



IMPACT COMBINING KETAMINE WITH PROPOFOL ON THE RECOVERY PROFILE IN PATIENTS UNDERGOING DAY CARE SURGERY

Anesthesiology

Dr. Harminder Kaur*	Junior Consultant, Department of Anaesthesia, Mohan Dai Oswal Hospital, Ludhiana, India. *Corresponding Author
Dr. Indu Verma Sood	Associate Professor, Department of Obstetrics and Gynecology, MMIMSR Mullana, Ambala, Haryana, India
Dr. Dinesh Sood	Professor, Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana, India.
Dr. Sunil Katyal	Professor and Head, Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana, India
Dr Anju Grewal	Professor, Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana, India.
Dr. Kuljyot Bajaj	Specialist Registrar, Department of Burns and Plastics, Queen Elizabeth Hospital, Birmingham, UK

ABSTRACT

INTRODUCTION: Day care surgical practice continues to increase in response to rising costs of inpatient hospital care. Hospital space limitations and the popularity of day care surgery with patients further encourage the growth of day care surgeries. Various anaesthetic techniques have been used to ensure rapid recovery from anaesthesia and home readiness. The purpose of this study is to compare the recovery profile after induction with different doses of ketamine combined with propofol in patients undergoing day care surgery.

MATERIAL AND METHODS: The study was conducted on 90 patients scheduled to undergo laparoscopic tubal ligation. Patients were divided into 3 groups of 30 each. Three different combinations of ketamine with propofol were administered to each group. Recovery profile was studied and results were analysed at the completion of study. Group I : 7 ml 1% propofol + 1 ml 5% ketamine + 2 ml Normal Saline ; Group II : 7 ml 1% propofol + 2 ml 5% ketamine + 1 ml Normal Saline ; Group III : 7 ml 1% propofol + 3 ml 5% ketamine (Normal Saline not given).

RESULTS: There was statistically significant difference in the mean dose used and recovery profile in Group III when compared to Group I and II. Group III promised a fastest recovery of the activity and consciousness level. The respiration, circulation and oxygen saturation were maintained throughout the surgery in patients having mild pain and nausea / vomiting after surgery which subsided by reassurance.

CONCLUSIONS: We recommend that the optimal dose of propofol and ketamine combination is 7ml 1% propofol + 3ml 5% ketamine, as it provides the best operative conditions for the surgery along with fastest recovery using minimum drug volume, dose requirement and produces least adverse outcomes.

KEYWORDS

Ketamine, Propofol, Day care Surgery, Laparoscopic Tubal Ligation.

INTRODUCTION:

Day care surgical practice continues to increase in response to rising costs of inpatient hospital care. Hospital space limitations and the popularity of day care surgery with patients further encourage the growth of day care surgeries. Laparoscopic tubal ligation is most widely used and trusted method or female sterilization done on day care basis. Various anaesthetic techniques have been used to ensure rapid recovery from anaesthesia and home readiness.

Ketamine and propofol are two of the commonly used intravenous induction agents. The trend towards more ambulatory surgery has fostered an interest in ketamine because of its acceptably short duration of action. Ketamine is pharmacologically classified as non-competitive N- Methyl -D-Aspartate (NMDA) receptor antagonist^[1] and chemically related phencyclidine which was first used in humans in 1965 by Corssen and Domino.^[2] It produces sedation, amnesia, profound analgesia but does not cause muscle relaxation. It provides adequate surgical anaesthesia which is characterized by rapid onset and short duration of action due to its redistribution from the brain and blood to other tissues in the body and has high margin of safety.^[3]

Its use in day care surgery has been limited because of the potential psychotomimetic side effects (illusions, disturbing dreams, delirium). Ketamine has unique cardiovascular effects; it stimulates cardiovascular system and is associated with increased arterial blood pressure, heart rate and cardiac output. The mechanism for ketamine induced cardiovascular effects is complex. Direct stimulation of the central nervous system leading to increase sympathetic nervous system outflow to be the most important mechanism for cardiovascular stimulation.^[4]

Ketamine causes increase in cerebral metabolism, cerebral blood flow and intracranial pressure. Because of its excitatory central nervous system effects, it increases CMRO₂. Postoperative nausea and vomiting has also been related to the use of ketamine^[5] which is the most common adverse events following surgery^[6] due to stimulation of chemoreceptor trigger zone (CTZ).

Unusually high doses of ketamine can produce respiratory depression,^[7] but this effect is seldom seen. Airway patency and respiratory function is preserved. Nevertheless, there are reported cases of pulmonary aspiration, prolonged apnoea^[8] and arterial hypoxemia.^[9] Salivary and tracheobronchial secretions are increased by ketamine.

There is evidence to suggest that ketamine does not cause hypoxic pulmonary vasoconstriction.^[10] It causes increase in intraocular pressure and skeletal muscle tone. Intramuscular ketamine has shown to cause irreversible inhibition of aggregation of platelets in baboons.^[11] However there was no increase bleeding from the experimental animals.

Propofol, (2, 6 - diisopropylphenol) an intravenous anaesthetic was introduced by Kay and Rolly^[12] in 1977 is unrelated to barbiturates, steroids, imidazole or eugenol agents. It was initially prepared in Cremophor EL. Propofol produces rapid, smooth induction and recovery of mental functions with a relatively few adverse effects.^[13] It is commonly used as inducing agent which causes decrease in arterial blood pressure, cardiac contractility, preload, cerebral blood flow and intracranial pressure. The mechanisms underlying the decrease in arterial pressure is believed to be inhibition of myocardial contractility, a decrease in peripheral vascular resistance and cardiac output.

The heart rate does not change significantly after and induction dose of propofol. It resets or inhibits baroreceptor reflex, thus reducing tachycardia response to hypotension.^[14,15]

It also has been associated with a modest reduction in postoperative nausea and vomiting.^[16,17] Propofol provides no analgesia,^[18] produce transient cognitive impairment^[19] and pain on intravenous injection.^[20] Propofol induces bronchodilatation in patients with chronic obstructive pulmonary disease^[21] It attenuates vagal (at low concentration) and methacholine (at high concentration) induced bronchoconstriction.

At subhypnotic doses, propofol has also been reported to relieve cholestatic pruritis and was effective as naloxone in treating pruritis induced by spinal opiates.^[22]

Propofol decreases polymorphonuclear leukocyte chemotaxis. It inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli* which increases the life threatening systemic infections associated with the use of propofol.^[23]

Various authors have tried the combination of propofol and ketamine to enhance the postoperative recovery profile while minimizing the untoward effects. A study was done using ketamine and propofol combination during monitored anesthesia care. The study showed that the adjunct use of ketamine during propofol sedation provides significant analgesia and minimizes the need for supplemental opioids.^[5]

Small dose of ketamine given immediately before propofol injection has shown to reduce the pain of propofol injection.^[24]

The co-administration of propofol and ketamine prevents ketamine induced psychic disturbances which is the main adverse event seen with ketamine which limit its use in ambulatory surgery. A study was done using ketamine and propofol in combination for sedation during laparoscopic tubal ligation. Ketamine in combination with propofol provided satisfactory sedation for outpatient laparoscopic tubal ligation. Compared to sedation with propofol alone, the combination of propofol and ketamine reduced propofol requirements as well as the need for supplementation with nitrous oxide.^[25]

We hypothesized that when a combination of ketamine and propofol is used, the adverse effects of one drug will be counteracted by the other drug, i.e., propofol causes hypotension while ketamine raises blood pressure, propofol is not an analgesic while ketamine is; ketamine causes emergence phenomenon while propofol blunts emergence and ketamine causes vomiting while propofol is an anti-emetic.^[26] Ketamine has also been shown to reduce pain cause by intravenous injection of propofol.^[27]

Till today, very limited data is available on the recovery profile of patients undergoing day care surgery after the use of different combinations of ketamine with propofol. Therefore, we endeavour to put forward a study to compare the effects of different doses of ketamine with propofol on the recovery profile in a group of patients undergoing day care surgery.

MATERIALS AND METHODS:

The present study was conducted in the Department of Anaesthesiology and Resuscitation, Dayanand Medical College and Hospital, Ludhiana, after approval by the Hospital Ethics Committee. A written informed consent was obtained from all patients selected for the study.

Inclusion Criteria:

A total of 90 female patients belonging to ASA (physical status) Grade I and II, scheduled for laparoscopic tubal ligation done on day care basis were included in the study.

Group Allocation:

This prospective and comparative study was conducted in a randomized double blind manner on 90 female patients. Patients were divided into 3 groups of 30 patients each and were induced by following drug combinations intravenously (Total volume made to 10 ml in the same syringe) in the respective groups.

Group I : 7 ml 1% propofol + 1 ml 5% ketamine + 2 ml Normal Saline

Group II : 7 ml 1% propofol + 2 ml 5% ketamine + 1 ml Normal Saline

Group III : 7 ml 1% propofol + 3 ml 5% ketamine (Normal Saline not given)

Drug Preparation:

A total of 90 coded envelopes were made and chosen randomly for each patient. The respective drug combinations were prepared in a 10 ml syringe and coded by a third person (who was not involved in the study). These combinations were decoded at the end of the study.

Pre-Anaesthetic Check-up:

A routine and a thorough pre anaesthetic check up comprising of general physical examination and systemic examination of all patients was conducted prior to surgery. Haemoglobin level was checked for all the patients.

Exclusion Criteria:

Following patients were excluded from the study:

1. Patient's refusal
2. Patients with cardiovascular, hepatic, renal or psychiatric diseases
3. Patients with history of allergy or hypersensitivity to either drugs being used in study

Anaesthetic Technique:

Patients were kept nil per orally for 6 hours and were administered injection Diclofenac Sodium 75 mg intramuscularly prior to surgery. After shifting the patient to operation theatre, monitor for pulse rate, non invasive blood pressure, electrocardiogram and arterial oxygen saturation was attached and monitored throughout the procedure. Intravenous access was secured under all aseptic conditions and intravenous Glycopyrrolate 0.2 mg was given. After pre-oxygenation with 100% O₂ for three minutes, patients were induced till the loss of eyelash reflex and verbal command with study drugs as per grouping protocol. Patients were maintained on spontaneous respiration with 100% O₂ and intermittent repeat doses of same drug combinations were used in the respective groups, as and when required, till the completion of surgery.

Postoperative Assessment:

After completion of the procedure, patients were shifted to the recovery room. The recovery profile of the patients and any side effects (pain on intravenous injection, hallucinations, others) of drug used was assessed every 30 minutes, commencing from the time of completion of the procedure till 3 hours post laparoscopic tubal ligation.

Recovery profile of the patients was assessed using the following three scoring system:

- 1) The Modified Aldrete scoring system^[28]
 - For determining when patients are ready for discharge from the Post-anaesthesia Care Unit
- 2) Revised Post-anaesthetic Discharge Scoring System (PADSS)^[29]
 - Measuring patient's home readiness.
- 3) Fast-track eligibility criteria^[30]
 - To determine whether out-patients can be transferred directly from the operating room to the Phase II recovery area.

Statistical Analysis:

On completion of study, the drugs were decoded, observations obtained were tabulated and analyzed. All results were tabulated and analyzed by working out critical difference through Analysis of Variance (ANOVA).

Level of significance of inter group as well as in intra group variation was seen by comparing the actual mean difference of the three values with critical difference. Variation against three groups was considered to be statistically significant if mean difference came to be equal to or more than the critical difference (CD). p value < 0.05 was considered to be significant.

The age, weight and BMI of patient were tested for significance by applying Chi-square test.

RESULTS AND DISCUSSION:

A wide range of intravenous anaesthetic agents are being used in day care surgeries, but an "ideal" drug is yet to be developed. An ideal intravenous induction agent should have a rapid and smooth induction and recovery with minimal side effects. It should have good analgesic

and non cumulative properties with minimal depression of cardiovascular and respiratory systems. It should be stable, water soluble and non irritant solution having long shelf life.^[31]

This study was conducted on 90 female patients of ASA (physical status) grade I and II. Patients were divided randomly into three groups of 30 patients each and were induced with one of the drug combinations intravenously as per the grouping protocol. We compared the recovery profile after induction with different doses of ketamine with propofol in patients undergoing day care surgery.

Age, Weight and Mean Body Mass Index:

The mean age, weight and BMI in group I were 29.27 ± 3.08 years, 50.37 ± 4.89 kg and 22.13 ± 1.96 kg/m². In group II the corresponding values were 28.13 ± 2.79 years, 51.40 ± 6.08 kg and 22.63 ± 2.20 kg/m². In Group III, these were 29.13 ± 1.96 years, 50.13 ± 3.79 kg and 21.90 ± 1.92 kg/m² respectively. All groups were statistically comparable as regards to age, weight and body mass index (p>0.10) with no significance difference.

Duration of Surgery:

In group I the duration of surgery was 11.00 ± 2.03 minutes, in group II was 10.83 ± 1.90 and in group III was 11.50 ± 2.67 minutes. The duration of surgery was comparable in all the groups and was statistically not significant (p>0.10). Duration of surgery lasted for ≤10 min in 80%, 83.33% and 66.67% of patients in group I, group II and group III respectively. In the remaining 20% (group I), 16.67% (group II) and 33.33% (group III) of patients, surgery lasted for 15 min.

Mean Drug Volume (ml/kg):

The mean drug volume was least in group III, 0.1332 ± 0.0238 ml/kg followed by group II, 0.2356 ± 0.0347 ml/kg and group I, 0.3747 ± 0.0362 ml/kg (Fig 1). There was a significant difference (p<0.01) in the mean drug volume given in all the three groups.

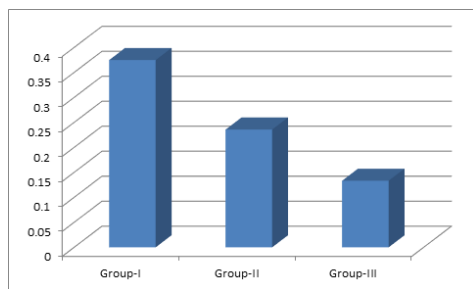


FIGURE 1: Mean Drug Volume (ml/Kg)

The mean dose of propofol and ketamine (µg/kg) administered was calculated based upon the total drug volume (ml) and the mean drug volume (ml/kg) (1ml Ketofol = 1ml propofol: 7000 µg + 1 ml: ketamine 5000 µg in Group I; 10000 µg in Group II; 15000 µg in Group III).

There was a significant difference (p<0.01) in the mean dose of propofol given in the three groups. In group III, least amount of mean dose of propofol (932.40 ± 166.6 µg/kg) was administered followed by group II (1649.20 ± 242.9 µg/kg) and group I (2619.54 ± 253.40 µg/kg) (Fig 2). The mean dose of ketamine given was comparable in group I (187.36 ± 18.1 µg/kg) and group III (199.80 ± 35.7 µg/kg) whereas in group II (235.60 ± 34.7), there was significant difference in the dose administered (Fig 3).

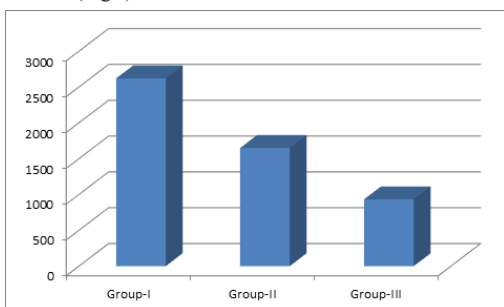


FIGURE 2: Mean Propofol Dose (µg/Kg)

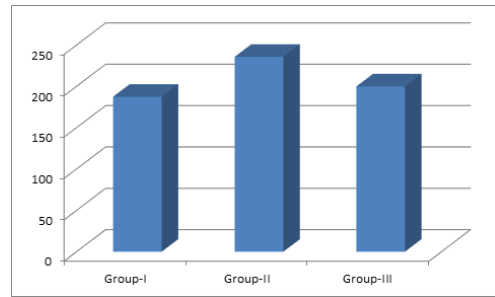


FIGURE 3: Mean Ketamine Dose (µg/Kg)

Even though the mean dose of ketamine administered was comparable in group I and III, the mean dose of propofol administered varied significantly in both the groups. This could be due to the lesser dose of ketamine administered in group I (0.5 mg/ml) as compared to group III (1.5 mg/ml).

The mean drug volume, mean propofol concentration and mean ketamine concentration were least in group III.

We have also found that the drug combination with high ketamine concentration required least volume of drug given intravenously as compared to drug combination having ketamine in low concentration.

Recovery Profile:

It was observed in our study that none of the patients could be transferred directly from the operation theatre to Phase II (recovery area) using Fast - Track eligibility criteria. Patients were shifted to Phase I where they were observed using Fast-track score till 3 hours post surgery (Fig 4). The observations were continued as we found that the parameters used in Fast-track eligibility criteria are similar to Modified Aldrete Scoring System and Revised PADSS except for the surgical bleeding which was present only in Revised PADSS. From the results obtained, it was seen that in group I recovery was most prolonged (150 min) using all the three scoring system. In group II, patients were ready to be discharged at 120 min using Modified Aldrete Scoring System (Fig 5) and at 150 min using Revised PADSS (Fig 6). The earliest recovery was seen in group III using Fast-Track eligibility criteria, wherein all the patients had score > 12 at 60 min and were ready for discharge at 90 min using both the Modified Aldrete Scoring System and Revised PADSS.

FIGURE 4

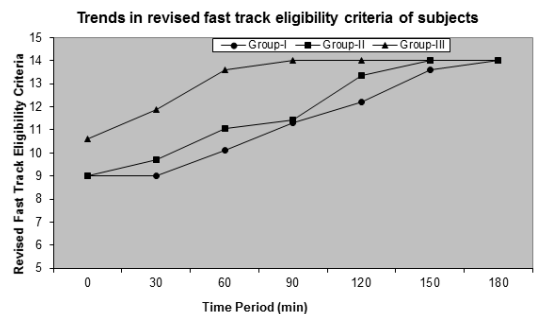


FIGURE 5

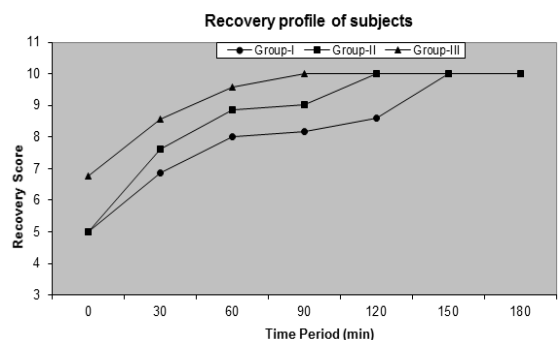
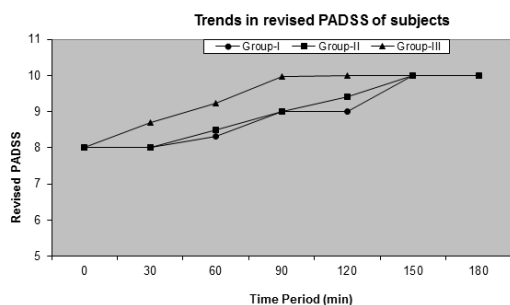


FIGURE 6



We have found that the patients in group I and II had delayed recovery as they had received a higher dose of propofol than group III. In group III, the recovery was earliest as these patients received the least amount of both propofol and ketamine. It is proposed that the early recovery in group III was due to the fact that the arousal effects of ketamine may have been partially antagonized by the sedative effect of propofol. As the dose of ketamine is decreased, the dose of propofol is increased in a drug combination. The recovery of the patients was delayed indicating that the use of propofol in a larger dose tends to delay recovery. It was also noted that even though statistically there was no significant difference in the duration of surgery in all the patients, in group III more number of patients (33.33%) had surgery lasting for 15 min as compared to group I (20%) and group II (16.67%). The mean total drug volume administered was the least in group III (6.63 ± 1.07 ml), followed by group II (11.93 ± 1.01 ml) and group I (6.63 ± 1.07 ml) respectively. Propofol provided sedation and ketamine contributed to analgesia in all the three groups without haemodynamics and respiratory depression or psychotomimetic side effects. However after extensive literature search, we were unable to find any study on the recovery profile of patients using the similar dosage combination as used in our study.

Respiration, Blood Pressure and Heart Rate:

In our study, patients in group I and II were able to maintain $O_2 > 92\%$ on room air and no intervention were required, even though shallow breathing was noted up to 60 min and 30 min in group I and II respectively. There was no such incidence noted in group III. We observed that the patients given highest dose of propofol had delayed recovery of respiration as compared to and patients receiving the least propofol dose having fastest recovery with no episodes of shallow breathing. In group III, large ketamine dose (1.5mg/ml) obviated the need for increase in propofol administration and avoided shallow breathing observed in patients given lesser ketamine dose (group I: 0.5mg/ml and group II: 1 mg/ml).

Statistically no significant changes in blood pressure and heart rate were observed in all the three groups. Ketamine directly stimulates the CNS leading to increased sympathetic nervous system outflow^[4] which counteracts the hemodynamic depression caused by propofol.

Conscious Level:

There was a significant difference in the level of consciousness in all the three groups. Using Modified Aldrete Scoring System, patients were fully awake at 60 min in group III, at 120 min in group II and at 150 min in group I. The observed difference may be due to the amount of propofol administered which was the least in group III and prolonged delay in return of consciousness level was observed in group I as it had the maximum amount of propofol being administered.

Oxygen Saturation:

The oxygen saturation was comparable and statistically insignificant in all the groups.

Nausea and Vomiting:

Statistically no significant difference was observed in all the three groups. Patients had mild nausea / vomiting which did not require treatment and subsided by reassurance. We assume that this is due to the antiemetic property of propofol which counteracted the nausea and vomiting seen with ketamine.

Pain and Surgical Bleeding:

a. Pain on intravenous injection: The addition of ketamine to propofol decreases the pain caused by intravenous propofol

injection which maybe the reason that none of the patients in our study had pain on intravenous administration of drugs in combination.^[32]

- b. Pain after surgery: In all the three groups, patients experienced mild pain (VAS 0-3). However none of the patients required additional analgesic medications. We opine that use of propofol and ketamine combination for general anaesthesia gives very good surgical anaesthesia without pain.^[33,34]
- c. In all the three groups, there were no statistically significant changes observed in surgical bleeding.

CONCLUSIONS:

Analysing the results of our study, we found that the combination of propofol (7 ml) with ketamine (3 ml) was most effective as the total drug volume used was the least and also with this combination, the mean dose of propofol and ketamine used was reduced significantly and patients were ready for discharge earliest as compared to other drug combinations. The volume of the drug reduced significantly as the amount of ketamine in the combination was increased. Patient receiving least propofol and ketamine concentration (group III) had the fastest recovery of the activity and consciousness level. The respiration, circulation and oxygen saturation was maintained throughout the study in all the three groups and patients had mild pain and nausea / vomiting after surgery which subsided by reassurance and did not require any treatment. In our study, no incidence of pain on intravenous injection and hallucinations were observed.

Hence, we recommend that out of the three dose combinations used in our study, the optimal dose of propofol and ketamine combination is 7ml 1% propofol + 3ml 5% ketamine (group III), as it provided the best operative conditions for the surgery along with fastest recovery using minimum drug volume, dose requirement and produced least adverse outcomes.

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