Original Research Paper

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COMPARISON OF KETAMINE AND FENTANYL AS ANALGESICS FOR TOTAL INTRAVENOUS ANESTHESIA USING PROPOFOL

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ABSTRACT **Background and Aims:** Keeping in consideration the merits of total intravenous anesthesia (TIVA), a genuine attempt was made to find the ideal drug combinations which can be used in general anesthesia. This study was conducted to evaluate and compare two drug combinations of TIVA using propofol-ketamine and propofol-fentanyl and to study the induction, maintenance and recovery characteristics following anesthesia with these techniques. **Settings and Design:** A case control study was conducted, which included 50 patients, in the department of Anesthesiology, Vishwabharathi Medical College, Kurnool, Andhra Pradesh. Patients and Methods: A hundred patients between the ages of 20 and 50 years of either gender were divided into two groups of 50 each, and they underwent elective surgery of approximately 1 h duration. Group I received propofol-ketamine while group II received propofol-fentanyl for induction and maintenance of anesthesia. All the results were tabulated and analyzed statistically with student's unpaired t-test and chi-square test. Results: Propofol-fentanyl combination produced a significantly greater fall in pulse rate (PK-74+/-3.27 and PF-76.56+/-3.267) and in both systolic (and diastolic blood pressures as compared to propofol-ketamine during induction of anesthesia. Propofol-ketamine combination produced stable hemodynamics during maintenance phase while on the other hand propofol-fentanyl was associated with a slight increase in both PR and BP. During recovery, ventilation score was better in group I while movement and wakefulness score was better in group II. Mean time to protrusion of tongue and lifting of head was shorter in group I. **Conclusions:** Both propofol-ketamine and propofol-fentanyl combinations produce rapid, pleasant, and safe anesthesia with only a few untoward side effects and only minor hemodynamic effects.

KEYWORDS : Propofol-ketamine, propofol-fentanyl, total intravenous anesthesia

INTRODUCTION:

The concept of total intravenous anesthesia has evolved from primarily intravenous induction of anesthesia to induction as well as maintenance of anesthesia with intravenously administered drugs. TIVA is defined as technique of general anesthesia using a combination of agents given solely by the intra venous route and in the absence of all inhalation agents including Nitrous oxide.

IDEAL DRUG PROPERTIES REQUIRED FOR TIVA

Water soluble
Stable in solution and on exposure to light for prolonged period
Sleep produced in one arm circulation
Non-irritant to blood vessels or tissues
Painless on injection
Be rapidly metabolized with no accumulation
Not increase muscle tone
Possess minimum cardiovascular effects
Have no effect on respiration
Have no interaction with other drugs
Have no allergic reactions
Not induce nausea or vomiting

INDICATIONS FOR TIVA

As an alternative to volatile agents
Provide sedation during local or regional anesthetic technique
For situations in which conventional anesthetics may be difficult to administer
Lack of appropriate anesthetic drugs
Lack of anesthesia equipment
Locations outside the operating rooms like WAR zones
Circumstances in which nitrous oxide may either be undesirable or relatively contraindicated

Example: Due to need for high inspired O2 concentrations
One lung ventilation
Middle ear surgery.

ADVANTAGES

Induction is very rapid in onset
Rapid onset of action independent from alveolar ventilation
Improved quality of emergence from anesthesia
Very smooth and peaceful recovery
No risk of environmental pollution
Reduction in the incidence of postoperative nausea and vomiting
Method of choice in patients at risk of malignant hyperthermia.
In patients undergoing airway procedures
Increased patient comfort.

Various drugs have been tried from time to time in TIVA. Since no single drug can provide all the characteristics of an ideal intravenous agent, several drugs are used in different combinations to provide balanced anesthesia in TIVA, that is, amnesia, hypnosis, and analgesia.

In the lookout for an ideal intravenous anesthetic agent in clinical practice, Kay and Rolly introduced propofol in 1977. [1] Its advantage in short surgical procedures relates to its rapid elimination from the blood (half-life 1-3 h due to high hepatic clearance) leading to rapid recovery of cognitive and psychomotor functions with a very low incidence of PONV. It is primarily a hypnotic and in sub hypnotic doses provides sedation and amnesia. Lack of analgesic properties of propofol has necessitated the need for supplementary analgesic agents during TIVA. Morphine and pethidine have been replaced by newer agents such as fentanyl, sufentanyl, alfentanyl and remifentanyl, which can be given either in multiple bolus incremental doses or in continuous infusion form. Ketamine in sub anesthetic doses has gained more attention as an analgesic for TIVA. [2]

Fentanyl is used extensively in TIVA now-a-days. It belongs to opioid group of drugs. It is hundred times more potent analgesic than morphine, and as a part of balanced anesthesia it relieves pain, reduces somatic and autonomic response to airway manipulation, provides hemodynamic stability and lesser respiratory depression.

MATERIALS AND METHODS

The purpose of the present study is to compare ketamine and fentanyl as analgesics for TIVA using propofol in short surgical procedures lasting 10-15 mins based on hemodynamic stability, time of recovery, incidence of post operative complications like nausea and vomiting and duration of pain relief post operatively.

This study was conducted in viswabharathi medical college, penchikalapadu, kurnool from NOV 2021 to MAY 2022 after ethical committee clearance, a total of 50 patients of ASA grade 1 and 2 aged between 20 to 50 years scheduled for elective short surgeries of 10 -15 min duration. Patients were randomly allocated into 2 groups

GROUP PK (n = 25) - Received Propofol and Ketamine
GROUP PF (n = 25) -Received Propofol and Fentanyl

All patients underwent minimum investigation as required in individual cases viz.haemogram, blood sugar, LFT, RFT, SE, Viral Markers, urine for routine and microscopic examination, ECG, x-ray chest if needed.

Anesthesia technique

All patients were kept nil orally for 8 hours before scheduled surgery and written informed consents were taken. All patients were premedicated with injection glycopyrrolate 10mcg/kg body weight intravenously (IV) and injection Ondansetron. Upon arrival of the patient in the operation room, intravenous access with one18 G cannula was established. 500 mL of crystalloid (Ringer lactate) solution started from one intravenous cannula. Electrocardiogram (ECG) leads placed, noninvasive arterial blood pressure (NIBP), pulse oximetry monitored. All baseline vital parameters, heart rate, respiratory rate, blood pressure, oxygen saturation (SPO2) was monitored. All the drugs, ketamine, propofol and fentanyl were administered by a person not involved in the study to avoid bias. Drugs were given by intravenous route (I/V) for induction of anesthesia and by infusion pump for maintenance of anesthesia.

Group PK (n = 25)- Received inj Propofol 2.5 mg/kg +inj Ketamine 1 mg/kg

Group PF (n=25) -Received inj Propofol 2.5 mg/kg +inj Fentanyl 1ug/kg .

All baseline hemodynamic parameters HR, SBP, DBP, SPO2 were recorded before induction and immediately after induction, then every 5 minutes till 30 minutes, then every 10 minutes till the end of procedure and every 10 minutes till 30 minutes postoperatively. The incidence of postoperative nausea and vomiting (PONV) hallucinations, hypertension, hypotension. Tachycardia, bradycardia, chest wall rigidity, nystagmus, myoclonic movements were monitored and were managed accordingly, recovery profile was assessed.

Induction of anesthesia

Induction of anesthesia in patients of group I was done with propofol 2.5 mg/kg body wt. and ketamine 1.0 mg/kg body wt. given as IV bolus doses. In group II, induction of anesthesia was done with propofol 2.5 mg/kg body wt. and fentanyl 1.0 µg/kg body wt. given as IV bolus doses.

In both the groups, injection succinylcholine was given as a muscle relaxant before intubation in doses of 1.5 mg/kg body wt. with maximum doses not exceeding 100 mg. Patients were ventilated with 100% oxygen via a facemask for 60-90 seconds with the help of Bains circuit, and intubation was done with an appropriate size of cuffed endotracheal tube. Hemodynamic and other monitoring parameters were observed continuously and recorded at an interval of 1 minute each for the first 5 minutes.

Maintenance of anesthesia

In group I, maintenance of anesthesia was achieved with infusion of propofol 2.0 mg/kg/h and ketamine 2.0 mg/kg/h, while in group II, maintenance of anesthesia was achieved with infusion of propofol 2.0 mg/kg/h and fentanyl 2.0 µg/kg/h.

Vecuronium bromide was used as a muscle relaxant in doses of 0.05-0.06 mg/kg body wt. as an initial bolus dose and supplemented with top-ups of 1 mg in both the groups. Hemodynamic and other monitoring parameters were observed continuously and noted at an interval of 5 minutes during the operation. Patients were ventilated with 100% oxygen with close circuit attached to circle absorber system.

Reversal of relaxant effect

All the anesthetic drugs were stopped 5-7 minutes before the anticipated end of surgery. At the end of surgery, neuromuscular blockade was reversed with injection neostigmine 40 µg/kg body wt. and injection glycopyrrolate 10 µg/kg body wt. which was given over 2-3 minutes. Extubation was done when the patients were able to maintain rhythmic respiration and adequate tidal volume. The monitoring parameters were observed continuously and recorded at the time of extubation and 5 minutes after that. The parameters were again recorded every 15 minutes in the recovery room.

METHOD OF STATISTICAL ANALYSIS

The observed data was subjected to statistical analysis using Chi-square test and Student t test

RESULTS

50 patients aged 20-50 yrs ASA Grade 1 and 2 posted electively for short surgical procedures of 10-15 min duration were included in the study . 25 of them received Propofol 2.5mg /kg +Ketamine 1mg/kg (Group PK) and other 25 received Propofol 2.5mg/kg + Fentanyl 1micro gram /kg (Group PF) iv for induction and maintenance.

Four patients (8%) from group I and five patients (10%) from group II had involuntary movements during the induction of anesthesia.

Parameters which were studied

1. baseline hemodynamics
2. Intraoperative and Postoperative Hemodynamics
3. Complications
4. Pain VAS scores

Table 1: PULSE RATE

	PULSE RATE (beats/min)				
	GROUP PK(PROPOFOL KETAMINE)		GROUP PF(PROPOFOL FENTANYL)		P value
	Mean	SD	Mean	SD	
Pre op	74.84	3.287	76.56	3.367	0.07
Intra op	80.68	3.637	69.60	2.273	0.001
Post op	79.76	4.075	71.28	2.762	0.01

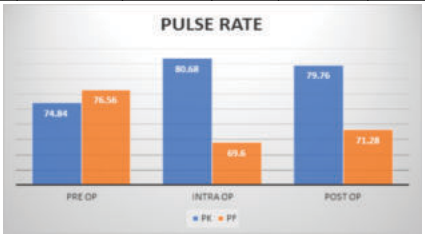


Figure 1: Patten of pulse rates in both the groups during various phases of surgery.

Mean preoperative pulse rates in both the groups were similar, Group PK 74+/- 3.27 and group PF 76.56 +/- 3.267.(P=0.07).

There was an increase in pulse rate in PK group to 80.68+/-3.637 while there was a decrease in PF group to 69.60 +/- 2.273 intra operatively, there difference being highly significant (P= 0.001). Post operatively, the pulse rate in PK was 79.76+/-4.075 compared to 71.28 +/- 2.762 in PF group, the difference being significant(P=0.01).

Preoperative blood pressures were similar in both the groups (p>0.05). There was an increase in both systolic and diastolic blood pressures in group PK intra operatively and a fall in PF group and the difference was statistically highly significant(P=0.001).

Post operatively, the pressures neared preoperative values in PK group. In PF group, the pressures increased but remained lower than the preoperative values and the difference was significant(P=0.01)

Table 2: SYSTOLIC BLOOD PRESSURE

.p	SBP (mm of Hg)				
	GROUP PK		GROUP PF		P value
	Mean	SD	Mean	SD	
Pre op	125.60	5.686	126.56	5.401	0.543
Intra op	133.28	5.350	114.08	6.620	0.001
Post op	130.72	5.941	119.28	5.564	0.01

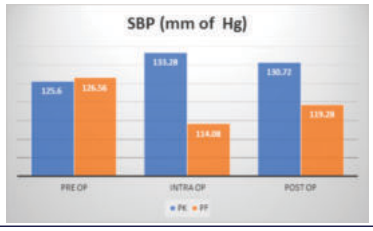


Figure 2: Patten of systolic blood pressures in both the groups during various phases of surgery

Table 3. DIASTOLIC BLOOD PRESSURE

	DBP (mm of Hg)				
	GROUP PK		GROUP PF		P value
	Mean	SD	Mean	SD	
Pre op	79.52	3.016	79.12	3.219	0.652
Intra op	81.52	3.177	71.68	4.190	0.001
Post op	80.72	2.821	73.52	3.364	0.01

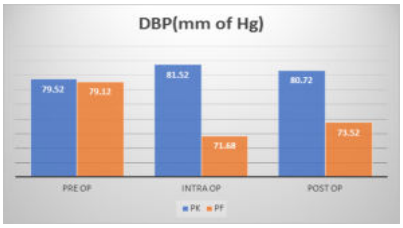


Figure 3: Patten of diastolic blood pressures in both the groups during various phases of surgery

Table 4:

	COMPLICATIONS				
	GROUP PK		GROUP PF		P value
	Number	%	Number	%	
IOP SPO2<93%	1	4%	2	8%	0.552
Nausea	0	0%	3	12%	0.074
Salivation	1	4%	0	0	0.312
Excitation	1	4%	0	0	0.312

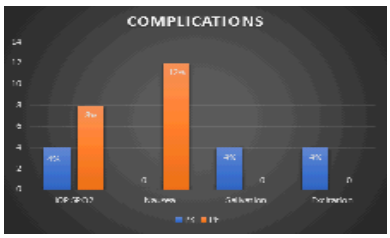


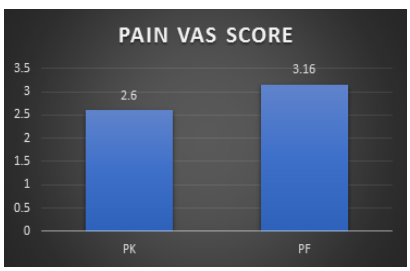
Figure 4: Complications in both the groups during various phases of surgery.

The difference in complications in both the groups was statistically insignificant in relation to saturation, nausea, salivation and excitation(P> 0.05).

Table 5: PAIN VAS SCORE

VAS SCORE	GROUP PK		GROUP PF		P VALUE
	Mean	SD	Mean	SD	
	2.60	0.645	3.16	0.746	0.007

Figure 5



The mean of VAS scores of pains in PK group was 2.60 +/- 0.645 and 3.16 +/- 0.746 in PF group and the difference was statistically significant(P=0.007).

Recovery

Ventilation score was better in group I during the first 10 minutes of recovery phase as compared to group II.

- Mean movement score was better in group II at 5 and 10 minutes.
- Wakefulness score was better in group II at 5 and 10 minutes as compared to group I.
- The mean time for appearance of protective airway reflexes (coughing and gagging), spontaneous eye opening, tongue protrusion and lifting of head was shorter in group II.
- One patient (2%) from group I and three patients (6%) from group II had nausea during the recovery phase while none of them had any episode of vomiting.

Secretions: In group II, four patients had oral secretions during recovery from anesthesia.

post-ketamine sequelae: Two patients (4%) from group I had excitation postoperatively while none of the patients from group II had excitation or any other post-ketamine sequelae like dreams, hallucinations, euphoria, etc. [4]

DISCUSSION

The same dosages of propofol and fentanyl have greater impact on elderly as compared to young patients. In older patients, the total dose of propofol administered decreases while other demographic features did not have any effect.

The demographic profile of this study was almost like many studies except that of Nielsen et al, which showed greater impact on hemodynamic parameters in elderly patients as compared to young patients. This difference can be attributed to the selection of older age group in their study and they used a higher dose of fentanyl 4 µg/kg as compared to the use of 2.0 µg/kg of fentanyl in this study.

As far as the hemodynamic parameters are concerned, there was a slight decrease in heart rate (9%) in propofol-fentanyl group as compared to propofol-ketamine combination in the study of Mayer et al and Mi et al[5]. Studies of Mi et al, also showed that after induction, the PR did not alter significantly when propofol was used alone but decreased between 5 and 35% in patients who were given fentanyl 4 µg/kg prior to the induction of anesthesia.

The results of this study are consistent with those obtained in the studies of Mayer and Mi. Increase in heart rate with propofol and ketamine can be explained on the basis of

- cardio stimulant effect of ketamine
- stress response during intubation.

The combination of propofol with fentanyl:

Mi et al[5], observed greater hemodynamic and electroencephalograph responses to intubation in patients who received propofol than in those who received both propofol and fentanyl (P < 0.05). Hernandez et al, [7] carried out a study with propofol-ketamine, midazolam-ketamine and propofol-fentanyl combinations and observed stable hemodynamics in patients who received propofol and ketamine, whereas patients who had received midazolam-ketamine had significantly higher number of hypertensive peaks. In this study, the increase in mean systolic and diastolic BP in group I patients at 2 minutes may be due to the cardiac stimulant effect of ketamine and mild stress response to intubation, while during induction, maintenance and recovery, BP remained near preinduction values mainly due to the antagonistic properties of propofol (decrease in BP) and ketamine (increase in BP). In group II patients, both the mean systolic and diastolic BP decreased during induction because of the additive action of propofol and fentanyl. Whereas at 2 minutes (just after laryngoscopy and intubation), stress response was prevented mainly by the action of fentanyl. During recovery period, the increase in both systolic and diastolic BP (1 minute after extubation) in both the groups was mainly due to the awakening response to extubation.

The extent and degree of various induction characteristics like loss of consciousness (onset of sleep), loss of eyelash reflex and apnoea during induction showed quite a few similarities as well as differences from other studies and this may be probably due to the variations in the dosages as well as combinations of anesthetic drugs used.

The incidence of side effects like excitatory movements (hiccups, hypertonus, twitching or tremors) was higher with propofol alone during induction than when used in combination with fentanyl. The differences from this study can be explained on the basis that they used

propofol alone and that too in higher doses. Pain at injection site, cough and involuntary movements during induction of anesthesia, were present to a lesser degree in this study, and the differences can be ascribed to diminishing of the excitatory effects of propofol at low doses and suppression of excitatory effects by fentanyl and ketamine. Similarly, absence of cough was due to lower dose (2 µg/kg) of fentanyl which was analgesic dose and not the induction dose

Recovery

A striking feature of the use of these drug combinations in TIVA has been the early recovery. In our study, two methods of recovery from anesthesia have been used.

The first method is the Steward Scoring System which evaluates the recovery from anesthesia by physical evaluation HERNANDEZ C, et al[7] (ventilation, movement, wakefulness). There was slight respiratory depression postoperatively in patients who received propofol-fentanyl as compared to patients who received propofol-ketamine. The slightly lower ventilation score with propofol-fentanyl combination was due to central respiratory depressant effect of fentanyl. Movement score was better in group II as shown by the earlier recovery of voluntary movements in patients as compared to group I patients and were most probably due to longer sedative action of ketamine which leads to late return of voluntary movements. Better wakefulness score in group II may be due to shorter duration of action of fentanyl as compared to ketamine which has increased sedating effect.

The second method of evaluation of recovery which was used in this study was by observing the return of protective airway reflexes like coughing and gagging and response to verbal commands like spontaneous opening of eyes, protrusion of tongue and lifting of head. GODAMBE et al [8]Spontaneous recovery was achieved much earlier in the propofol-fentanyl group as compared to the propofol-ketamine group. Except for slight respiratory depression which was caused by fentanyl, better recovery score in group II was most probably due to lesser sedative effects of fentanyl as compared to ketamine.

Side effects during recovery

SUKHMINDER et al[3]The increased incidence of oral secretions in four patients of group I as compared to none in group II postoperatively may be due to the salivatory effect of ketamine. Slightly higher incidence of nausea in group II may be due to the central emetic effects of fentanyl. But lower incidence of nausea and no incidence of vomiting are attributed to the antiemetic effect of propofol. This is more important at low doses and we have used propofol in low doses in this study. Propofol has been used successfully to treat postoperative nausea in a bolus dose of 10 mg and has been successfully used to treat refractory PONV.

Two patients (4%) from GUIT JB et al[9] group I had excitation postoperatively while no patient from group II had this side effect, and this can be explained on the basis of lower dosage of ketamine used (1 mg/kg) in this study. There were no other complication like awareness, mood changes, agitation, and all the patients were satisfied with the anesthetic technique used and described it as pleasant.

POST OPERATIVE ANALGESIA

MAYER M et al [10] also found fewer patients in ketamine group required rescue doses of analegesics post operatively than in fentanyl group.

Similarly, BADRINATH et al[6] also concluded that use of ketamine during propofol sedation provided analgesia and minimized need for supplemental opioids.

SUMMARY

In conclusion, the results of this study suggest that both propofol-ketamine and propofol-fentanyl combinations produce rapid, pleasant, and safe anesthesia with only a few untoward side effects and only minor hemodynamic fluctuations.

Although propofol-fentanyl combination produced hypotension during induction of anesthesia, it prevented stress-response during laryngoscopy and intubation.

Propofol-ketamine combination produced stable hemodynamics during maintenance phase, while on the other hand propofol-fentanyl was associated with slight increase in both PR and BP during maintenance phase. There was a slight respiratory depression during recovery in patients who received propofol-fentanyl as was evident from the ventilation score. But on the other hand other recovery characteristics like awakening time and response to verbal commands were better in the propofol-fentanyl group.

However, as far as recovery is concerned, one of the most important areas in evaluating day care surgical procedures, both propofol-ketamine and propofol-fentanyl are associated with smooth and swift recovery with minimal residual impairment of mental functioning which are due to their significant metabolism, short elimination half-life and extremely high total body clearance.

So, it may be recommended that both propofol-ketamine and propofol-fentanyl can be used as an excellent combination in TIVA for both elective and day care surgery where minimal side effects and early recovery are desired.

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