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Comparison of Fentanyl-Propofol and Ketamine-Propofol Combination in Induction and Maintenance with Intravenous Anesthesia for Short Surgical Procedures at Moderate Elevations

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ABSTRACT

Background: The aim of the study is to evaluate the efficacy of Ketamine-Propofol compared to Fentanyl-Propofol combination during induction and maintenance of total intravenous anesthesia for short surgical procedures at moderate elevation.

Methods: A prospective pilot study was done comparing between Fentanyl (1.2 mcg/kg)- Propofol and Ketamine (0.5mg/kg)-Propofol with 30 in each group at moderate altitude of approximately 2514 meters for the requirement of positive pressure ventilation, changes in heart rate and mean arterial pressure intraoperatively, total Propofol consumption and time to attain Modified Steward Score of 6.

Results: Requirement for positive pressure ventilation was significantly high in Fentanyl-Propofol group 18 (60%) compared to Ketamine-Propofol 1 (0.03%) [$P = 0.00$]. Fall in oxygen saturation was significant at 2 minute of Ketamine or Fentanyl [95% CI, 3.10-5.76, $P = 0.00$], after induction with Propofol [95% CI, 2.30-4.03, $P = 0.00$], 5 minute [95% CI, 1.66-3.54, $P = 0.00$], 10 minutes [95% CI, 0.55-2.32, $P = 0.02$], 15 minutes [95% CI, 0.50-2.09, $P = 0.00$] and 20 minutes [95% CI, 0.43-2.23, $P = 0.00$] respectively after study drug between the groups. Total Propofol consumption was significantly higher [95% CI, 0.19-0.43, $P = 0.00$] in KP (1.55 ± 0.27mg/kg) compared to FP (1.23 ± 0.16 mg/kg).

Conclusions: At moderate elevations of 2514 meters, during the induction and maintenance of intravenous anesthesia, Ketamine-Propofol causes significantly less fall in oxygen saturation in the first 20 minutes requiring lesser need of positive pressure ventilation with comparable least fall in heart rate and mean arterial pressure with higher total Propofol consumption when compared to Fentanyl-Propofol. It took a significantly longer time to recovery with Modified steward score of maximum 6 with Ketamine-Propofol.

Keywords: Fentanyl; intravenous anesthesia; ketamine; moderate altitude; propofol

INTRODUCTION

Fentanyl-Propofol (FP) is a commonly used combination for intravenous anesthesia, but it has the tendency to decrease respiratory rate, oxygen saturation, and blood pressure compared to Ketamine-Propofol (KP).[1,2] KP had been shown to improve respiratory rate, reduce hypotension when used for procedural sedation and analgesia with minimal increase in psychomimetic complications, muscle rigidity, nausea and vomiting.[3] Ketamine had proven efficacy of maintaining response to hypoxia, maintain respiratory rate and blood pressure, preserve airway reflexes in animal models.[4,5] Ketamine had been recommended while delivering anesthesia at high altitude due to its advantages of preservation of airway reflex and maintaining hypoxic responses. However, most of the evidence has been derived from case reports, and series done by primary care physicians, and anesthesiologists working in camps or during emergency cases.[6-8] The aim of the study was to compare the efficacy of KP compared to FP combination during induction and maintenance of intravenous anesthesia for short surgical procedures at moderate elevations of approximately 2514 meters.

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METHODS

This was a prospective pilot study in two groups of patients. One group received Fentanyl-Propofol and other group received Ketamine-Propofol. Ethical clearance (Reference Number: 544) for the study was obtained from the ethical review committee of the National Health Research Council, Nepal. Study participants were counselled and written informed written consent was taken before the start of the study. The study was done in Karnali Academy of Health Sciences, Jumla, which is situated at an altitude of approximately 2514 meters from sea level in a hilly district of Nepal that provides healthcare services to natives of high altitudes. [9] It was done for a period of six months from September 15, 2017 to March 15, 2018.

A minimal sample of 30 was taken in each group taking into consideration the difficulties of recruiting participants at high altitude. The patients were recruited into the study based on convenience sampling, after taking into account the maximum volume of patients seeking anesthesia care for short surgical procedures being approximately 160 patients in the yearly audit of the hospital in the previous year, study duration, and exclusion of patients who were elderly, in the pediatric age group, patients with comorbidities, and the duration of procedure exceeding 30 minutes. Those who are born in the high altitude and residing as a native, betwen 16-50 years of age, American Society of Anesthesiologists physical status I were included in the study. Patients undergoing superficial and minor surgical (incision and drainage), gynecological (manual vacuum aspiration) and orthopedic (closed reduction and casting) procedures which was estimated to be maximum of 30 minutes after the induction of anesthesia were recruited in the study. Pregnant, lactating mother, those with a history of allergy to egg and the other study drug were excluded from the study. Procedures which was estimated to exceed the surgical duration of more than 30 minutes and requiring endotracheal intubation were also excluded from the study. The patients were evaluated for the requirement for positive pressure ventilation (PPV) with bag and mask despite oxygen supplementation and airway manipulation for 10 seconds after a fall in oxygen saturation of ≤ 92 %. They were also evaluated for changes in oxygen saturation (SPO_2) in %, heart rate (HR) in beats/minute, and mean arterial pressure (MAP) in mm of Hg, after induction of anesthesia with the study drug in 5, 10, 15, 20, 25, 30 minutes. Total Propofol consumption was evaluated and measured as titrating induction dose and the top off dose during the entire procedure. Recovery profile was assessed using Modified Steward Score (MSS) which was taken after the completion of procedure for first 1 minute, then 3 minute and every 5 minutes thereafter, till the maximum score of 6 is reached which correspond to patients being fully awake, able to move extremities purposefully and coughs on command.[10] Incidences of emergent reactions and postoperative nausea and vomiting (PONV) was also noted between the groups. Age (years), Weight (kg), gender (Male/Female), Surgical duration (in minutes) which were identified as the potential confounders were also recorded and assessed between the groups.

Patients were randomized based upon the lottery method to two study groups by blinded healthcare workers, with the alternate sample being different group from the first lottery. The anesthesiologist who performed the entire procedure couldn't be blinded due to the limitation of manpower availability at this high altitude. Study drugs also couldn't be blinded taking into account the safety of the patient and risk of a potential exaggerated response to the study drugs at this altitude. Patients were also evaluated preoperatively, and kept nil per oral for at least 6 hours before the start of the procedure. During the day of the procedure, the weight (kg) of the patient was taken. Intravenous cannula with 18 or 20 G was accessed in all cases. Monitors with heart rate (HR), mean arterial pressure (MAP), electrocardiogram, and oxygen saturation (SPO_2) were attached and baseline vitals were taken. Injection Midazolam 0.04mg/kg was given followed with Intravenous Ketamine (0.5 mg/kg) or Intravenous Fentanyl (1.20 mcg/kg) depending upon group allocation. After 2 minutes of the analgesic drug, Intravenous Propofol 1% 2ml (10mg/ml) was given as the induction agent in incremental dose every 5 seconds till the patients lost verbal response and eyelash reflex. HR, MAP, and SPO_2 were taken 2 minutes after Ketamine or Fentanyl and then after titrating dose of Propofol. Taking analgesic drug dose as zero time, readings were taken every 5 minutes throughout the procedure. End-tidal Carbon dioxide could not be measured due to lack of equipment. All other necessary airway equipment preparation, presence of an anesthesiologist and an assistant trained in anesthesia was ensured throughout the perioperative period. Supplemental Oxygen was given via facemask at the rate of 6 liters per minute before the induction of anesthesia. Fall in SPO_2 of ≤ 92 % even with supplemental oxygen at the rate of 6 liters/minute and not responding to airway manipulation with head tilt, chin lift and jaw thrust for more than 10 seconds were intervened with positive pressure ventilation with bag and mask with 100 % oxygen and noted. Maintenance of anesthesia was done with an incremental dose of 10 mg Propofol (1ml) based upon

observation of repeated spontaneous movement of trunk and extremities, increase in respiratory rate, heart rate and blood pressure more than 20 % above from the baseline. Duration of the surgical procedure was also noted. After the completion of the procedure, the patient was transferred to the recovery room kept in lateral decubitus position with oxygen supplementation.

Data were collected and entered in Microsoft Excel 2010. Data were presented as Mean and Standard Deviation for continuous variable or Count (%). Outcome and potential confounding variables were identified. Independent t-test was used for continuous variables (age, weight, Duration of surgery, different surgical procedures, MSS score, total Propofol consumption, SPO_2, HR, MAP) and Chi-square test (Presence or absence of PPV, Gender, Incidences of emergent reaction, PONV) was used for categorical variables using statistical software R Programming.

RESULT

During the study period, only 62 study participants who were eligible for the study gave informed written consent for enrollment in the study. Out of 31 participants in each group, one in each group exceeded the time limit of 30-minute surgical duration. Finally 30 patients in each group were analyzed in the study (Figure 1).

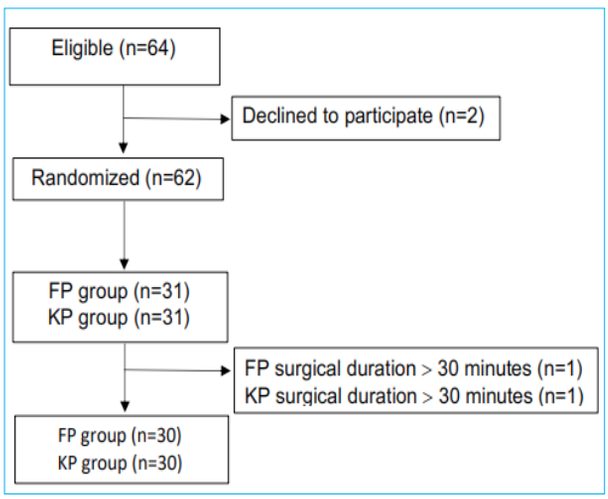

Figure 1. Flow diagram of study participant. FP indicates Fentanyl-Propofol; KP, Ketamine-Propofol.

As illustrated in Table 1, Age, weight and Male to Female ratio and duration of surgery and different surgical indications were not significant between the groups.

Table 1. Baseline characteristics and surgical duration between the Ketamine-Propofol and Fentanyl-Propofol group.

	Ketamine-Propofol (n=30),	Fentanyl-Propofol (n=30),	p-value*
Age (Years), mean (SD)	28.67 (8.07)	31.13 (9.85)	0.293
Weight (Kg), mean (SD)	46.30 (10.13)	53.77 (10.32)	0.06
Male/Female	16/14	17/13	0.795†
Duration of Surgery (minutes), mean (SD)	22.27 (4.660)	20.83 (5.266)	0.269
Closed reduction of fracture	28 (93.33)	27 (90.00)	0.64
Manual Vacuum Aspiration	1 (0.03)	1 (0.03)	1.00
Incision and Drainage	1 (0.03)	2 (0.06)	0.60

**independent t-test, †Chi-square test*

As illustrated in Table 2, requirement for PPV was significantly high in FP 18 (60%) compared to KP group 1 (0.03%) [*P* = 0.00]. Time taken for MSS score to reach maximum value of 6 was significantly higher [95% CI, 2.81-5.85, *P* = 0.00] in KP group (9.50 ± 2.73 minutes). Total Propofol consumption was significantly higher [95% CI, 0.19-0.43, *P* = 0.00] in KP group (1.55 ± 0.27 mg/kg). Incidences of PONV and emergent reaction was only 2 (0.06%) respectively in Ketamine group (Table 2). Fall in oxygen saturation was significant in FP group at 2 minutes of ketamine or fentanyl [95% CI, 3.10-5.76, *P* = 0.00], then after induction with Propofol [95% CI, 2.30-4.03, *P* = 0.00]. Values were still significant at 5 minutes [95% CI, 1.66-3.54, *P* = 0.00], 10 minutes [95% CI, 0.55-2.32, *P* = 0.02], 15 minutes [95% CI, 0.50-2.09, *P* = 0.00] and 20 minutes [95% CI, 0.43-2.23, *P* = 0.00] (Figure 2) of the analgesics Ketamine or Fentanyl and induction with Propofol. Heart rate was not significantly decreased in both the groups except at 5 minutes [95% CI, 0.63-9.96, *P* = 0.027] after FP combination (62.80 ± 7.823 beats/minute) compared to KP (68.10± 10.073 beats/minute) (Figure 3). MAP although decreased was not significantly different between the groups at similar time interval.

Table 2. Anesthetic outcome variables between and Ketamine-Propofol group.

Parameters	Fentanyl-Propofol (n=30)	Ketamine-Propofol (n=30)	P-value
Requirement for positive pressure ventilation	18	1	0.000*
MSS time till 6 is achieved (minutes), mean (SD)	9.50 (2.73)	13.83 (3.13)	0.000†
Total Propofol consumption (mg/kg), mean (SD)	1.23 (0.16)	1.55 (0.27)	0.000†
PONV	1	2	0.554*
Emergent reactions	0	2	0.150*

**Chi-square test, †Independent t-test, FP, Fentanyl-Propofol; KP, Ketamine-Propofol; MSS, Modified Steward Score; PONV, Postoperative nausea and vomiting; PPV, Positive pressure ventilation*

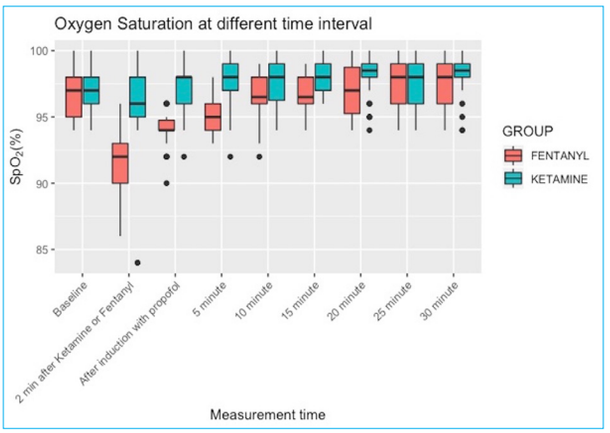

Figure 2. Oxygen saturation (SPO_2) at different time intervals.

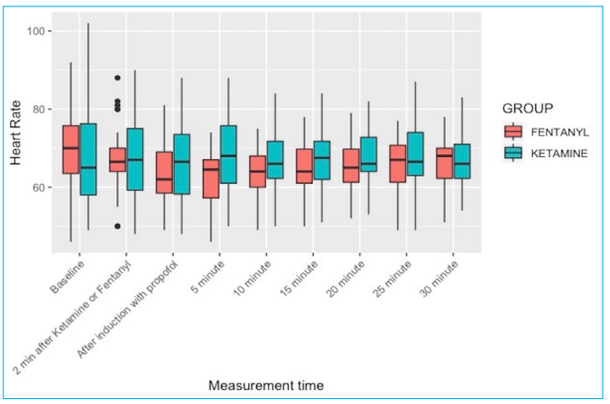

Figure 3. Heart rate at different time intervals.

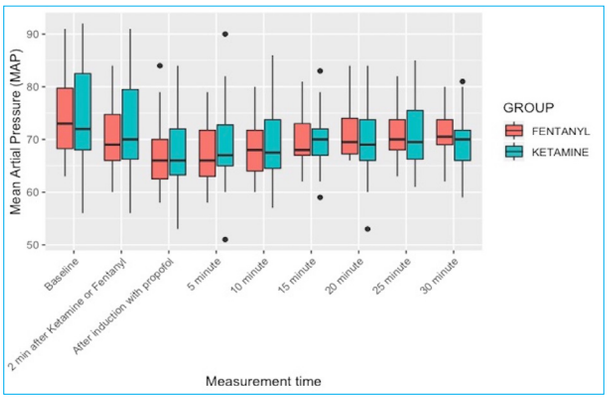

Figure 4. Mean arterial pressure at different intervals.

DISCUSSION

Analgesia and sedation for emergency trauma done in low altitude showed 2 (2.86 %) PPV requirement in Fentanyl(1mcg/kg)-Propofol compared to 1 in Ketamine(1mg/kg)-Propofol.[11] There was also increased incidences of desaturation for closed reduction of fractures requiring 25.5% PPV in Fentanyl (1mcg/kg)-Propofol(1mg/kg) compared to 6.3% in Ketamine(0.5mg/kg)-Propofol(1mg/kg).[12] TIVA for short orthopedics surgery shows higher incidences (16.9%) of fall in oxygen saturation with Fentanyl (1.2 mcg/kg) compared to Ketamine (2 mg/kg) however most didn't require PPV.[13] In contrast, the requirement for PPV is proportionately very high in our study with FP (60%) used for similar procedures done at an almost similar dose in lower altitudes which highlights the exaggerated ventilatory depression effect of Fentanyl at this elevation (Table 2). At the same time, only 3% KP required the PPV at a comparable dose used at a lower altitude which may be due to a lesser ventilatory suppression of Ketamine to hypoxia. Besides, SPO_2 remained significantly low despite oxygen supplementation and airway manipulation till 20 minutes after the induction of anesthesia in FP nonetheless, it remained more stable in KP (Figure 2). Exposure to recurrent hypoxia in animal models has been shown to increase the sensitivity to Fentanyl and Morphine by upregulation of opioid receptors and hypoxia-inducible factor in the medulla.[14,15] Studies at 3399 meters elevation done for cleft lip and palate surgery demonstrated the decrease in opioids requirement by 40% and cited reasons of altered baroreceptor reflexes and genetic factors for altered carotid body sensitivity.[16] At doses of 2mg/kg, Ketamine with Midazolam (0.05mg/kg) was safe in terms of fall in oxygen saturation and hemodynamics in a high altitude of 3900 meters while

performing surgical procedures. Interestingly, even with baseline oxygen saturation of 88-90%, 1 out of 9 highlanders who underwent procedures with Ketamine only required oxygen supplementation and most patients improved with the airway manipulation and physical stimulation.[6] Ketamine can be an ideal drug at high altitude due to minimum respiratory depression and preservation of airway reflexes in animal models.[4,17] Even at 4243 meters altitude, Ketamine was found to be effective in emergency situations where maintenance of airway reflexes and blood pressure is prudent.[18]

There were higher incidences of hypotension, bradycardia reported with the use of Fentanyl (1.5mcg/kg) compared to Ketamine for procedural sedation.[2] At doses of Fentanyl(1mcg/kg) compared to Ketamine (0.5 mg/kg), there is a nonsignificant reduction in HR and systolic blood pressure for closed reduction of orthopedic procedures.[12] MAP and HR also do not show any significant changes when similar doses were used for breast lumpectomy.[19] However, in our study, there was a significant reduction in HR with FP at 5 minutes which can be due to the additive effect of Fentanyl and Propofol after induction in hypoxic situations (Figure 3). MAP decreased in both the groups but was not noteworthy (Figure 4). Studies in mice suggest Ketamine at a dose of 1-5 mg/kg does not alter baroreceptor control of vascular resistance.[5] Even at high altitude, case reports suggest Ketamine as the choice of anesthetic drug in patients who are susceptible to hemodynamic instability.[18] Attenuated response of HR to endotracheal intubation and surgical incision to natives in high altitude was reported suggesting lesser autonomic reactivity.[20] Genetic adaption to active baroreceptor reflex with lower sympathetic activation was also proposed.[21] More than 90 % of the procedures were performed as closed reduction of fractures with comparable age and weight characteristics between the groups (Table 1), which can account for the accuracy of the invasiveness of the procedure, individual dose of Fentanyl and Ketamine used with different dose of Propofol. Although, not evident in the table, most procedures didn't require the additional dose of Propofol during maintenance of anesthesia after the induction dose. At the same time, lesser autonomic reactivity of high altitude inhabitants may be another reason for the stable nature of hemodynamics throughout the procedure.

At low altitude, mean Propofol consumption in emergency procedures was shown to be comparable when used with Ketamine (0.5mg/kg) compared to Fentanyl (1 mcg/kg).[12] Other studies also report a non-significant increased requirement for higher doses of Propofol for sedation and analgesia in Ketamine (0.3mg/kg) compared to Fentanyl (1.5 mcg/kg).[22] Probably, more painful nature of the surgical procedure and usual dose of Ketamine as compared to other drugs might be the reason for an increased requirement of Propofol in the Ketamine group (Table 2).

No emergent phenomenon was reported at a dose of 0.3 mg/kg ketamine for short surgical procedures.[22] Even at doses of 1 mg/kg of Ketamine with Propofol (0.5mg/kg), the recovery profile is comparable with Fentanyl (1mcg/kg)-Propofol for traumatic procedures.[11] Agitation (12.5 %) was reported in breast lumpectomy surgery for Ketamine (0.5mg/kg)-Propofol with no midazolam compared to none with Fentanyl (1mcg/kg)-Propofol.[19] Similarly, Ketamine (2mg/kg)-Propofol with Midazolam (0.04mg/kg) was shown to have slightly higher incidences of agitation (3/54) and emesis (2/54) with none in Propofol-Fentanyl (1.2 mcg/kg) for procedural sedation[13] At 3900 meter altitude, titrating Ketamine (2mg/kg) with midazolam had no emesis and agitation in case reports.[6] Use of Ketamine (0.5mg/kg) at an elevation of 4243 meters for postpartum hemorrhage management had no emergent phenomenon and emesis.[18] It is difficult to understand this phenomenon at this ketamine dose only with case reports. Only 0.06 % of emergent reaction in our study (Table 2) may be due to the use of midazolam as premedication or process completely not understood due to chronic hypoxia. Time required to reach MSS score of 6 in our study (Table 2) is almost similar to studies performed at low altitudes[2] which may be due to a similar phenomenon at low elevations and probably not related to hypoxia.

This study has many limitations mostly attributed to less number of patients seeking services at that altitude. The required sample size may not be adequate to justify the desired effect; however, the finding can be a pilot study for further well-designed research. Blinding was difficult due to safety reasons of an exaggerated response to study drug.

CONCLUSIONS

At moderate elevations of approximately 2514 meters from sea level, KP causes significantly less fall in oxygen saturation requiring lesser need of PPV with least fall in HR and MAP but with higher total Propofol requirements when compared to FP. The fall in SPO_2 was significant for the first 20 minutes of induction and maintenance with TIVA in FP. It takes a longer time to achieve MSS maximum 6 with KP combination but with minimal incidence of emergent reaction and PONV. The study gives the insight to the use of proper dose and choice

of drugs for conduction of TIVA and also highlights the vigilance required in hypoxic condition.

CONFLICT OF INTEREST

None

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