Drugs combination in total intravenous anesthesia Propofol-ketamine Vs. propofol-fentanyl

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Abstract:

Background: Keeping in consideration the benefits of total intravenous anesthesia (TIVA), a genuine attempt was made to find the ideal drug combination which can be used in general anesthesia.

Objectives: 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.

Patients and Methods: A case comparison study (Clinical Trial) was conducted, which included 100 patients, which randomly allocated in two equal groups.

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 hour duration. Group K received propofol-ketamine while group F 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 (PR; 9.28% versus 0.23%) and in both systolic (7.94% versus 0.12%) and diastolic blood pressures (BP; 8.10% versus 0.35%) as compared to propofol-ketamine during induction of anesthesia. 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 K while movement and wakefulness score was better in group F. Mean time to protrusion of tongue and lifting of head was shorter in group K.

Conclusion: 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

General anesthesia should provide quick and pleasant induction, predictable loss of consciousness, stable operating conditions, minimal adverse effects, rapid and smooth recovery of protective reflexes and psychomotor functions.

This study was conducted to evaluate and compare two drug combinations of TIVA using propofol-ketamine and propofol-fentanyl and to study the induction characteristics, maintenance of anesthesia and recovery characteristics following anesthesia with these techniques.

Till recently, inhalational agents have remained the routine choice for maintenance of anesthesia. One of the principle reasons is the availability of sophisticated delivery systems for volatile anesthetics, which allows the anesthetists to have a fine degree of control on the concentration administered to the patient. Moreover, monitoring systems that permit nearly accurate measurement of end-tidal concentration of the volatile anesthetics as well as the introduction of new potent volatile agents provide a wider choice of drugs.

In spite of all these advantages, inhalational agents have their own drawbacks and shortcomings that are as follows:

- cost factor
- different specific vaporizers require repeated maintenance
- pollution of operation room environment
- measurement of end-tidal gas concentration not always available

TIVA has many advantages over inhalational anesthesia [1] such as

- no operating room pollutions
- minimal cardiac depression
- lesser neuro-humoral response
- decreased oxygen consumption by the brain
- 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)

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.

Propofol 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. Fentanyl and ketamine in sub-anesthetic doses has gained more attention as an analgesic for TIVA. [2]

The combination of these drugs provides complete and balanced anesthesia and has advantages such as high potency, lower dosages and fewer side effects [3].

Objective:

The objective is to find the efficacy and safety of fentanyl-propofol and ketamine-propofol combinations in total intravenous anesthetics.

Patients and methods:

One hundred adult patients of age between 20 and 60 years and of ASA grade I or II of either sex who underwent elective surgery at were included in the study. Patients were divided randomly into two

groups of 50 patients each depending upon the drug combination used.

The following patients were excluded from study: history of allergy to any particular drug, allergy to egg or fat, pregnant females, patients on Monoamine oxidase inhibitors, history of jaundice, extremes of age, and duration of surgery lasting for more than 80 minutes.

Study medications were prepared in advance, and submitted to the blind anesthetist in the operating room.

A: Anesthetic technique

Standard anesthetic technique was used in all the patients. After securing intravenous line, monitoring gadgets were attached this included ECG, SPO_2 and noninvasive BP cuff. Baseline parameters were observed and recorded. Injection tramadol (2 mg/kg with maximum dose of 100 mg) was given intravenously 2 minutes before the induction of anesthesia in both the groups.

The ketamine solution and fentanyl solution were prepared in the preparation room away from both the anesthesiologist and the patients by a well trained anesthetist nurse staff, to keep out the results from any intentionally or non-intentionally bias. The solutions were labeled as solution No.1 and solution No.2. The solution number1 was containing ketamine 500mg in 500 ml 0.9% normal saline, and solution number 2 containing 500µg fentanyl in 500 ml 0.9% normal saline.

B: Induction and maintenance of anesthesia

The infusion of the test drugs started in both groups after the injection of (0.1 mg/kg body wt. as a loading dose) pancronium bromide as a muscle relaxant before the administration of the induction agents. Induction of anesthesia in patients of group K was done with propofol 1.0 mg/kg body wt. and ketamine 1.0 mg/kg body wt. (the ketamine syringe was blinded and labeled as solution No.1) given as IV bolus dose. In group F, induction of anesthesia was done with propofol 1.0 mg/kg body wt. and fentanyl 2.0 µg/kg body wt. (fentanyl syringe was blinded and labeled as solution No.2) given as IV bolus doses.

Patients were ventilated with 100% oxygen via a facemask for 60-90 seconds with the help of Bain's 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. In group I, maintenance of anesthesia was achieved with infusion of propofol 2.0 mg/kg/h (500mg propofol in 500 ml 0.9% normal saline) and solution No.1, while in group II, maintenance of anesthesia was achieved with infusion of propofol 2.0 mg/kg/h and solution No.2. Pancronium bromide supplemented with top-ups of 1mg in both the groups each 20-25 min.

Hemodynamic and other monitoring parameters were observed continuously and noted at an interval of 5minutes during the operation. Patients were ventilated with 100% oxygen with the application of IPPV set.

C: 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 atropine 20 µg/kg body wt. which was given over 2-3 minutes period. 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.

Results:

All the results were tabulated and analyzed statistically with Student's t-test and Chi-square test for the non-parametric data. $P < 0.05$ was considered statistically significant.

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

A: Pulse rate:

There was an increase in PR in group K, while there was a slight decrease in PR in group F patients after induction of anesthesia which returned gradually toward baseline during the maintenance phase of anesthesia in both groups. The difference between both groups was statistically significant ($P < 0.05$). PR increased in both groups at 1 and 5 minutes after extubation [Table 1].

B: Blood pressure:

There was a fall in BP (systolic and diastolic) during the induction of anesthesia in group F, while there was a slight increase in BP in group K after induction and intubation which was statistically significant ($P< 0.05$). During maintenance there was gradual recovery toward baseline in group K. During recovery period in both groups, the BP increased again (1minute after extubation), which was statistically significant ($P< 0.05$) but returned toward baseline in the next 20 minutes [Table 2] and [Table 3].

Table 1: comparison of pulse rate in both groups at different stages of anesthesia

Anesthesia stage	Time / min.	Mean PR±SD in group K	Mean PR±SD in group F	P
Pre-induction	0	84.08±5.18	84.18±5.28	> 0.05
Induction	1	84.28±5.28	76.36±4.52	< 0.05
Intubation	2	90.64±5.30	78.36±4.40	< 0.05
Intra-operative	3	90.84±5.14	77.32±4.36	< 0.05
	4	90.72±5.20	77.20±4.29	< 0.05
	5	90.76±5.31	76.96±4.33	< 0.05
	10	86.32±5.11	85.20±4.31	< 0.05
	20	84.52±5.32	88.00±4.79	< 0.05
	30	84.32±5.06	87.68±4.64	< 0.05
	40	84.92±5.19	87.32±4.52	< 0.05
	50	84.56±5.09	87.07±4.48	< 0.05
	60	84.28±5.04	87.36±4.12	< 0.05
Postoperative	1	86.56±4.96	89.24±3.97	< 0.05
	5	84.36±5.12	85.32±4.95	< 0.05
	10	84.28±5.29	84.80±4.00	> 0.05
	15	84.40±5.39	84.04±4.85	> 0.05
	20	84.56±5.43	84.12±5.11	> 0.05

C: SPO_2:

It was found in both groups there was a very little change in mean SPO_2 values during induction and maintenance of anesthesia as well as during recovery phase.

D: Recovery:

Ventilation score was better in group K during the first 10 minutes of recovery phase as compared to group F [Table 4]. Mean movement score was better in group F than group K at 5 and 10 minutes [Table 5]. Wakefulness score was better in group F at 5 and 10 minutes as compared to group K [Table 6].

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 F. One patient (2%) from group K and three patients (6%) from group F had nausea during the recovery phase while none of them had any episode of vomiting.

E: Secretions:

In group F, four patients had oral secretions during recovery from anesthesia.

F: Post-ketamine sequelae:

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

Table 2: A comparison between systolic blood pressure records in both groups at different stages of anesthesia

Anesthesia stage	Time / min.	Mean Systolic BP±SD in group K	Mean Systolic BP±SD in group F	P
Prei-nduction	0	125.96±955	126.40±9.67	> 0.05
Induction	1	125.80±9.16	116.36±9.50	< 0.05
Intubation	2	136.08±9.67	122.16±9.31	< 0.05
Intra-operative	3	135.68±9.64	121.28±9.37	< 0.05
	4	132.04±9.68	121.28±9.37	< 0.05
	5	130.28±9.47	120.20±9.27	< 0.05
	10	129.76±9.47	126.20±9.20	< 0.05
	20	128.66±9.48	130.28±9.14	< 0.05
	30	128.24±9.73	132.04±8.59	< 0.05
	40	128.04±9.82	130.24±8.47	< 0.05
	50	127.92±0.36	132.08±8.53	< 0.05
	60	127.88±9.27	134.10±8.52	< 0.05
Postoperative	1	132.24±9.65	136.12±8.52	< 0.05
	5	128.36±9.79	128.32±9.25	> 0.05
	10	128.24±9.74	126.28±9.18	> 0.05
	15	128.04±9.60	125.20±9.23	> 0.05
	20	127.80±9.60	125.64±6.28	> 0.05

Table 3: A comparison between diastolic blood pressure records in both groups at different stages of anesthesia

Anesthesia stage	Time / min.	Mean Diastolic BP±SD in group K	Mean Diastolic BP ±SD in group F	P
Pre-induction	0	80.54±3.56	80.09±3.55	> 0.05
Induction	1	80.32±3.55	73.60±3.61	< 0.05
Intubation	2	86.24±3.76	75.72±3.54	< 0.05
Intra-operative	3	86.68±3.86	75.48±3.44	< 0.05
	4	86.44±3.73	75.32±3.53	< 0.05
	5	86.92±3.55	75.20±3.47	< 0.05
	10	81.84±3.63	81.12±3.57	< 0.05
	20	81.32±3.99	83.48±3.51	< 0.05
	30	81.28±3.95	84.44±3.52	< 0.05
	40	81.44±4.04	83.96±3.39	< 0.05
	50	81.36±4.32	84.84±3.38	< 0.05
	60	81.52±3.90	85.24±3.35	< 0.05
Postoperative	1	82.04±4.03	86.36±4.17	< 0.05
	5	79.12±3.85	80.84±3.57	> 0.05
	10	78.72±4.11	80.40±3.42	> 0.05
	15	78.60±4.33	79.80±3.00	> 0.05
	20	78.56±4.21	79.76±3.53	> 0.05

Table 4: Recovery (ventilation score) of both groups

Time interval	Ventilation score (mean±SD) in group K	Ventilation score (mean±SD) in group F	Difference	P
1 min.	0.06±0.23	0.0	0.06	> 0.05
5 min.	0.84±0.37	0.58±0.49	0.26	< 0.05
10 min.	1.90±0.30	1.50±0.58	0.40	< 0.05
15 min.	1.94±0.23	1.86±0.55	0.08	> 0.05
20 min.	2.0±0	1.94±0.25	0.06	> 0.05

Table 5: Recovery (movement score) in both groups

Time interval	Movement score (mean±SD) in group K	Movement score (mean±SD) in group F	Difference	P
1 min.	0.0	0.0	0.06	> 0.05
5 min.	0.48±0.50	0.78±0.41	0.30	< 0.05
10 min.	1.20±0.49	1.50±0.50	0.30	< 0.05
15 min.	1.90±0.30	1.96±0.19	0.06	> 0.05
20 min.	2.0±0	2.0±0	0.0	> 0.05

Table 6: Recovery (wakefulness score) in both groups

Time interval	Wakefulness score (mean±SD) in group K	Wakefulness score (mean±SD) in group F	Difference	P
1 min.	0.0	0.0	0	> 0.05
5 min.	0.44±0.50	0.64±0.48	2.02	< 0.05
10 min.	0.80±0.49	1.04±0.28	2.97	< 0.05
15 min.	1.68±0.47	1.70±0.46	0.21	> 0.05
20 min.	1.94±0.23	2.0±0	1.76	> 0.05

Discussion:

The same dosages of propofol and fentanyl have greater impact on elderly as compared to young patients.[4] In older patients, the total dose of propofol administered decreases while other demographic features did not have any effect. [5]

The demographic profile of this study was almost similar to 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 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,[6] and Mi et al. [7] 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. [4, 7]

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

Mi et al [7], 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, [8] carried out a study with propofol-ketamine, midazolam-ketamine and propofol-fentanyl combinations and observed stable hemodynamic 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 K 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 F patients, both the mean systolic and diastolic BP decreased during induction because of the additive action of propofol and fentanyl. [9] 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 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), [10] loss of eyelash reflex [11] and apnea during induction [10],[12] 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.[13] The differences from this study can be explained on the basis that they used propofol alone and those in higher doses too developed pain at injection site, cough and involuntary movements during induction of anesthesia.[5,14] Similarly, absence of cough was due to lower dose (2 μg/kg) of fentanyl which was analgesic dose and not an induction dose.

Recovery:

The striking feature of the use of drug combinations in TIVA was the early recovery. In our study, two methods of assessment of recovery from anesthesia have been used.

The first method was Steward Scoring System [15] which evaluates the recovery from anesthesia 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. [6, 16] Movement score was better in group F as shown by the earlier recovery of voluntary movements in patients as compared to group K patients and were most probably due to longer sedative action of ketamine which leads to delay return of voluntary movements.[6]

Better wakefulness score in group F may be due to shorter duration of action of fentanyl as compared to ketamine which has increased sedating effect. [8]

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 F was most probably due to lesser sedative effects of fentanyl as compared to ketamine. [16,17 ,18, 19, 20]

Steward recovery score criteria	Score
Consciousness	
1. Awake	2
2. Responding to stimuli (arousable)	1
3. Not responding	0
Airway	
1. Coughing on command or crying	2
2. Maintaining good airway	1
3. Airway require maintenance	0
Movement	
1. Moving limbs purposefully	2
2. Non-proposefull movements	1
3. Not moving	0

Side effects during recovery:

The increased incidence of oral secretions in four patients of group K as compared to none in group F postoperatively may be due to the salivatory effect of ketamine. Slightly higher incidence of nausea in group F may be due to the central emetic effects of fentanyl. [21] 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 [22, 23, 24].

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 group K had excitation postoperatively while no patient from group F had this side effect, and this can be explained on the basis of lower dosage of ketamine used (1 mg/kg) in this study.[8, 25]

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.

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.

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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