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Comparison of Two Drug Combinations in Total Intravenous Anaesthesia: Propofol-Ketamine and Propofol-Fentanyl

Jeet R Arya[1], Bhavna H Sojitra[2], Malti J. Pandya[3]

Authors' Affiliations: [1,2,3]Surat Municipal Institute of Medical Education & Research, Surat, India
Corresponding Author: Dr. Jeet R Arya, **Email:** jeetrahularya@gmail.com

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ABSTRACT

Introduction: TIVA has many advantages over inhalational anaesthesia such as minimal cardiac depression, decreased oxygen consumption, avoids postoperative diffusion hypoxemia, decreases the incidence of postoperative nausea and vomiting etc. This study was conducted to evaluate and compare two TIVA drug combinations using propofol- ketamine and propofol-fentanyl, and to examine the characteristics of induction of anaesthesia, maintenance, and recovery.

Method: 34 patients of ASA grading 1,2 and 3 aged between 20 to 65 years of either sex undergoing short surgical procedures were included in the study. According to Comparison of systolic blood pressure of both the groups at intubation time of anaesthesia in group I and group II. Patients in group I received propofol and ketamine intravenously (IV) to induce anaesthesia. For group II, fentanyl and propofol were administered as IV bolus doses. All the results were tabulated and analyzed statistically.

Result: Propofol-fentanyl combination produced a significantly greater fall in pulse rate and in both systolic and diastolic blood pressures as compared to propofol-ketamine during induction of anaesthesia. Propofol-ketamine combination produced stable hemodynamic 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.

Conclusions: Both propofol-ketamine and propofol-fentanyl combinations produce rapid, pleasant and safe anaesthesia with only a few untoward side effects and only minor hemodynamic effects.

Keywords: Total Intravenous Anaesthesia, propofol, ketamine, fentanyl.

INTRODUCTION

Total intravenous anesthesia (TIVA) is a method of general anesthesia that uses a mix of medications administered solely intravenously (IV) rather than orally (including nitrous oxide); oxygen, compressed air, or helium are the exceptions.

Since its inception into clinical practise, TIVA has undergone a great number of advancements. Even this recently modified form has undergone significant advancements.

Up until recently, inhalational medications were the standard option for keeping anaesthesia. The capacity of anaesthetists to precisely control the concentration of volatile anaesthetics supplied to the patient is made possible, among other things, by the development of sophisticated delivery systems for volatile anaesthetics.

Despite all of these benefits, inhalational agents have the following drawbacks and shortcomings like cost factor, different specific vaporizers require repeated maintenance and scavenging system is necessary; otherwise, pollution of operation room environment is a big hazard.

TIVA has many advantages over inhalational anaesthesia like no operating room pollutions, minimal cardiac depression, lesser neurohumoral response, decreased oxygen consumption, avoids distension of air-filled spaces within the patient's body, thus producing optimum operating conditions for the surgeon, avoids postoperative diffusion hypoxemia, decreases the incidence of postoperative nausea and vomiting (PONV) and In day care surgery, etc.[1]

Moreover, TIVA can be employed in rural locations with only oxygen and ventilation facilities in addition to well-equipped hospital settings.

In TIVA, many medicines have occasionally been explored. A number of medicines are employed in various combinations to induce balanced anaesthesia in TIVA, that is, amnesia, hypnosis, and analgesia, because no one medication can fulfil all the qualities of an ideal intravenous agent.[1]

Kay and Rolly introduced propofol in 1977 while searching for the ideal intravenous anaesthetic in clinical practise. Its benefit in short surgical procedures stems from its rapid elimination from the blood (half-life 1-3 h due to strong hepatic clearance), which results in a rapid recovery of cognitive and psychomotor functioning with a very low incidence of PONV. It is predominantly hypnotic and induces sedation and amnesia in sub hypnotic doses. Propofol's lack of analgesic qualities has made it necessary to use additional analgesic drugs during TIVA. Newer drugs like fentanyl, sufentanyl, alfentanyl, and remifentanyl, which can be

administered in numerous bolus incremental doses or as a continuous infusion, have replaced older drugs like morphine and pethidine. Ketamine has gained extensive attention as a TIVA analgesic when used in subanaesthetic doses.[1]

Fentanyl is used extensively in TIVA now-a-days. It is a member of the opioid drug class. It is a hundred times stronger analgesic than morphine at reducing pain, somatic and autonomic response to airway manipulation, hemodynamic stability, and respiratory depression.[1]

This study was conducted to evaluate and compare two TIVA drug combinations using propofol-ketamine and propofol-fentanyl, as well as to examine the characteristics of induction of anaesthesia, maintenance, and recovery using these methods.

Keeping in consideration the merits of TIVA, a case control study was conducted on 34 patients in Department of Anaesthesiology SMIMER Medical college, Surat.

AIMS AND OBJECTIVES

The main aim of study was to compare two combinations of drugs: 1) Propofol and ketamine and 2) Propofol and fentanyl in TIVA for short surgical procedures.

MATERIALS AND METHODS:

This observational study was conducted among indoor patients admitted to our tertiary care hospital.

Patients between the age group of 20 years to 65 years, ASA group I, II and III of either sex undergoing short surgical procedures were included in the study. Pregnant females and in whom the duration of surgery was more than 80 minutes were excluded from the study.

Sample Size: Sample size (n=34 cases) was calculated by using OpenEPI software according to Comparison of systolic blood pressure of both the groups at intubation time of anaesthesia in group I and group II from previous study of Bajwa SJ. [1] According to this study mean systolic blood pressure in patients receiving propofol and ketamine was 136.08 ± 9.67 mmHg and mean systolic blood pressure in patients receiving propofol and fentanyl was 122.16 ± 9.31 mmHg. Taking confidence interval 99% and power 95%, the calculated sample size:34 (Group 1=17 and Group 2=17)

Pre-operative assessment: Preoperative evaluation of patient was done before the surgery by taking history, general and systemic examination, vitals and necessary investigations and fitness for anaesthesia was decided according to ASA standard. Written informed consent was taken. NBM status of patient was noted. After securing intravenous line, monitoring gadgets were attached which included ECG, SpO2 and non-invasive BP cuff. Injection midazolam (0.08 mg/kg with maximum dose of 5 mg) was given IV 2 minutes before the induction of anaesthesia in both the groups.

Intra Operative procedure:

Induction of anaesthesia: Patients in group I received 1.0 mg/kg of propofol and 1.0 mg/kg of ketamine intravenously to induce anaesthesia. For group II, fentanyl 2.0 μg/kg body weight and propofol 1.5 mg/kg body weight were administered as IV bolus doses to induce anaesthesia. In both the groups, injection succinylcholine was given as a muscle relaxant before intubation in doses of 1.5 mg/kg body weight 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 anaesthesia: In group I, maintenance of anaesthesia 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 weight 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 anaesthetic 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.

Statistical Analysis: All data collected was analyzed and expressed as Mean ± standard deviation or percentage as applicable. Comparison between two groups done using students paired t test for quantitative data. P value < 0.05 is considered significant. Data were collected, tabulated, coded then analyzed using SPSS @ Computer version 29.0. Numerical variables were presented as Mean ± standard deviation, while categorical variables were presented as percentage.

RESULTS

One patient (6%) from group I and two patients (12%) from group II had involuntary movements during the induction of anaesthesia.

Pulse rate: There was an increase in PR in group I, while there was a slight decrease in PR in group II patients after induction of anaesthesia which returned gradually toward baseline during the maintenance phase of anaesthesia in both the groups, but the difference in both the groups was statistically significant ($P < 0.05$). PR increased in both the groups after ex-tubation.

Table:1 Comparison of mean pulse rate of both the groups at different stages of anesthesia in group I and group II

Anaesthesia stage	Time interval	Group	Mean +SD	t value	p value	significance
Preinduction		I	80.05±2.27	-	>0.05	Non-significant
		II	79.82±2.15			
Induction	1 min	I	81.00±3.87	2.84	<0.05	Significant
		II	77.70±4.99			
Intubation	2 min	I	89.11±4.44	7.44	<0.05	Significant
			76.47±3.77			
	5 min	I	90.00±6.10	7.85	<0.05	Significant
		II	74.17±5.07			
Intraoperative	10 min	I	86.41±3.64	3.83	<0.05	Significant
		II	83.29±2.61			
	30 min	I	82.29±4.14	3.94	<0.05	Significant
		II	88.82±4.48			
	60 min	I	83.00±3.20	2.25	<0.05	Significant
		II	86.00±3.80			
Postoperative	1 min	I	83.94±3.86	1.79	<0.05	Significant
		II	86.82±4.14			
	10 min	I	84.32±2.82	1.93	>0.05	Non-significant
		II	84.52±2.55			

Table 2: Comparison of systolic blood pressure of both the groups at different stages of anesthesia in group I and group II

Anaesthesia stage	Time interval	Group	Mean +SD	t value	p value	significance
Preinduction		I	122.70±3.78	1.28	>0.05	Non-significant
		II	122.23±3.25			
Induction	1 min	I	126.58±7.70	3.22	<0.05	Significant
		II	116.94±8.17			
Intubation	2 min	I	136.52±5.98	7	<0.05	Significant
		II	124.82±5.83			
	5 min	I	129.47±6.50	4.64	<0.05	Significant
		II	119.23±5.97			
Intraoperative	10 min	I	130.00±5.90	2.09	<0.05	Significant
		II	126.11±5.32			
	30 min	I	124.17±5.05	3.92	<0.05	Significant
		II	131.05±5.60			
	60 min	I	124.17±5.05	3.92	<0.05	Significant
		II	131.05±5.60			
Postoperative	1 min	I	133.47±5.25	2.56	<0.05	Significant
		II	137.11±5.93			
	10 min	I	128.17±3.71	0.33	>0.05	Non-significant
		II	128.41±3.50			

Table 3: Comparison of diastolic blood pressure of both the groups at different stages of anesthesia in group I and group II

Anaesthesia stage	Time interval	Group	Mean +SD	t value	p value	significance
Preinduction		I	80.17±4.79	-	>0.05	Non-significant
		II	80.89±3.01			
Induction	1 min	I	80.58±5.81	4.2	<0.05	Significant
		II	72.52±5.59			
Intubation	2 min	I	83.64±5.66	11.05	<0.05	Significant
		II	74.11±5.10			
	5 min	I	81.94±4.84	2.9	<0.05	Significant
		II	75.70±6.13			
Intraoperative	10 min	I	82.41±5.43	2.15	<0.05	Significant
		II	78.64±5.71			
	30 min	I	80.00±4.79	5.32	<0.05	Significant
		II	86.94±5.69			
	60 min	I	81.29±5.07	5.425	<0.05	Significant
		II	87.76±4.86			
Postoperative	1 min	I	80.11±5.85	2.36	<0.05	Significant
		II	84.82±7.34			
	10 min	I	79.05±5.67	0.08	>0.05	Non-significant
		II	79.11±5.76			

Table 4: Recovery (ventilation score) of both the groups

Time Interval	Group	Mean ± SD	t value	p value	Significance
1 m	I	0.11±0.33	1.46	>0.05	Non-significant
	II	0			
5 m	I	1.00±0.70	2.31	<0.05	Significant
	II	0.47±0.51			
10 m	I	1.47±0.62	2.13	<0.05	Significant
	II	1.05±0.55			
20 m	I	1.76±0.43	0	>0.05	Non-significant
	II	1.76±0.43			

Table 5: Recovery (movement score) of both the groups

Time Interval	Group	Mean ± SD	t value	p value	Significance
1 m	I	00.0±0	1.46	>0.05	Non-significant
	II	0.11±0.33			
5 m	I	0.31±0.47	2.61	<0.05	Significant
	II	0.62±0.50			
10 m	I	1.11±0.48	3.04	<0.05	Significant
	II	1.64±0.49			
20 m	I	2.00±0	1.76	>0.05	Non-significant
	II	2.00±0			

Table 6: Recovery (wakefulness score) of both the groups

Time Interval	Group	Mean ± SD	t value	p value	Significance
1 m	I	00.0±0	0	>0.05	Non-significant
	II	00.0±0			
5 m	I	0.23±0.43	2.7	<0.05	Significant
	II	0.70±0.46			
10 m	I	1.23±0.43	2.38	<0.05	Significant
	II	1.64±0.49			
20 m	I	1.82±0.39	1.76	>0.05	Non-significant
	II	1.82±0.39			

Blood pressure: There was a fall in BP (systolic and diastolic) during the induction of anaesthesia in group II, while there was a slight increase in BP in group I after induction and intubation which was statistically significant ($P < 0.05$). During maintenance there was gradual recovery toward baseline. During recovery period in both the groups, the BP increased again (1 minute after extubation), which was statistically significant ($P < 0.05$) but returned toward baseline in the next 20 minutes.

SPO $_2$: It was found in both the groups that there was very little change in mean SpO_2 values during induction and maintenance of anaesthesia as well as during recovery phase.

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. No patient from group I and one patient (6%) from group II had nausea during the recovery phase while none of them had any episode of vomiting. Secretions: In group I, two patients (12%) had oral secretions during recovery from anaesthesia. Post-ketamine sequelae: Two patients (12%) 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.

Table 7: Postoperative side effects in both the study-groups

Side effects	Group I (%)	Group II (%)
Nausea	-	1 (6%)
Vomiting	-	-
Secretions	2 (12%)	-
Laryngospasm/bronchospasm	-	-
Venous sequelae	-	-
Post ketamine sequelae	-	-
Excitation	2 (12%)	-
Hallucinations	-	-
Euphoria	-	-
Any other	-	-

DISCUSSION

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,2]* and Mi *et al.*[3] Studies of Mi *et al*, also showed that after induction, the Pulse Rate 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 anaesthesia.[3,4]

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 based on hhhcardio stimulant effect of ketamine and stress response during intubation.

The combination of propofol with fentanyl leads to decrease in heart rate due to the prevention of stress response by fentanyl and its myocardial depressing effect.

Mi *et al*, 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*, [5] 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 pre induction 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. [6] 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 ex-tubation.

The extent and degree of various *induction characteristics* like loss of consciousness (onset of sleep), [7] loss of eyelash reflex [8] and apnoea during induction [7],[9] 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 anaesthetic 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. [10] 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 anaesthesia, [11],[12] 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 anaesthesia have been used.

The first method is the Steward Scoring System [13] which evaluates the recovery from anaesthesia by physical evaluation (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. [2],[14] 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. [2] 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.[5]

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. 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. [14],[15],[16],[17],[18]

Side effects during recovery: 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.[19] But, as a whole, lower incidence of nausea and no incidence of vomiting are attributed to the antiemetic effect of propofol. This is all the 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 (12%) from 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. [5] There were no other complications like awareness, mood changes, agitation, and all the patients were satisfied with the anaesthetic technique used and described it as pleasant.

CONCLUSIONS:

In conclusion, the results of this study suggest that both propofol-ketamine and propofol-fentanyl combinations produce rapid, pleasant, and safe anaesthesia with only a few untoward side effects and only minor hemodynamic fluctuations. Although propofol-fentanyl combination produced hypotension during induction of anaesthesia, it prevented stress-response during laryngoscopy and intubation. Propofol-ketamine combination produced stable hemodynamic 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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