tramadol infusion was discontinued approximately 10-15 minutes before anticipated patient awakening. The induction parameters chosen were non-responsiveness to verbal commands & loss of eyelash reflex. Awakening time and orientation time is recorded. The recovery characteristics - time to eye opening to verbal command, time to orientation (to place and person), from the last dose administered were assessed. Moderate to severe pain (VAS score exceeding 4 points during surgery) not responding to an adjustment in the study drug infusion was treated by injecting pethidine 10-20 mg IV. Patients with postoperative nausea and vomiting were treated with ondansetron 100-150 µg/kg IV. Episodes of hypoxia (arterial O2 saturation <85%) or hypotension (SBP<90 mmHg) were also noted. Apnea was managed by decreasing or discontinuing the treatment and with positive pressure ventilation, if necessary. Airway obstruction was managed with standard airway maneuvers such as chin lift, jaw thrust, and the use of oral or nasal airways, if necessary. Patients were discharged when appropriate criteria were met including stable vital signs, lack of post-procedure nausea and vomiting, ability to tolerate oral intake and return of mental status and ambulation to baseline. Data are presented as mean ± SD and percentage as appropriate. Statistical analyses were performed using Graph pad prism, version 6. The within group changes were tested with analysis of variance (ANOVA) for repeated measures and the differences in responses within time between the groups were compared with unpaired t test. A p-value less than 0.05 were considered statistically significant.

RESULTS

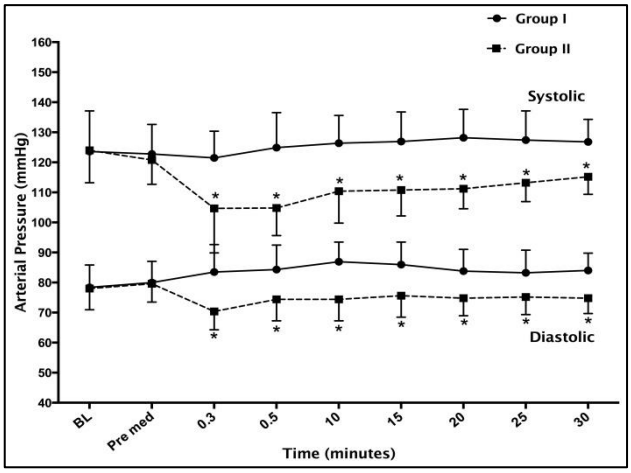
A total of 65 patients were screened for eligibility and 50 patients were consented and randomly assigned to the treatment. Patient characteristics are shown in table 1. There were no significant differences in age, gender distribution, weight, blood pressure and heart rate. The distribution of surgical procedures, (mostly lower limb orthopaedic) is also shown in table 1. Furthermore, baseline values (premedication) of BP, HR, respiration rate, SpO2, sedation and pain scores were similar between groups.

Table 1: Patient Characteristics. Data present as Mean±SD or numbers of patients. Group I: propofol/ketamine, Group II: propofol/Tramadol.

	Group I (n=25)	Group II (n=25)
Age (yrs)	39.56±10.45	37.8±9.22
Gender (M/F)	17/8	18/7
Weight (Kg)	48.92±6.32	48.72±6.71
ASA class I/II		
Preoperative SBP (mmHg)	123.60±13.50	124±10.80
Preoperative DBP (mmHg)	78.40±7.46	78±7.07
HR (beats/min)	77.88±5.59	78.92±7.09
Surgical procedures		
Dislocation of shoulder	3	4
Evans Fracture	5	2
Dorsal ganglion	2	1
Dislocation of Hip	2	3
Olecranon fracture	2	0
Fracture femur	4	6
Comminuted Fracture	1	0
Fracture radius	2	1
Dislocation of Shoulder	2	4
Debridement	0	1
Fracture Patella	0	2

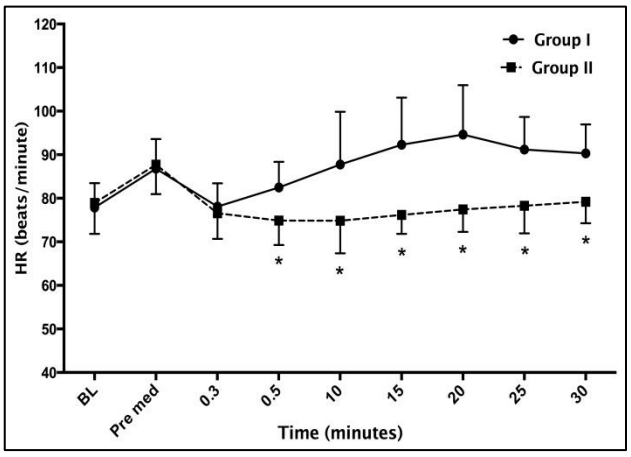
The haemodynamic variables throughout the peri-operative period for both groups are shown in Figure 1, 2. Arterial pressure (SBP & DBP) was stable in the patients who received propofol /ketamine. Fifteen minutes after induction, systolic and diastolic pressures increased by 4.39 % and 7.45 % (p>0.05), respectively. However the HR decreased significantly at 15 minutes following induction. In patients, who received propofol/ tramadol, both systolic and diastolic pressures and HR decreased significantly at 3, 5, 10, 15 and 20 minutes after induction, but tend to return to normal after 25 minutes. When compared to propofol/ketamine, tramadol in combination with propofol significantly decreased the SBP, DBP and HR at all the time points post induction.

The oxygen saturation in both the groups did not alter significantly and remained high at an average of approximately 99% in all stages post induction. However a minimal decrease in oxygen saturation at 5 minutes was noted in propofol/tramadol group compared to propofol/ketamine group, which was found to be significant (Group I 98.4±1.0 Vs Group II 96.84±2.39; P<0.05).



*Significant difference (P<0.05), group I compared to group II. BL: Baseline; Pre: premedication

Figure 1: Systolic and diastolic pressures (Mean±SD); Group I: propofol/ketamine, Group II: propofol/tramadol.



*Significant difference (P<0.05), group I compared to group II. BL: Baseline; Pre: premedication.

Figure 2: Mean change in heart rate (Mean±SD); Group I: propofol/ketamine, Group II: propofol/tramadol.

The respiratory rate was found to be stable in propofol/ketamine group. The mean respiratory rate in group I was 16 breaths/min at all-time points. In group II, the respiratory rate at premedication was 16.76±0.97 per minute and decreased significantly (P<0.05 range:11.96±2.95 breaths/min to 15±1.32 breaths/min) at all-time points compared to premedication following induction, but returned to normal at 30 minutes. When compared to group I, propofol/tramadol combination

significantly decreased the respiratory rate at all-time points post induction.

The mean sedation score pre induction was 0 in both the groups. The sedation score in both the groups was 3 post induction and was comparable at 10, 15, 20, 25 and 30 minutes following induction. The mean pain intensity at the beginning of the study was VAS 3.0±0 in the propofol/ketamine group and VAS 3.0±0 in the propofol/tramadol group respectively. Pain intensity was reduced to 0 on VAS in all patients of both groups within 10 minutes post induction. Mean pain scores were comparable at different time intervals in both groups except at 3 min (group I 1.73±0.43 group II 1.72±0.45) and 5 min, (group 0.2±0.40 group II 0.12±0.33). Patients who received propofol/ketamine demonstrated a significantly longer awakening time and orientation time than patients given propofol/tramadol (awakening time: group I 12.88±4.90 min; group II 3.42±1.79 min; P<0.01; orientation time: group I: 13.28±7.32 min; group II 2.08±1.10 min, P<0.01).There were no significant differences in time to full recovery in both the groups (group I: 13.66±1.04 min; group II 13.54±1.28 min).

The overall frequency of adverse effects (n=7, 28%) was similar in both groups. Hypoxia occurred in 1/25 (4%) and 3/25 (14%) of patients in the group I and group II respectively. Most of the hypoxia was caused by airway obstruction and responded to standard maneuvers such as chin lift and jaw thrust. One patient in the group II developed apnea that required management by mask-bag ventilation. Four patients (16 %) reported hallucinations/dreaming during the surgery in group I. Cough occurred in two patients (8%) in group I. Hypotension occurred in 1/25 (4%) of patients in the group II. The episodes of hypotension resolved after administration of IV fluid bolus and/or phenylephrine or ephedrine. Bradycardia occurred in 2 patients in group II and was treated with Atropine 0.6 mg IV. Overall, 1 patient in group I and 5 patients in group II required resuscitative interventions. Both groups had no post-operative complications like nausea or vomiting.

DISCUSSION

Hemodynamic changes due to anesthesia in various surgeries have become a great concern in physicians operation room and evidence shows that changes in blood pressure, either increase or decrease, independently are associated with side effects and complications in patients undergoing surgery.[18] During anesthesia, most patients experience periods of hemodynamic instability, which healthy individuals can tolerate, but are usually catastrophic in hypertensive patients due to the wide pressure fluctuations and sympathetic hyperactivity.[19] TIVA with propofol is similar to inhaled anaesthetics with regard to hemodynamic stability, emergence times, extubation times, early cognitive function, and adverse events. Propofol potentiates $GABA_A$ receptor activity, has a rapid onset of action and it is very short acting. It has a neuroprotective effect during cerebral ischemia, lowering intracranial pressure, cerebral blood flow, cerebral metabolism and oedema, and improving cerebral perfusion pressure and mean arterial pressure (MAP).[20-22]

However, propofol has a narrow therapeutic index and lacks intrinsic analgesic properties. Patients generally receive a combination of anesthetic and analgesic agents to induce and maintain an adequate depth of anesthesia and analgesia. Traditional opioids produce analgesia but also cause constipation, respiratory depression, and sedation, as well as having a significant abuse potential.[23] Feld JM et al has shown that non-opioid drug combination produced adequate anesthesia with less cardiovascular stimulation and rapid recovery compared to opiate induced anesthesia during gastric bypass surgery.[8]

In this study, the effect of two different anesthetic techniques, i.e., propofol/ketamine and propofol/tramadol for induction of anesthesia on hemodynamic variables and pain were compared in patients undergoing orthopaedic surgery. TIVA with both techniques is comparable, but propofol and tramadol combination may be considered an appropriate choice when hemodynamic stability is of great importance especially in hypertensive patients. Blood pressure variations under propofol/ketamine anesthesia were minimal compared with propofol/tramadol anesthesia. A stable arterial pressure throughout the operative period was observed, compared with the lower blood pressure found in the patients given propofol/tramadol. In the present study, there was a slight increase in SBP, DBP and HR after induction with propofol/ketamine anesthesia, which slowly reduced to normal values. These minimal changes might be due to antagonistic properties of propofol (decrease in blood pressure) and ketamine (increase in blood pressure).[24] Both Kamalipour et al and Mayer et al showed a moderate decrease in MAP and no change or a significant increase in HR after induction with propofol/ketamine anesthesia.[25,26] The decrease in SBP, DBP and HR with propofol/tramadol anesthesia may be due to fact that tramadol has no clinically relevant haemodynamic effects. In healthy volunteers, BP and HR were very slightly and transiently elevated following intravenous tramadol 100 mg.[27] The effects of tramadol on HR and BP were variable but these changes were not statistically significant or were transient, occurring in the first 5 to 10 minutes after injection and are considered because of an opioid sympathomimetic mechanism. In both the groups, deep levels of sedation were maintained throughout the study and also there were no incidents of oxygen desaturation. Both the groups showed significantly improved postoperative analgesia. Mean pain scores were comparable between the two groups at almost all time intervals. Patients in both the groups had significantly less pain compared to premedication, and required less analgesic medication, and were physically more active after discharge. Respiratory depression was defined as a reduction of oxygen saturation below 90 %.

Co-administration of propofol/ketamine resulted in no significant respiratory depression, though it is associated with small doses of ketamine (<1 mg/kg IV).[28,29] In the present study, propofol/tramadol combination caused significantly less respiratory depression compared to pre-treatment in only few patients, but returned to normal after 20 minutes. Studies have shown that tramadol rarely causes respiratory or cardiovascular depression, even in large doses and this sets it apart from all other opioid agonists. In the present study, anesthesia related complications were minimal in both the groups. Therefore, it appears that the type and the dose of analgesic supplements used during propofol sedation have a differential impact on outcome. Tramadol is as effective as and safer than equianalgesic doses of opiates because it has been associated with less sedation, cardiovascular effects, respiratory depression, and minimal gastrointestinal dysfunction, which are favourable for sedation in patients undergoing surgical procedures.[30]

CONCLUSION

In conclusion, the results of this study suggest that both propofol/ketamine and propofol/tramadol combinations produced stable hemodynamics, adequate sedation, ventilation and satisfactory induction in patients undergoing orthopaedic surgery. These combinations provided rapid, pleasant and safe anesthesia with only a few side effects and minor hemodynamic fluctuations. There were no adverse hemodynamic changes from induction until the end of our investigation. Additional studies using a larger group of patients are warranted to detect the small but potentially clinically significant differences between the two groups.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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