Original Research Article

# Comparative Evaluation of Propofol-Ketamine and Propofol-Fentanyl for Quality of Surgical Anaesthesia in Short Surgical Procedures

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## Abstract

**Background**: Multiple drug combinations have been tried and tested for Total Intravenous anaesthesia (TIVA). When using drugs in combination, the effects or adverse reactions cannot be exactly predicted from the doses of the individual agents used. **The aim of study:** to compare the efficacy of the drug combinations, propofol-ketamine and propofol-fentanyl in terms of haemodynamics parameters and recovery profiles when used as continuous infusions for maintenance of anaesthesia. **Materials and Methods:** A double blind randomized prospective study was designedand 120 patients belonging to ASA 1 & II were enrolled to evaluate the two drug combinations of either propofol-ketamine (Group A) or propofol-fentanyl (Group B) for assessing the quality of surgical anaesthesia. Intraoperatively, hemodynamic and respiratory parameters and recovery profile were recorded. Analysis was done using SPSS version 20 and a p-value of $\leq 0.05$ was considered statistically significant. **Results**: Group B had statistically significant fall in heart rate and blood pressure in the intraoperative period, whereas it was maintained in Group A. Recovery profile was better for Group B. Both the groups showed no significant adverse effects requiring intervention. **Conclusion**: Both ketamine and fentanyl provide excellent surgical anaesthesia in combination with propofol for short surgical procedures with minimal adverse effects and can be considered a good alternative for procedural sedation outside the operating room.

**Keywords**: TIVA, Propofol , Ketamine, Fentanyl, surgical anaesthesia.



## Introduction

Total intravenous anesthesia (TIVA), a modified form of general anaesthesia, is defined as a techniquewhich involves the use of only intravenous drugs to anaesthetize the patient without the use of inhalational agents.[1]TIVA has many effects including sleep hypnosis, analgesia, suppression of somatic and autonomic reflex response. With TIVA it is possible to provide a truly balanced anaesthesia and better titrate each components to the desired clinical effect.[2]Propofol has pharmacokinetic profiles that favour administration by continuous intravenous infusion.[2,3]The prompt recovery without residual sedation and low incidence of nausea and vomiting make propofol particularly well suited to ambulatory anaesthesia techniques. As Propofol has very little nociceptive effect, it is generally combined with an analgesic, the popular combination being either Propofol-Fentanyl or Propofol-Ketamine.[4]Ketamine is a potent analgesic which has very high margin of safety, no irritation of the veins and no negative influence on ventilation or circulation. [5]Preliminary studies indicate that ketamine may be a useful alternative to opioids as adjuncts to propofol for TIVA. Fentanyl on other hand is the most frequently used opioid in clinical practice today.[6] It has a rapid onset and short duration of action and has been shown to reduce the intra operative requirement of propofol. Therefore, it can be ascertained that the combination of Propofol with either Ketamine or Fentanyl should provide ideal anaesthetic conditions and should suffice all the components of balanced anaesthesia.Though there are a plethora of literature available for drugs that can be used for TIVA, to the best of our knowledge there is inadequate evidence in comparing the efficacy of the drug combinations, propofol-ketamine and propofol-fentanyl in terms of haemodynamics parameters and recovery profiles when used as continuous infusions for maintenance of anaesthesia.

**Aims and objectives**

The aim of the study was to compare and evaluate the effectiveness of two drug combinations using propofol-ketamine and propofol-fentanyl for total intravenous anaesthesia.

- Primary objectives : to compare the haemodynamic parameters and the quality of surgical anaesthesia in the intra-operative period.
- Secondary objectives: to compare the recovery profile, time to discharge from the post anaesthesia care unit and incidence of any adverse effects.

**Materials and methods**

Following approval of institutional ethics committee(KIMS/KI IT/IEC/155/2018) and CTRI registration(CTRI/2019/06/019790) a randomized double blind study was conducted from June 2019 to July 2020.

Sample size: By considering power (1-beta) =0.90 and alpha (type-1 error) =0.05, the sample size was calculated as 120 patients for our study. 100 patients were recruited for the study and they were divided randomly into two groups using a computer generated randomization list and the patients were allocated to one of the two groups by the opaque sealed envelope technique and received either of the two regimen.

After obtaining a written informed consent, female patients aged 18-60 years belonging to American society of Anesthesiologist (ASA) physical status I and II scheduled for elective surgical procedures of duration less than 30 minutes were enrolled. Patients with history of

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allergy to any particular drug used in the study, egg allergy, history of substance abuse, opioid tolerance, American society of anaesth-esiologists (ASA) physical status III or IV and surgeries requiring a secure airway were excluded from the study. Pre-anaesthetic check up was done with routine investigations.A double blind technique was followed, where an anaesthesiologist who is not part of the study prepared the drug solution according to the allocated group. The solution was then handed over to the investigator who administered the drugs.

**Solutions for induction:**

Group A: 100mg of propofol (10ml) +100mg ketamine (2ml) diluted to 15 ml at 0.15ml/kg slow iv (over 10 sec)

Group B:100mg of propofol (10ml) +100mcg fentanyl (2ml) diluted to 15 ml at 0.15ml/kg slow iv (over 10 sec)

**Solutions used for maintenance:**

Group A: 100mg of propofol (10ml) +50mg ketamine (1ml) diluted to 20ml at 0.4ml/kg/hour

Group B:100mg of propofol (10ml) +50mcg fentanyl (1ml) diluted to 20ml at 0.4ml/kg/hour

If required bolus doses were given with 2ml of the same solution.

**Table 1:Dose profiles**

| | GROUP A | GRO UP B |
|---|---|---|
| Induction | Propofol 1 mg/kg<br>Ketamine 1mg/kg | Propofol 1 mg/kg Fentanyl 1mcg/kg |
| Maintenance | Propofol 2mg/kg/hour ketamine 1mg/kg/hour infusion | Propofol 2mg/kg/hour fentanyl 1mcg/kg/hour infusion |

**Anesthetic technique**

Standard anesthetic technique was used in all the patients. Baseline parameters were recorded Premedication was given with injection glycopyrrolate 0.2 mg i.v followed by injection midazolam 1mg i.v.

**Induction and maintenance of anesthesia**

Induction of anaesthesia was done with the prepared drug mixture for induction 0.15ml/kg slow iv over 10 seconds or till point of induction. The maintenance drug mixture was started immediately afterwards at 0.4ml/kg/hour. In case of any response to surgical stimulation, bolus doses were given with 2 ml of the maintenance drug mixture. Total number of bolus doses needed was noted.The study drug was discontinued at the end of the surgical procedure and the total amount of drug consumed was recorded. The recovery time i.e the time from discontinuation of the infusion to the achievement of Ramsay Sedation score 3 was noted and patients were transferred to recovery room. The recovery room anaesthetist was blinded to the study drug received by the patient. Any incidence of desaturation, hypotension, nausea, vomiting or pain was managed as necessary.Patients were discharged from the recovery room after attaining a Modified Aldrete score 9.

**Results**

**Statistical Analysis**

The statistical analysis was done for 100 patients enrolled in the study. The continuous variables are presented as mean ± SD and the categorical variables are presented as frequency and percentage. Chi-square test was used to check the association between two categorical variables. Student's t-test was used to test the significance in difference between two groups. Statistical analysis was done by using the SPSS software version 20 and P-value $\leq$0.05 was considered as statistically significant.

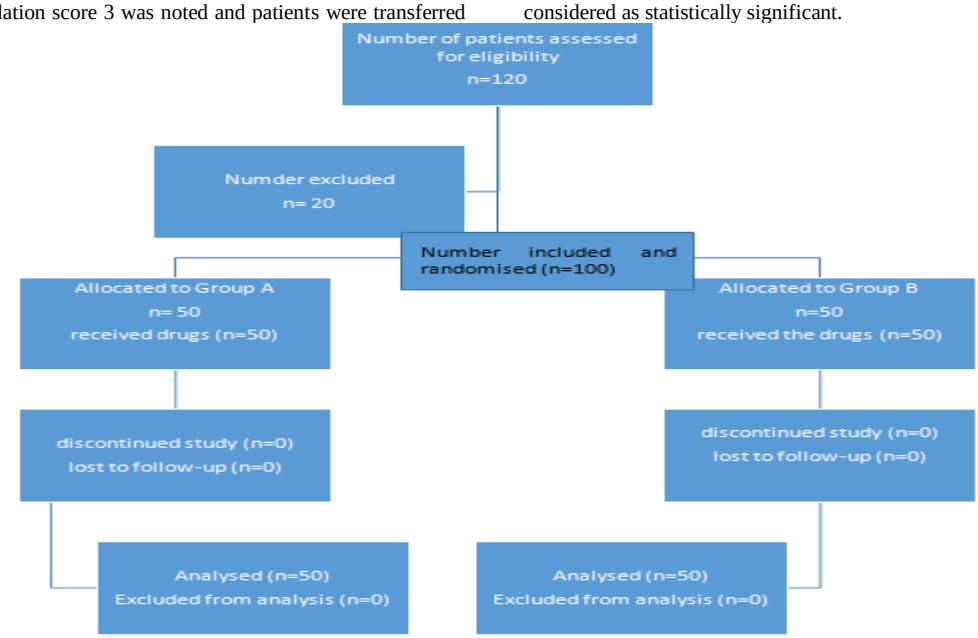


**Fig 1 : Consort**

**Table 1 : Demographic Characteristics**

| MEAN | GROUP A | GROUP B | P VALUE |
|---|---|---|---|
| AGE (YEARS) | 40.14 ± 10.25 | 41.94 ± 12.01 | .422 |
| HEIGHT(Cm) | 156.82 ± 4.75 | 157.46 ±5.06 | .516 |
| WEIGHT(Kg) | 59.32 ± 8.19 | 60.70 ± 9.32 | .434 |
| BMI(Kg/M$^2$) | 23.87 ± 2.95 | 24.15 ±3.27 | .652 |

Table 1 shows the demographic parameters of the patients enrolled in the study, where no statistical significance was observed between Group A and Group B. All the patients in the study population were females.

**Table 2: Comparison Of Haemodynamic Parameters At Different Time Intervals**

| TIME | HEART RATE | | p-value | MAP | | p-value |
|---|---|---|---|---|---|---|
| BASELINE | GROUP A | 89.68+12.70 | .93 | GROUP A | 93.34 ± 11.87 | .62 |
| | GROUP B | 89.88+13.55 | | GROUP B | 94.46 ±10.68 | |
| 5 MIN | GROUP A | 92.62+12.31 | .00 | GROUP A | 95.50±11.27 | .00 |
| | GROUP B | 82.62+12.73 | | GROUP B | 85.76±8.86 | |
| 10MIN | GROUP A | 89.26 + 11.91 | .03 | GROUP A | 92.42±10.40 | .00 |
| | GROUP B | 84.22+11.57 | | GROUP B | 76.88 ±9.01 | |
| 15MIN | GROUP A | 88.83 +11.85 | .05 | GROUP A | 93.76 ±12.13 | .00 |
| | GROUP B | 83.84 + 10.46 | | GROUP B | 77.84 ±9.76 | |
| 20 MIN | GROUP A | 89.60 +13.55 | .12 | GROUP A | 98.50 ±10.26 | .00 |
| | GROUP B | 81.40 + 8.27 | | GROUP B | 74.30 ±11.99 | |
| 25 MIN | GROUP A | 75.33 + 5.74 | .28 | GROUP A | 92.67±10.01 | .28 |
| | GROUP B | 82.67 + 10.01 | | GROUP B | 85.17 ±8.81 | |
| 30 MIN | GROUP A | 77.00 + 5.56 | .17 | GROUP A | 97.33 ±15.94 | .45 |
| | GROUP B | 86.17 + 9.43 | | GROUP B | 91.17 ±8.42 | |

Table 2 shows the comparison of the heart rate and mean arterial blood pressure between the two groups at different time intervals throughout the surgery. There was a statistically significant fall in the heart rate at 5 min, 10 min and 15 min post induction in group B, whereas there was an slight increase in the same, in Group A, compared to the baseline. The heart rate was maintained during the rest of the procedure at 15, 20, 25 and 30 minutes. Similarly, there was a statistically significant fall in mean arterial pressures in Group B when compared to group A. This fall in pressures were sustained till 20 minutes post induction after which the pressures stabilized. In Group A, the mean arterial pressures were maintained on the higher side throughout the duration of surgery.

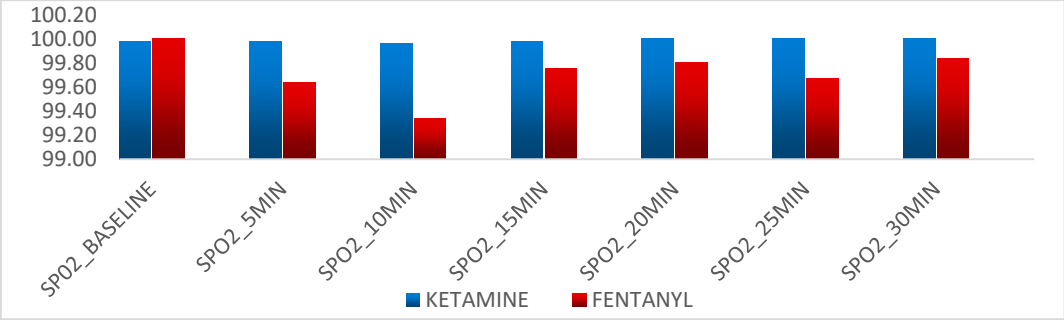


**Fig 1: Comparison of peripheral $O_2$ saturation at different time intervals**

Figure 1 shows the peripheral oxygen saturation. As is seen in the diagram, there was a fall in saturation in group B intermittently, whereas it was maintained throughout the surgery in group A. This fall in saturation was not clinically significant.

**Table 3: Comparison Of Quality Of Anaesthesia And Recovery Profile**

| | GROUP A | GROUP B | p-value |
|---|---|---|---|
| TIME TO REACH RSS 3 | 8.76 +1.82 | 4.40+1.05 | .000 |
| TOTAL AMOUNT OF DRUGS | 13.62+4.25 | 12.89+3.77 | .370 |
| TIME TO MAS=9 | 33.42+5.05 | 24.50+4.95 | .000 |
| NUMBER OF BOLUS DOSES | 0.48± 0.7 | 0.24± 0.4 | .055 |

In table 3, comparison was done between the two groups in terms of time taken to reach a Ramsay Sedation Score of 3, total amount of drug consumed, total number of bolus doses required and the time to reach modified Aldrete Score of 9. Patients in Group B took significantly less time to reach a RSS of 3 when compared to group A. The time to reach MAS of 9 was 24.5 min in Group B where as it was 33.4 minutes in group A. This difference was statistically significant.The total amount of drugs needed and the number of bolus doses were similar in both groups.

**Table 4: Postoperative Parameters**

| POSTOPERATIVE | | GROUP A | GROUP B |
|---|---|---|---|
| NEED FOR RESCUE ANALGESIC | COUNT | 6 | 5 |
| | % | 12 | 10 |
| EMERGENCE REACTION | COUNT | 3 | 0 |
| | % | 6 | 0 |
| VOMITING | COUNT | 3 | 4 |
| | % | 6 | 8 |

Table 4 shows the postoperative parameters observed during the study. Six patients in group A and five patients in group B needed rescue analgesics. Three patients in group A experienced emergence reactions in terms of hallucinations and irrelevant talks. Three patients in group A and four patients in group B had emesis and required rescue antiemetic.

**Discussion**

The pharmacokinetic characteristics of propofol like its rapid onset of action, short duration of action and short context sensitive half life make this drug an ideal and desirable drug for induction and maintenance of anaesthesia. However its cardiovascular effects and lack of analgesic property have limited its use as a sole agent for maintenance of anaesthesia. To mitigate these effects other drugs like ketamine and fentanyl can be combined with propofol.There was a statistically significant fall in the heart rate at 5 min, 10 min and 15 min post induction in group B, whereas there was an slight increase in the same in group A compared to the baseline. Our results were also in agreement with several studies like Pawar et al. [7] and Saha et al. [8] who found statistically significant changes in pulse rate in propofol–ketamine and propofol–fentanyl groups but no episodes of bradycardia or tachycardia.The slight increase in the heart rate in the immediate post induction period observed in Group A may be attributed to the sympathomimetic actions of ketamine, which to an extent is balanced by the cardiac depressant effect of propofol. Although fentanyl has no innate cardiac depressant activity, it maintains or slightly decreases the heart rate. So, in a two drug combination of propofol and fentanyl, a mild to moderate degree of fall in heart rate may be expected.There was a decrease in the mean arterial blood pressure in group B following induction of anaesthesia at 5 minutes (85.76±8.86 ), whereas the mean blood pressure was maintained in group A at 5 minutes post induction (95.5 ± 11.27). Throughout the duration of surgery, the mean arterial blood pressure in group B was maintained at a lower range than the preoperative values. There was high statistical significance for the same between the two groups at 5,10,15 and 20 minutes. Bajwa S.J.S. et al observed that ketamine–propofol provide better control of systolic blood pressure as compared to propofol-fentanyl. Similar results were observed by Kb et al[9] and Bahrami et al[10] Their findings are well in accordance with our study.The peripheral oxygen saturation was maintained throughout the duration of surgery in group A, whereas there was intermittent fall in saturation in group B (2 patients). This fall in saturation was relieved with manouvres such as jaw thrust along with delivering 100% oxygen via closed circuit and was not clinically significant. This fall in saturation could be because of the unfavorable effects of both propofol and fentanyl on the respiratory system. Propofol abolishes the airway reflexes and fentanyl can cause respiratory depression. Similar results were also observed by Messenger et al [11] ,whereas the study conducted by AL Sayed mostafa et al[12], showed no significant changes in the peripheral oxygen saturation between the two groups and there was no significant respiratory depression with either of the two groups postoperatively. The total amount of drug used, number of bolus doses and the time to first bolus dose was comparable in both groups. Only 10 people in group A and 6 people in Group B needed bolus doses.Throughout the duration of the surgery, patients were comfortable. No gross limb movements or complications due to lighter plane of anaesthesia were noted.The recovery profile of the patients was assessed using Ramsay Sedation Score (RSS). Patients were shifted out of the operating room, into the post anaesthesia care unit (PACU) after achieving a RSS of 3. In Recovery Profile (Table - 3) the patients in Group A required more time as compared to Group B to reach a RSS of 3, which was highly statistically significant. Similarly, the time taken to achieve a modified Aldrete score of 9 was higher in Group A in comparison with Group B. Although these values were statistically significant, they were not of much significance clinically. Recovery time was found to be higher in the ketamine group as compared to the fentanyl group in a study conducted by Pawar et al in 2015. Similar results were obtained in the study conducted by AL Sayed Mostafa et al, Pierre et al[13], Hernandez et al[14] and Saha et al.[8] In our study, no serious complications were noted in the intraoperative period. Only six patients in Group A and five patients in Group B needed rescue analgesics in the post operative period and the mean time to rescue analgesic was similar in both groups with no statistical significance. Three patients in Group A reported episodes of postoperative vomiting as compared to four in group B.Both the drug combinations ensured safe anaesthetic conditions and a smooth recovery.

Limitations of our study

- We did not investigate the effect of these infusion doses on the requirements of opioids or other analgesics after being shifted from postoperative care unit.
- We could recruit and analyse only 100 patients due to SARS Cov 2 pandemic.
- The dose ratios of drugs used were selected based on our own clinical experience.
- The intraoperative sedation was assessed on clinical basis and depth of anaesthesia monitoring was not used.

**Conclusion**

The synergistic mechanism of action of the three drugs enabled us to choose them while designing the study.The drugs used in the doses and ratios 1:1 for induction and 2:1 for maintenance seems to be an ideal dose in combination for conducting procedural sedation. Also either of the drug combinations can give good results for painful procedures outside the operating room in terms of haemodynamic parameters, recovery profile and minimal side effects. So,we would like to recommend either of the above mentioned drugs in combination and doses as regimes to be used to improve the quality of surgical anaesthesia in short surgical procedures.

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