

## A HOSPITAL BASED PROSPECTIVE STUDY TO COMPARE OF KETAMINE-PROPOFOL VERSUS PROPOFOL AS INDUCTION AGENTS ON HEMODYNAMIC PARAMETERS IN PATIENTS UNDERGOING ELECTIVE SURGICAL PROCEDURES UNDER GENERAL ANAESTHESIA AT TERTIARY CARE CENTRE

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### ABSTRACT

**Background:** Propofol and Ketamine are commonly used intravenous agents for the induction of general anaesthesia. While Propofol causes vasodilation and myocardial depression, Ketamine stimulates cardiovascular and respiratory systems. Combining them as ‘ketofol’ may yield synergistic benefits by balancing haemodynamic effects and minimising adverse effects. The results of this study may help in determining the role of both Propofol and Ketamine in Ketofol as compared to Propofol, so far as haemodynamic and recovery profile of patients undergoing surgical procedures under general anaesthesia are concerned. **Materials and Methods:** In 40 ASA status I patients, who were randomly assigned into two groups, Group KP, Ketamine-Propofol Group were administered 0.75mg/kg of ketamine and 1.5mg/kg of Propofol. Group P – Propofol Group were administered 2mg/kg of Propofol for induction. Airway is secured with LMA and patients of either group were maintained on O<sub>2</sub>, N<sub>2</sub>O and Sevoflurane. Baseline hemodynamics, Heart Rate, NIBP, Spo<sub>2</sub>, respiratory rate was noted at intervals of 3 minutes for the next 15 minutes. Post-operatively, each patient was assessed for pain scores. Any patient who complains VAS>3 was administered additional analgesia. **Results:** The hemodynamic changes following LMA insertion in systolic, diastolic, mean arterial blood pressures and heart rate were significantly higher in Group KP compared to Group P. Group KP experienced longer recovery times, lower VAS scores immediate post-operatively with fewer analgesic requirements. There was no incidence of apnoea/hypoventilation/emergence reactions in either group. **Conclusion:** Ketofol is a combination of ketamine and Propofol which has several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and potent post-procedural analgesia. Therefore, we recommend Intravenous Ketofol as induction agent especially in patient undergoing short surgical procedures.

## INTRODUCTION

Procedural Induction agents and analgesia (PSA) are pivotal in ensuring the humane and efficient performance of painful procedures during surgery or emergencies. Propofol and ketamine, widely used sedative agents, have distinct advantages and limitations that have prompted interest in their combined use as "ketofol".<sup>[1]</sup>

Propofol, a commonly used agent for induction and maintenance of general anaesthesia,<sup>[2]</sup> is ideal for short and ambulatory surgical procedures requiring general anaesthesia, as onset and recovery is rapid with fewer

unwanted side effects.<sup>[3]</sup> However, when used as the sole induction agent, it may cause significant reduction in arterial blood pressure and cardiac output.<sup>[4]</sup> It produces a decrease in systemic arterial pressure greater than that with a comparable dose of thiopentone.<sup>[5]</sup> The decrease in blood pressure is due to both a decrease in systemic vascular resistance and a reduced myocardial contractility. Despite a decrease in arterial pressure, the heart rate remains unchanged due to depression of baroreceptor response.<sup>[2]</sup>

Ketamine is a potent analgesic which also releases catecholamines, with subsequent tachycardia and

hypertension.<sup>[6]</sup> Intravenous ketamine causes a rise in systemic and pulmonary arterial blood pressure, heart rate, cardiac output and myocardial oxygen requirement.<sup>[7]</sup> Direct stimulation of the central nervous system leading to increased sympathetic nervous system outflow seems to be the most important mechanism for cardiovascular stimulation.<sup>[7]</sup> Administration of ketamine before induction with propofol has been shown to produce more hemodynamic stability as compared to Propofol alone.<sup>[8]</sup>

Ketofol has successfully been used in brief, painful interventions in emergency departments; for sedation in pediatric cases; for regional anesthesia; and in anesthesia applications in electroconvulsive therapy.<sup>[7,8]</sup> The aim of this study to compare of Ketamine-propofol versus propofol as induction agents on hemodynamic parameters in patients undergoing elective surgical procedures under general anaesthesia.

## MATERIALS AND METHODS

This is a hospital based prospective study done on 40 Patients aged between 18-60 years, American Society of Anesthesiologists (ASA) status I posted for surgical procedures under general anaesthesia in Government Medical College & attached District Hospital, Dausa, Rajasthan, India during one-year period.

### Inclusion Criteria

50 patients of ASA status I, aged between 18-60 years who are to undergo elective general, orthopedic, plastic, or gynecologic surgery under general anaesthesia.

### Exclusion Criteria

- Emergency surgery.
- Patients undergoing neurosurgical procedures.
- Clinically significant cardiac/renal disease/liver disease.
- Pregnant or breast feeding women.
- Patients with significant hemodynamic instability.
- Patients having significant respiratory disorders.
- Patient with psychiatric disorders.
- Any known contraindications to ketamine or propofol.

**Methods:** ASA status I posted for surgical procedures will be divided into 2 groups (KP and P), on the basis of random sampling.

After explaining the procedure, written informed consent will be obtained from the patients, pre anesthetic evaluation for all patients will be done and allotted into two groups:

**Group KP – Ketamine-Propofol Group:** Patients in this group, as a part of induction, will be given 0.75mg/kg of ketamine and 1.5mg/kg of propofol. If any patients respond to stimulus after induction, then they receive an additional 0.25mg/kg of ketamine and 0.5 mg/kg of propofol thereby receiving a total of 1mg/kg of ketamine and 2mg/kg of propofol.

**Group P – Propofol Group:** Patients in this group, as a part of induction, will be given 2mg/kg of propofol. If the patients respond to stimulus after induction, then they receive an additional 1mg/kg of propofol thereby receiving a total of 3mg/kg of propofol.

Patients from both groups will be kept nil per oral from solids for 6 hours and from clear fluids for 2 hours.

After the patients are shifted to the operation room, electrocardiogram (ECG) leads, Non-Invasive Blood Pressure (NIBP) cuff and Pulse Oximetry will be connected. Baseline vitals are recorded and I.V. fluids are administered as routine protocol. All patients will be given Inj. Glycopyrrolate 0.005mg/kg i.v. and Inj. Fentanyl 2µg/kg i.v. and preoxygenated with 8l/min of Oxygen via. mask, using Bains circuit for 3 minutes prior to induction. After induction, patients of either group will receive O<sub>2</sub> 33%, N<sub>2</sub>O 66% and 1 MAC of Sevoflurane (age related iso-MAC values) as maintenance of anesthesia. The patient will be on assisted or spontaneous ventilation using Bains circuit. Baseline hemodynamics, Heart Rate, NIBP, oxygen saturation, respiratory rate will be noted (0th interval).

Airway is secured with Laryngeal Mask Airway (LMA) and ETCO<sub>2</sub> connected. Any apnoeic incidence, secretions and any untoward events are noted on insertion of LMA. Patient will be on assisted or spontaneous ventilation, and anesthesia is maintained with 1MAC Sevoflurane. Baseline hemodynamics is recorded at interval of 3 minutes for the next 15 minutes.

Laryngospasm, if any, is treated with I.V. Inj. Succinylcholine (Sch) and the study continued. If it is not possible to secure the airway with LMA, I.V. Inj. Sch is administered, patient trachea is intubated with Endo Tracheal Tube (ETT) and the patient will be excluded from the study.

In cases where LMA ventilation is found inadequate, the LMA is removed, I.V. Inj. Vecuronium (dose 2×ED<sub>95</sub>) administered, airway is secured with ETT and the patient will be excluded from the study.

Till the first 15 minutes of insertion of LMA (study period) surgical stimulus is avoided. Surgery proceeds after 15 minutes of LMA insertion and the duration of surgery is noted. Once the surgery is completed, patient is allowed to recover from anaesthesia.

In the post anesthesia care unit (PACU), all patients will receive oxygen using face mask at 5 L/minute for 30 minutes. ECG, NIBP and SPO<sub>2</sub> are connected and observed.

All patients will receive fixed dose of oral or parenteral tramadol 50mg 8th hourly or NSAID's as routine analgesia.

Each patient will be assessed for pain scores through Visual Analogue Scale (VAS), at intervals VAS<sub>0</sub> (immediate post-operatively). Any patient who complains VAS>3 will be noted and additional analgesia (I.V. Inj. Tramadol 50mg) is administered.

Hemodynamics – Incidence of hypotension (<30% of baseline), bradycardia (<20% of baseline) or increase in NIBP or heart rate (> 30% of baseline) are noted. Adverse effects like Apnoea/ Hypoventilation/ Desaturation/ emergence reactions are noted.

**Statistical Analysis:** Hemodynamic data such as heart rate, mean arterial pressure, SBP, DBP and MAP were analyzed using unpaired t test. The data collected are presented as mean, SD for quantitative observations and proportions (%) for qualitative observations. A “p” value less than 0.05 was considered as the minimum value for statistical significance.

## RESULTS

A total of 40 patients were included for this study and randomly allocated to one of two groups, named as Group 1 and Group 2 representing Ketamine and Propofol combination and Propofol used for the study. Each group was comprised of 20 patients. There are no statistically significant differences among the groups regarding age, weight, sex, or baseline hemodynamic parameters ( $p > 0.05$  for all comparisons). This similarity in baseline data ensures that subsequent differences in outcomes could be more confidently attributed to the allocated study interventions. The VAS scores were significantly lower with fewer analgesic requirement post-operatively in Group KP compared to the Group P [Table 1].

There was significant difference in the heart rate between the two groups at 3rd minute to 15th minute following induction. There is a significant rise in heart rate in the group KP and a fall in the group P. The peak effect of rise in heart rate in Group KP was seen in the 6th minute (18.73% of baseline) whereas peak fall in heart rate in the P group was in the 6th minute (9.04% of baseline) [Table 2].

As seen in table no. 3 there is a significant difference in the systolic BP between the two groups from the 3rd minute (t3) to 15 minutes following induction. The peak fall in the systolic BP was in the 6th minute in both groups, group P (19.25% of baseline) and Group KP (8.5% of baseline).

DBP in both the groups was compared at baseline and at various intervals. There are statistically significant lower values of DBP in Group P compared to Group KP at 3rd minute (T3) to 15th minute (T15) following induction. The peak fall in the diastolic BP in Group P was seen in the 6th minute (20.51% of baseline) and a peak fall of 8.5% of baseline was seen in Group KP at the 6th minute [Table 4].

MAP in both the groups was compared at baseline and at various intervals. There are statistically significant lower values of MAP in Group P compared to Group KP at 3rd minute (T3) to 15th minute (T15) following induction. Peak fall in Group P was in the 6th minute (19.96% of baseline) and peak fall in group KP was in the 6th minute (7.47% of baseline) [Table 5]. There was a significant difference between the two groups in the time for recovery and for orientation [Table 6].

**Table 1: The comparison of age, weight, sex and duration of surgery in between groups**

Variables	Group KP	Group P	P-value
Mean age (yrs)	37.45±2.78	36.92±2.43	>0.05
Mean Weight (Kgm)	55.26±3.93	56.72±3.17	>0.05
Sex	Male	12	>0.05
	Female	8	
Duration of surgery (Mins.)	27.82±1.452	25.24±1.213	>0.05
VAS (Vo)	3.263±0.124	2.486±0.132	<0.0001

**Table 2: Heart rate comparison between two groups**

HR	Group P (Mean±SEM)	Group KP (Mean±SEM)	P value
Pre-op	82.66 ± 1.782	78.66 ± 1.315	>0.05
T0	79.72 ± 1.703	80.43 ± 1.450	>0.05
T3	75.70 ± 1.782	92.36 ± 1.812	< 0.0001
T6	72.35 ± 1.507	94.72 ± 1.672	< 0.0001
T9	72.70 ± 1.688	95.42 ± 1.724	< 0.0001
T12	72.37 ± 1.604	92.74 ± 1.921	< 0.0001
T15	72.42 ± 1.466	93.18 ± 1.924	< 0.0001

**Table 3: SBP comparison between the two groups**

SBP	Group P (Mean±SEM)	Group KP (Mean±SEM)	P value
Pre-op	125.7 ± 1.124	127.3 ± 1.174	>0.05
T0	128.6 ± 0.873	127.8 ± 1.12	>0.05
T3	106.9 ± 1.024	119.6 ± 1.062	< 0.0001
T6	103.5 ± 0.886	116.3 ± 1.127	< 0.0001
T9	107.6 ± 1.173	121.6 ± 1.124	< 0.0001
T12	110.2 ± 0.854	123.4 ± 0.912	< 0.0001
T15	114.3 ± 0.786	125.3 ± 0.685	< 0.0001

**Table 4: SBP comparison between the two groups**

DBP	Group P (Mean±SEM)	Group KP (Mean±SEM)	P value
Pre-op	81.34 ± 0.4483	81.48 ± 0.5340	>0.05
T0	81.58 ± 0.3523	82.98 ± 0.7424	>0.05
T3	68.76 ± 0.5432	79.96 ± 0.7824	< 0.0001
T6	64.84 ± 0.5152	77.46 ± 0.8926	< 0.0001
T9	68.42 ± 0.5737	79.80 ± 0.8428	< 0.0001
T12	72.32 ± 0.5726	81.64 ± 0.6536	< 0.0001
T15	72.98 ± 0.5963	81.76 ± 0.4626	< 0.0001

**Table 5: MAP comparison between the two groups**

MAP	Group P (Mean±SEM)	Group KP (Mean±SEM)	P value
Pre-op	96.22 ± 0.6818	96.62 ± 0.6872	>0.05
T0	97.30 ± 0.4242	97.92 ± 0.8126	>0.05
T3	81.66 ± 0.6736	93.48 ± 0.8532	< 0.0001
T6	77.95 ± 0.5982	90.66 ± 0.8924	< 0.0001
T9	81.56 ± 0.7334	93.62 ± 0.8272	< 0.0001
T12	84.42 ± 0.6148	96.18 ± 0.7165	< 0.0001
T15	86.70 ± 0.6452	96.38 ± 0.4934	< 0.0001

**Table 6: Comparison of recovery time between the two groups**

Recovery time	Group P (Mean±SEM)	GROUP KP (Mean±SEM)	P value
Time for spontaneous eye opening (seconds)	192.4 ±2.453	218.5 ±0.6424	< 0.0001
Time for extubation (second)	202.6 ±2.460	225.8 ±0.6982	< 0.0001
Time for orientation (seconds)	312.6 ±3.126	401.6 ±1.642	< 0.001

## DISCUSSION

The use of Propofol for general anesthesia is associated with decrease in arterial pressure which is due to reduction of myocardial contractility, peripheral vascular resistance and sympathetic tone.<sup>[9,10]</sup> Vagotonic effects of Propofol reduce the HR that may cause severe bradycardia, complete atrio-ventricular block and cardiac arrest.<sup>[9,10]</sup> Sympathetic stimulation by ketamine increases MC and vascular resistance which in turn leads to increased arterial pressure and HR.<sup>[11,12]</sup> Increases in plasma concentrations of epinephrine and norepinephrine occur as early as 2 minutes after intravenous administration of ketamine and return to control levels 15 minutes later.<sup>[13]</sup>

Clinical effects of Propofol and ketamine seem to be complementary. When propofol and ketamine are administered in combination, doses of both agents decrease and unwanted effects are minimized.<sup>[14]</sup>

Various investigators have studied the effects of sub anaesthetic doses of ketamine on propofol sedation. The effects of sub anaesthetic doses of ketamine in combination with propofol to propofol alone in terms of respiration, pain relief (use of additional analgesics) intraoperatively, and postoperatively have been evaluated.

Various doses of ketamine and fentanyl have been reported in literature. Hamdani et al found a dose of 0.3mg/kg of ketamine insufficient for analgesia of cervical dilatation.<sup>[15]</sup> Kaushik Saha et al,<sup>[16]</sup> found excellent analgesia with ketamine 0.5mg/kg. As our study involved procedures approximately of 30 minutes duration we chose 0.75 mg/kg, of ketamine, only at induction.

The interactions of propofol and ketamine in terms of the hypnotic end point (failure to open eyes to command) and anaesthetic end point (failure to move

in response to 5 second transcutaneous tetanic stimulus) were studied by T.W. Hui et al in 1995 at the Department of Anaesthesia Chinese University of Hong Kong.<sup>[11]</sup> The sedative effects of ketamine and propofol were found to be additive at these end points. This has been of interest because, ketamine, by antagonizing the NMDA receptor, has a distinct mode of action in comparison to opioid combination with thiopentone or propofol (GABAa or opioid receptor systems).

Kaushik Saha et al too found a statistically significant decrease in the induction dose of propofol in combination with ketamine, in comparison to fentanyl (67±/ 13.25mg Vs 78.16±/ 15.2 mg).<sup>[16]</sup>

In view of the vasodilatory property and apnoeic potential that propofol possesses, the reduction in the induction dosage of propofol has obvious advantages. Hence, we used Propofol 1.5mg/kg in Group KP as compared to Propofol 2mg/kg alone in Group P.

Tosunetal,<sup>[17]</sup> reported that hemodynamic parameters were similar in both groups when 1mg/kg ketamine or 1 mg/kg fentanyl was added to Propofol for sedation in children with burns. Likewise, in a study by Erdenetal,<sup>[18]</sup> propofol-fentanyl and propofol-fentanyl-ketamine combinations provided similar hemodynamic stability in children.

In our study, Ketamine-Propofol Group showed an increase in HR and decrease in SBP, DBP and MAP values after induction while the Propofol Group showed a fall in all the four parameters. However, the SBP, DBP and MAP measurements were significantly higher in Group KP compared to Group P.

Iwata et al,<sup>[19]</sup> could not achieve hemodynamic stability with 0.5mg/kg or 1mg/kg ketamine applied before 2mg/kg Propofol for anesthetic induction in the double-lumen tube application. Those authors pointed out that this might be due to use of fentanyl

and sevoflurane in both groups. Similarly, use of fentanyl before induction may have impaired the hemodynamic effects of Ketofol in our study.

Mortero et al in 2001 found that sub anaesthetic doses of ketamine produced a “high” feeling on recovery in volunteers. They attributed this to the NMDA receptor blockade by this drug.<sup>[20]</sup>

In our study the recovery times and time for orientation were prolonged in Group KP in comparison to Group P. J.B.M. Guit et al too found a slower recovery (17 min) in the propofol-ketamine group and 13 min in the Propofol-fentanyl group.<sup>[21]</sup>

The longer durations of recovery in their study can be attributed to the infusions of ketamine and fentanyl that were used by them. Hernandez et al too found longer awakening times in the propofol-ketamine (Propofol-fentanyl-midazolam-ketamine) group. They advised that the infusion that was used had to be stopped early for early awakening.<sup>[22]</sup>

Ravindra V. Prasad et al in 1991 and Rosendo Mortero et al in 2001 found a significant reduction in the incidence of emergence delirium when propofol and ketamine were used in combination to ketamine alone.<sup>[20,23]</sup> They found that ketamine produces positive mood effects without changes in perception and may provide an early recovery of cognition. Guit et al reported that no patients reported dreaming during or after the operation.<sup>[21]</sup> Hernandez et al found that though both the techniques did not completely prevent the psychotomimetic effects of ketamine, there was a higher incidence of emergence delirium in the midazolam-ketamine group compared to the propofol-ketamine group.<sup>[22]</sup> This proves that propofol decreases the psychotomimetic effects of ketamine.

In a qualitative systematic review of the role of NMDA receptor antagonists in preventive analgesia, ketamine produced a significant preventive analgesic benefit in 58% of studies.<sup>[24]</sup> Ketamine appears less effective when given after surgical stimulus. Apart from the timing of treatment, route of administration, insufficient afferent blockade, use of opioids during surgery, intensity of noxious stimulus, and outcome measurement problems seem to be important factors responsible for lack of evidence for preemptive effects.<sup>[25]</sup>

Optimal dosage of ketamine for preemptive analgesia is another controversial area. Due to high affinity of ketamine for NMDA receptors, it has been observed that smaller the dose, the more selective the ketamine interaction with NMDA receptors. The low-dose ketamine is defined as a bolus dose of less than 2 mg/kg when given intramuscularly or less than 1 mg/kg when administered via IV route. For continuous IV administration, low-dose ketamine is defined as a rate of  $\leq 20$   $\mu\text{g}/\text{kg}/\text{min}$ .<sup>[26]</sup>

Similar results have been reported in other different studies. Stubhaug et al., infused ketamine for three days after nephrectomy and found that ketamine reduced the area of punctuate mechanical hyperalgesia surrounding the surgical incision for the seven post-operative days.<sup>[27]</sup> With preemptive

administration of ketamine, a decrease in post-operative morphine consumption was observed for two post-operative days after abdominal surgery.<sup>[28]</sup>

Nitrous oxide, used in the present anesthetic technique, may have enhanced NMDA receptor inhibition by ketamine because nitrous oxide too has been reported to exert NMDA antagonist properties.<sup>[29]</sup> However, it is unlikely that nitrous oxide confounded our results as it was also present in the control group. The combination of Ketamine-Propofol significantly improved postoperative analgesia in our study. The Group KP had less pain, immediate postoperatively in comparison to the Group P.

There are some limitations to our study. First, we were unable to measure anesthetic depth, so LMA insertion conditions may have been adversely affected and changes may have been observed in hemodynamic parameters. Second, use of fentanyl in both groups before induction may have impaired the hemodynamic effects of the agents.

## CONCLUSION

Ketofol is a combination of ketamine and Propofol which has several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and potent post-procedural analgesia. Therefore, we recommend Intravenous Ketofol as induction agent especially in patient undergoing short surgical procedures.

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