Comparison of ketamine and fentanyl with propofol in total intravenous anesthesia: a double blind randomized clinical trial

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Citation

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Abstract

Background: Propofol has emerged as a gold-standard for total inrtravenous anesthesia (TIVA) for short surgical interventions but lack of analgesia remains it's main shortcoming therefore it is always combined with an analgesic. Ketamine and fentanyl are the popular analgesic in this context. This study was carried out to compare these drugs with propofol to assess hemodynamic and recovery profile of either combination.Methods: Hundred consenting patients undergoing short elective surgeries were randomly allocated into two groups of fifty each: group PF received propofol 2 mg/kg + fentanyl 2 g/kg for induction and propofol 4 mg/kg/hr + fentanyl 1g/kg/hr for maintenance of anesthesia and group PK received propofol 2mg/kg + ketamine 1mg/kg for induction and propofol 4mg/kg/hr + ketamine 1 mg/kg/hr for maintenance of anesthesia. Hemodynamic variables were recorded pre, intra and postoperatively at regular intervals. At the end of drug infusion(s), time to spontaneous eye opening and response to postoperative questionnaire was noted to assess recovery. All the data presented as mean + standard deviation and number of patients. Results: Patients in both did not differ significantly in demographic and hemodynamic profile. Time to spontaneous eye opening was similarly comparable in both the groups (8±3 min and 8±2 min) (p=0.53). Response to postoperative questionnaire at 30 minutes after anesthesia was good in both the groups. Incidence of postoperative nausea and vomiting was also insignificant statistically between both the groups. (p=0.74)Conclusion: We concluded that both ketamine and fentanyl are equally safe and efficacious with propofol for short surgical procedures.

INTRODUCTION

The concept of intravenous anaesthesia (IV) has progressed over a period of time from induction of general anesthesia to modern day Total Intravenous Anaesthesia (TIVA) largely due to the better understanding of drug kinetics and dynamics along with the development of Intravenous (IV) drug delivery systems that are able to titrate and deliver accurately the infusion dose of a given Intravenous agent. Outpatient ambulatory surgery is the fastest growing segment of surgery and anaesthesia. Seventy percent of all anaesthesia given in the United States is done on an ambulatory basis. (1,2) The goals of outpatient ambulatory anaesthesia include a rapid and smooth induction, effective intraoperative anaesthesia and a smooth and prompt recovery with minimal, if any, postoperative side effects so that an early discharge is possible.(3) Of all the intravenous anaesthetic agents that are available, Propofol's pharmacokinetic profiles favor administration by continuous intravenous infusion. (4, 5) As Propofol has very little nociceptive effect, it is generally combined with an analgesic, the popular combination being either Propofol with Fentanyl or Propofol with Ketamine. Pain relief to patient is an important constituent of balanced anaesthesia. Ketamine is a potent analgesic, its anaesthetic and analgesic effects have been suggested to be mediated by different mechanisms. It has very high margin of safety, no irritation of the veins and no negative influence on ventilation or circulation. Its main disadvantages are that it produces hypertension and precipitates psychomimetic emergence phenomena. (6) Fentanyl on other hand is the most frequently used opioid in clinical anaesthesia today. Its disadvantage is its negative influence on ventilation and postoperative nausea and vomiting. (5) One of the main drawbacks with Ketamine anaesthesia has been emergence delirium, which Propofol seems to be effective in eliminating.(6) In this study, the combination of Propofol-Ketamine was compared to the combination Propofol-Fentanyl in patients undergoing general anaesthesia for short elective surgeries. Haemodynamic variables, the time to recovery and patient acceptability were compared.

METHODS

This prospective randomized study was conducted between May 2006 & June 2008 on 100 patients scheduled for short surgeries including suction and evacuation, dilatation and curettage, debridement, close reduction in orthopedics, skin grafting, incision and drainage of abscess and cyst removal etc. Sample size was determined using power analysis and a pilot study with 85% power to detect a difference. The approval of institutional ethical committee on research and informed consent from patients was obtained. Patients between the age group of 15-65 years, ASA physical status I and II and with no significant systemic medical disease were included in the study while patients less than 15 years and more than 65 years, patient refusal, with ASA physical status III or more, known hypersensitivity to drugs used, difficult intubation and pregnant and/or lactating mothers were excluded. The patients were randomly allocated (computer generated by statistician) into two groups as follows:-

Group PF (n = 50) received propofol 2mg/kg + fentanyl 2μg/kg for induction and propofol 4mg/kg/hr + fentanyl 1μg/kg/hr for maintenance of anesthesia.

Group PK (n = 50) received propofol 2mg/kg + ketamine 1mg/kg for induction and propofol 4 mg/kg/hr + ketamine 1 mg/kg/hr for maintenance of anesthesia.

All patients were premedicated with injection glycopyrrolate 4μg/kg intramuscularly (IM) 30 minutes before shifting to Operation Theatre. On arrival in the operation theatre baseline measurement of pulse rate, blood pressure, respiratory rate and SpO_2 were recorded. An intravenous cannula was placed for administration of fluids and medicines. All patients were given injection Midazolam (0.03 mg/kg) IV before induction of anesthesia. Patients were preoxygenated for 3 minutes with 100% oxygen and the induced as aforementioned.

The study was kept double blind by one anesthetist preparing the drug and other conducting the anesthesia while monitoring was done by resident anesthetist unaware of the procedure. Blood pressure and heart rate were monitored at basal level, after induction and in perioperative period after starting infusion every 5 minutes till 30 minutes and then every 10 minutes till the end of the procedure. Incidence of hypotension, hypertension, changes in ECG and other complications during procedure were noted and appropriate corrective measures were taken. The continuous infusion of drugs was stopped at the end of surgery. Time from the end of the infusion to spontaneous eye opening, adequate depth of respiration and maintenance of airway was noted. Arterial pressure, heart rate and the response of the patient to command was noted in the recovery room. Other parameters observed included postoperative nausea, vomiting, emergence reaction like nystagmus, hallucination and the need for rescue analgesic.

The following questions were asked after 30 minutes:

- What is your name?
- Where do you live?
- What is date today?
- What is present time?
- Are you having pain?

Each patient was interviewed on the day after surgery about side effects, awareness and their opinion about the anesthesia technique.

Statistical analysis: - All the data presented as mean ± standard deviation and number of patients. Statistical analysis was done using computer software package “SPSS version 14.0 and Graph Pad (Graph Pad Prism 4)” for windows. Z-test was applied for numerical data like duration and hemodynamic variables. Contingency tables and χ2 test was used for comparing the frequencies. P value of <0.05 was considered significant.

RESULTS

Demographic data of the groups were similar for mean age, weight, and sex ratio. There was no exclusion from the study because of technical failure. There was no significant difference in duration of surgery and anesthesia.

Figure 1

Table 1: demographic profile

Variable(s)	Group PK *(n=50)*	Group PF *(n=50)*	P value
Age*(years)*	35±13	38±15	0.80
Weight*(kg)*	53±11	53±13	0.52
Sex*(m/f)*	24/26	21/29	0.54
Time of surgery *(min)*	49±6	51±4	0.051
Time of anesthesia *(min)*	58±7	59±5	0.38

Values are shown as number of patient or mean ±SD. P value >0.05 is non significant. PK=propofol-ketamine, PF=propofol-fentanyl.

The mean pulse rate was 75±4 per minute and 77±8 per minute in PK and PF group respectively at basal level and the difference was statistically not significant. There was slight increase in pulse rate after induction in both the groups which was statically not significant. After starting the infusion pulse rate did not show any significant difference.

Figure 2

Table 2: Comparison of changes in pulse rate

Time	Group PK *(n=50)*	Group PF *(n=50)*	p-value
Pre-op	75±4	77±8	0.181
After induction	82±4	84±5	0.068
5 min	80±5	83±7	0.061
10 min	80±6	80±7	0.931
15 min	80±6	77±6	0.093
20 min	81±7	79±6	0.063
25 min	81±5	79±5	0.069
30 min	79±5	77±6	0.128
40 min	79±6	78±5	0.327
50 min	78±6	76±5	0.211
60 min	79±5	78±4	0.243

Values are shown as mean ±SD. P value >0.05 is non significant.

The mean systolic blood pressure was 117±6 mmHg and 120±5 mmHg in PK and PF groups respectively at basal level and the difference was statistically not significant. (p=0.15) However there was statistically significant fall in systolic blood pressure after induction in Propofol Fentanyl group (P value 0.0001). After starting the infusion systolic blood pressure did not show any significant difference.

Figure 3

Table 3: Comparison of changes in systolic blood pressure (mmHg)

Time period	Group PK *(n=50)*	Group PF *(n=50)*	P value
Pre-op	117±6	120±5	0.15
After induction	116±14	107±9	0.0001
5 min	117±8	115±11	0.470
10 min	117±7	115±12	0.273
15 min	116±7	118±17	0.630
20 min	116±6	117±16	0.634
25 min	117±7	120±18	0.218
30 min	117±6	114±12	0.152
40 min	116±7	112±10	0.019
50 min	116±6	114±12	0.230
60 min	117±7	113±10	0.075

Values are shown as mean ±SD. P value <0.05 is significant & >0.05 is non significant.

As can be seen in table 4 that mean diastolic blood pressure were 77±7 mmHg and 75±6 mmHg in PK and PF group respectively at basal level and the difference is statistically not significant. (p=0.17) After induction there was statistically no significant difference in both the groups. After starting the infusion diastolic blood pressure did not show any significant difference.

Figure 4

Table 4: Comparison of changes in diastolic blood pressure (mmHg)

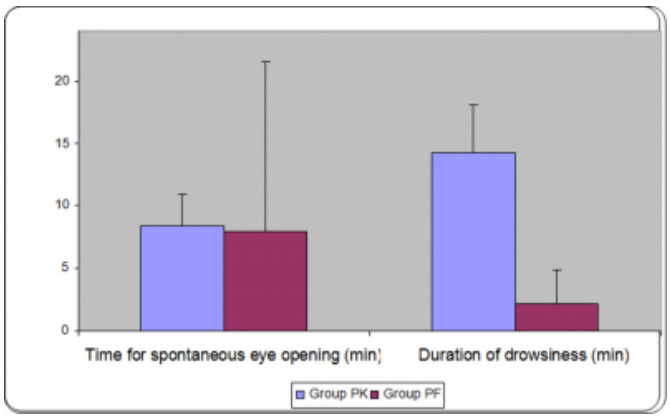
Time	Group PK *(n=50)*	Group PF *(n=50)*	P-value
Pre-op	77±7	75±6	0.17
After induction	74±5	73±6	0.54
5 min	77±4	76±6	0.10
10 min	77±7	75±5	0.07
15 min	77±6	74±6	0.08
20 min	78±6	76±7	0.07
25 min	77±6	75±7	0.30
30 min	77±6	76±7	0.65
40 min	76±7	75±7	0.44
50 min	77±6	75±6	0.25
60 min	76±5	74±6	0.12

Values are shown as mean ±SD. P value <0.05 is significant & >0.05 is non significant.

The mean time for spontaneous eye opening was 8±2 minutes in PK group and 8±3 minutes in PF group. The difference was not statistically significant. Whereas duration of drowsiness was 14±2 minutes in PK group and 13±2 minutes in PF group which was statistically insignificant. (p=0.53) Response to five questions at 30 minutes after anesthesia was good in both the groups.

Figure 5

Graph 4: Comparison of duration of spontaneous eye opening & drowsiness



Postoperative nausea and vomiting was reported in 6 patients in PF group and 5 in PK. The difference was not statistically significant in both the groups. Hypotension (<20% of basal blood pressure) was reported in 5 patients of Propofol Fentanyl group whereas none in Propofol Ketamine group. Other side effects like diplopia, confusion, hallucination and nystagmus were noted in 8 patients of Propofol Ketamine group and none in Propofol Fentanyl group.

Figure 6

Table5: Incidence nausea & Vomiting

Nausea/vomiting	Group PK *(n=50)*	Group PF *(n=50)*	P value
Yes	5/50	6/50	p-value=0.74
No	45/50	44/50	

Values are shown as number of patients. P value >0.05 is non significant.

DISCUSSION

In last few decades, many new sedative-hypnotic drugs with improved induction, maintenance and recovery profiles have been introduced into clinical practice. Propofol is a substituted phenol anesthetic, which is associated with smooth induction, good maintenance and rapid recovery. (7, 8)

Ketamine, a powerful analgesic has a high margin of safety. It produces no negative influence on ventilation or circulation. Its main disadvantage is emergence delirium. (9, 10, 11) Fentanyl, a phenylpeperidine derivative has analgesic potency 50-100 times that of morphine. But it is associated with respiratory depression and post operative nausea and vomiting. (12)

Patients in both the groups did not differ significantly with respect to the demographic data as well as duration of surgery and anesthesia (table1). These findings are consistent with those of Guit J.B. et al who in their study used Propofol 2 mg/kg for induction, maintenance with Propofol 12 mg/kg/hr for first 30 minutes, 9 mg/kg/hr for next 30 minutes and then 6 mg/kg/hr thereafter. Ketamine was used as 1 mg/kg for induction followed by maintenance dose of 2 mg/kg/hr. It was compared with Fentanyl 3 μg/kg bolus and 1.5μg/kg/hr for maintenance. Propofol-Ketamine combination resulted in hemodynamically stable anesthesia without the need for additional analgesics. (13)

There was gradual increase in mean pulse rate in Propofol-Ketamine group and in Propofol-Fentanyl group which returned to baseline after 30 and 15 minutes respectively. Guit JB et al have also reported that heart rate was stable except for an increase in mean heart rate by 24% after induction in Propofol-Ketamine group. (13) Heart rate does not change significantly after an induction dose of Propofol. Propofol either resets or inhibits baro-reflector reflex. There is reduction in the techycardic response to hypotension.(14,15) Propofol has no direct effect on sinoatrial node, atrioventricular node and accessory conduction pathway.(16) Heart rate may increase(17,18) or decrease(19,20) or may remain unchanged(19) when anesthesia is maintained with Propofol. Ketamine increases heart rate by 0-59% after induction.(21) The hemodynamic effects of Ketamine are not dose dependent.(22) The effect is due to increase in central sympathetic tone.(23) Ketamine causes release of nor epinephrine which can be blocked by barbiturates, droperidol and benzodiazepine.(24,25) Fentanyl causes dose dependent decrease in heart rate. Carotid sinus baro receptor reflex control of heart rate is markedly depressed by Fentanyl. These findings are also consistent with those of Shyamala Bardrinath, et al who in their study concluded that, Ketamine induced tachycardia and hypertension was not evident in hemodynamic response of patients treated with the propofol-ketamine combination.(26) Hui TW et al also concluded that heart rate and peripheral vascular resistance are increased due to Ketamine. Heart rate is frequently slowed with more significant vagotonic effects of large doses of Propofol. The effect of individual drugs on heart rate and blood pressure counterpart each other when used in combination.[42]

There was fall in systolic blood pressure in Propofol Fentanyl group after induction as compared to propofol-ketamine group. After starting of infusion the systolic blood pressure did not show any significant change in perioperative period. Guit JB et al have also reported similar trend though both groups were haemodynamically stable.(13) Ketamine stimulates cardiovascular system associated with increase in blood pressure, cardiac index by 0-40% and 0-42% respectively. Propofol decreases mean arterial pressure and cardiac index by 10-40% and 10-30% respectively. Modest doses of diazepam and midazolam attenuate hemodynamic effects of Ketamine when given as continuous infusion with it. (26) The hemodynamic stability of propofol-ketamine combination makes it suitable for use during out patient anesthesia. (27)

Groups did not differ significantly in relation to the time to spontaneous eye opening and duration of drowsiness. Responses to 5 questions were good in both groups. All patients were well oriented in time, place and person at 30 minutes. (13) Postoperative behavior was normal in all patients and no patient reported dreaming during or after the operation. Propofol seems to be effective in eliminating the side effects of subanaesthetic dose of Ketamine in humans. (26, 28) Similarly time required for ambulation was also comparable in both the groups. (29)

Hypotension (<20% of basal blood pressure) was reported in 5 patients of Propofol-Fentanyl group which was corrected by fluid infusion. None of the patients required any vasopressor support to maintain blood pressure.(13) Incidence of nausea was more in propofol-fentanyl whereas dizziness was more in propofol-ketamine.(26) There was no difference in surgery and recovery time, incidence of PONV requiring treatment in either of the groups. We therefore conclude that both ketamine and fentanyl in propofol based anesthesia are equally safe and efficacious in elective surgical cases and fentanyl can be substituted with ketamine in TIVA in case of unavailability of the former.

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