ORIGINAL ARTICLE

RESPIRATORY EFFECTS OF PROPOFOL-KETAMINE AND PROPOFL-FENTANYL COMBINATIONS FOR TOTAL INTRAVENOUS ANAESTHESIA

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ABSTRACT

Background: propofol combined with other intravenous analgesic agents has been used as the sole anaesthetic agent to provide hypnosis and analgesia for various minor and major surgeries. However, because it lacks analgesic property, propofol in large doses causes respiratory depression. Combination of propofol with other analgesic agents reduces the dose of propofol necessary for procedural sedation. **Objectives**: This study evaluated the respiratory effects of two drug combinations: propofol-ketamine and propofol-fentanyl used as the sole anaesthetic agents. **Method**: one hundred and eight adults aged 18 to 50 years of either gender with ASA physical status I & II, randomly grouped into K and F, comprising of 54 patients each. Group K received propofol-ketamine while group F received propofol-fentanyl for induction and maintenance of anaesthesia. Respiratory Rate (RR) and Oxygen saturation ($SpO_{2)}$ were recorded before and one minutes after induction of anaesthesia and thereafter every five minutes till the end of procedure and at recovery till the patient is fully recovered. **Results**: Demographic and clinical characteristics such as age, sex, weight, duration of surgery, types of surgical procedures and volumes of drugs used were comparable between the two groups. Fall in respiratory rate was greater in propofol-fentanyl group compared to propofol-ketamine group during maintenance and early postoperative period ($p<0.05$). **Conclusion**: Both propofol-ketamine and propofol-fentanyl combinations produced safe and effective anaesthesia. Propofol-ketamine results in a more stable respiratory profile.

Keywords: Propofol, Fentanyl, Ketamine, Short surgical procedures.

INTRODUCTION

Propofol when used in the experienced hand is found to have a rapid recovery profile and less incidence of postoperative nausea and vomiting, however propofol when used in high doses depress the respiratory centre causing apnoea. This has led to various trial of drug combinations with propofol to augment for analgesia so that lower dose of propofol may be used to eliminate the respiratory depression associated with higher doses. A trial of propofol in combinations with opioids, NSAIDs, magnesium sulphate, ketamine has been tried with considerable success.

Ketamine is readily available and cheap, with ease of storage, preserves airway reflexes, it possesses hypnotic, analgesic with amnesic effects. Ketamine is used for induction and maintenance of general anaesthesia, as well as post-operative analgesia at

sub-anaesthetic doses. The analgesic effect of ketamine has been used with good result for pre-emptive analgesia in gynecological patients as demonstrated by Amanor-Boadu *et al*.[1]Ketamine also increases blood pressure and heart rate;thus, cardiac output is usually maintained. These changes are probably via direct myocardial and sympathetic stimulation. This effect limits the use of ketamine in severe ischaemic heart disease and chronic hypertension.

Atropine or glycopyrrolate is administered with ketamine to reduce or suppress the excessive salivation associated with ketamine. Glycopyrrolate compared to atropine, was found to offer better cardiovascular stability.[2]

Fentanyl is a synthetic opioid, more potent than morphine in the acute setting, although it is approximately 30 - 40 times as potent when given chronically.[3,4,5] Fentanyl is very lipophilic with a relatively short duration of action. Fentanyl is associated with respiratory depression when used in high dose thereby causing apnoea. It also depresses the myocardium causing hypotension. Fentanyl is predominantly metabolized in the liver to norfentanyl which is inactive. The metabolite is excreted in the urine over a few days.The combinations of ketamine or fentanyl with propofol has advantages such as high potency, lower dosages, rapid recovery and stable cardio-respiratory effects.

This study, therefore seeks to compare the respiratory effect of propofol-ketamine vs propofol-fentanyl in patients undergoing short surgical procedures in Aminu Kano Teaching Hospital, Kano.

MATERIALS AND METHOD

The study was a prospective randomized double-blind trial conducted on 108 adult patients scheduled for elective short surgical procedures in Aminu Kano Teaching Hospital Kano.

An ethical approval was obtained from the Ethical Committee of the hospital. Patients' informed consent to participate in the study was obtained, patients with American Society of Anesthesiologists (ASA) physical status I and II, aged 18 to 50 years, scheduled for elective short surgical procedures were included in the study.

Preoperative assessment was carried out a day before or on the day of the procedure. Basic investigations were checked. Patients were instructed to fast for at least 6 hours. Informed consent was obtained after a thorough explanation of the study procedure. Clinical and demographic data were gathered from the case note and the patients. Patients enrolled into the study were randomly allocated into two groups, K and F, fifty-four each, representing the two study groups: propofol/ketamine and propofol/fentanyl respectively. The investigating anaesthetist and the patient were blinded to the group allocated. Patients were weighed at the theatre reception by a research assistant. On the operating table an intravenous line was set with size 18G cannulaand 0.9% saline set running. Baseline vital signs including respiratory rate, pulse rate, non-invasive blood pressure, oxygen saturation and ECG were monitored. The anaesthetic machine and resuscitative equipment were checked. Glycopyrrolate 0.2mg was given to all patients as antisialagogue. The preparation of study drugs was doneby a registered nurse anaesthetist who was not allowed to take further part in the study. The drugs were prepared as follows: Group K: Using a 20ml syringe, 2ml of ketamine (50mg/ml) was withdrawn and diluted by 8ml of 0.9% saline to make a solution of 10mg/ml of ketamine. Ten milliliters of 1% Propofol (10mg/ml) was withdrawn using the same syringe containing ketamine to make a Propofol/Ketamine solution (Propofol: 5mg/ml and ketamine: 5mg/ml).Group F: Using a 20ml syringe, 2ml of Fentanyl (50mcg/ml) was withdrawn and diluted by 8ml of 0.9% saline to make a solution of 10mcg/ml of fentanyl. Ten milliliters of 1% Propofol (10mg/ml) was withdrawn using the same 20mls syringe containing fentanyl to make a Propofol/Fentanyl solution (Propofol: 5mg/ml and Fentanyl: 5mcg/ml).

Induction of anaesthesia in each of the two study groups was achieved with a sleep dose of the drug combination after three minutes of pre-

oxygenation with 100% oxygen. In both groups, the primary end point for induction was loss of verbal contact. Immediately after induction of anaesthesia, Blood pressure was measured continually every 5 minutes while the pulse rate, respiratory rate and SpO_2 were measured continuously but recorded at five minutes intervals using the multi parameter monitor until the end of the procedure. Continuous ECG monitoring was ensured. Patients were allowed to breathe room air spontaneously after induction of anaesthesia unless where oxygen saturation was observed to drop to 93% then oxygen supplement via facemask or nasal prong was administered. Where there was evidence of airway compromise, jaw thrust was applied to maintain the airway patency. Apnoea observed in some of these patients immediately on induction of anaesthesia was managed with Bag mask ventilation with 100% oxygen until patient regained spontaneous breathing. However, no patient was allowed to de-saturate below SpO_2 <93% and no patient was intubated.Maintenance of anaesthesia was achieved in both groups with an average infusion of 0.4ml/kg/hr of the study regimen i.e. propofol-ketamine and propofol-fentanyl. However, a bolus dose of 1-2 ml of the study regimen was administered when a patient showed signs of discomfort.Administration of all anaesthetic drugs was stopped at the end of the procedure. Monitoring of patient was ensured till when the patient was fully recovered.

All results obtained were analyzed using statistical package for social science (SPSS) version 22.0 for windows (SPSS, IBM Corporation). Values were expressed in numbers, means, standard deviations and results presented as tables and graphs. Student's t-test was used for analysis of continuous variables. P value less than 0.05 was regarded as statistically significant.

RESULTS

A total of 108 patients that took part in the study were included in the final analysis (propofol-ketamine group 54; propofol-fentanyl group 54)

Table 1 shows the demographic characteristics of the two study groups. There is no significant difference with respect to ages, weight and sex between the two groups (P>0.05). The mean age of the patients in the propofol-ketamine (K) group was 33.1 years (±9.3) and 31.6 years (±9.1) in propofol-fentanyl (F) group (p=0.44). The mean weights were 58.8kg (±9.7) in the propofol-ketamine (K) and 58.76kg (±9.7) in propofol-fentanyl (F) groups (p=0.98). The Male/Female distribution was 35/19 in group K and 38/16 in group F (p=0.68).

Table 2 showed the distribution and duration of surgical procedures. The types of surgical procedures were comparable between the two groups (P>0.05). The mean duration of surgery was 37.5 minutes (±10.3) for propofol-ketamine (K) and 37.4 minutes (±10.0) for propofol-fentanyl (F) (p=0.77).

Table3 showed the mean Respiratory Rate at different stages of anaesthesia. Respiratory rate at induction of anaesthesia decreased in group F but the differences between the two groups at first minute after induction was not significant (p=0.10). Thereafter, five-minute measurement of the RR during maintenance stage of anaesthesia showed a reduction of the RR in group F which was significant compared with group K (p<0.05). In the immediate postoperative period, the RR was significantly lower in group F compared to group K at first minute (P=0.01) and at 5^{th} minute (p=0.01). From the 10^{th} minute postoperatively the RR showed no significant difference between groups K and F (P>0.05) (figure 4).

Table 4 Showed the mean oxygen saturation (SpO_2) among the two groups perioperatively. There was no fall in SpO_2 below 94% among the two groups. However, the SpO_2 reading of patients in group K was higher than the reading obtained on patients in group F, even though the difference is not significant (p>0.05).

Table 5showed the incidence of adverse events among group K and group F.

Apnoea after induction of anaesthesia- defined as the loss of respiratory effort for more than 20 seconds duration or fall in SpO_2 below 94%- loss of respiratory effort on induction of anaesthesia, for 20 seconds was observed in ten patients (19%) among propofol-fentanyl group and six patients (11%) among propofol-ketamine group (p=0.41).

Hypoxia (defined as SpO_2 value of less than 94%) was not observed in any of the group because all the patients in both groups were pre-oxygenated with

100% oxygen prior to induction of anaesthesia. However, patients in group F experienced transient decrease in SpO_2 from the baseline compared to group K (p>0.05)

Table 1: Demographic characteristic of group K and F

Variables	K(mean±SD)	F(mean±SD)	P value
Age	33.1±9.3	31.6±9.1	0.44
Sex Male / female	35/19	38/16	0.68
Weight	58.8±9.7	58.7±9.7	0.98

K; Propofol-ketamine F; Propofol-fentanyl

Table 2: Distribution and duration of surgical procedures among group K and F

Types of surgery	K	F	P value
Herniorraphy	7	5	0.55
Cystoscopy/EUA	12	13	0.99
Stent removal	11	13	0.81
excision of lipoma/ganglion	8	7	0.99
Closed reduction of fractures	3	2	0.99
Wound debridement	4	5	0.99
Circumcision	1	0	0.99
Others	8	9	0.99
Duration of surgery(min)	37.5±10.3	37.4±10.0	0.77

K; Propofol-ketamine F; Propofol-fentanyl

Table 3: Mean respiratory rate perioperatively

	Time interval in minute	K(Mean±SD)	F(Mean±SD)	P value
Pre-induction	0	18.9±0.6	18.8±0.6	0.50
Induction	1	18.1±0.6	17.5±0.9	0.10
	5	18.6±0.9	16.0±0.7	0.01
	10	19.2±0.7	17.0±1.0	0.01
	15	18.1±0.8	16.0±1.2	0.01
	20	18.1±0.9	16.1±0.8	0.01
	25	18.2±0.8	16.1±0.6	0.01
	30	18.1±1.0	15.9±1.0	0.01
	35	19.1±0.7	17.2±1.0	0.01
	40	18.0±0.9	15.9±0.9	0.01
Postoperative	1	18.8±0.8	17.1±0.6	0.01
	5	17.9±0.7	16.9±0.6	0.01
	10	19.0±0.8	18.9±0.6	0.42
	15	19.2±0.7	19.2±0.7	0.60

K; Propofol-ketamine F; Propofol-fentanyl

Table 4: Mean oxygen saturation (SpO_2) perioperatively

	Time interval in minute	K(Mean±SD)	F(Mean±SD)	Pvalue
Pre-induction	0	97.02±0.7	97.07±0.7	0.70
Induction	1	99.06±0.5	98.96±0.8	0.28
	5	98.04±0.4	98.00±0.3	0.60
	10	97.02±0.6	96.95±0.8	0.30
	15	97.03±0.9	96.90±0.7	0.20
	20	97.61±0.7	97.47±0.7	0.38
	25	99.05±0.5	98.96±0.7	0.23
	30	98.04±0.4	98.01±0.3	0.60
	35	97.05±0.6	96.92±0.8	0.24
	40	97.13±0.9	96.70±0.7	0.12
Postoperative	1	97.23±0.9	96.80±0.7	0.12
	5	99.06±0.5	98.96±0.7	0.28
	10	99.05±0.6	98.86±0.7	0.24
	15	98.32±0.6	98.02±0.4	0.50

K; Propofol-ketamine F; Propofol-fentanyl

Table 5: Complications reported in both groups

Adverse effects	Group K n=54	Group F n=54	P value
Apnoea	6(11%)	10(19%)	0.41
Hypoxia	0(0%)	0(0%)	
Laryngospasm	0(%)	0(0%)	

K; Propofol-ketamine, F; Propofol-fentanyl

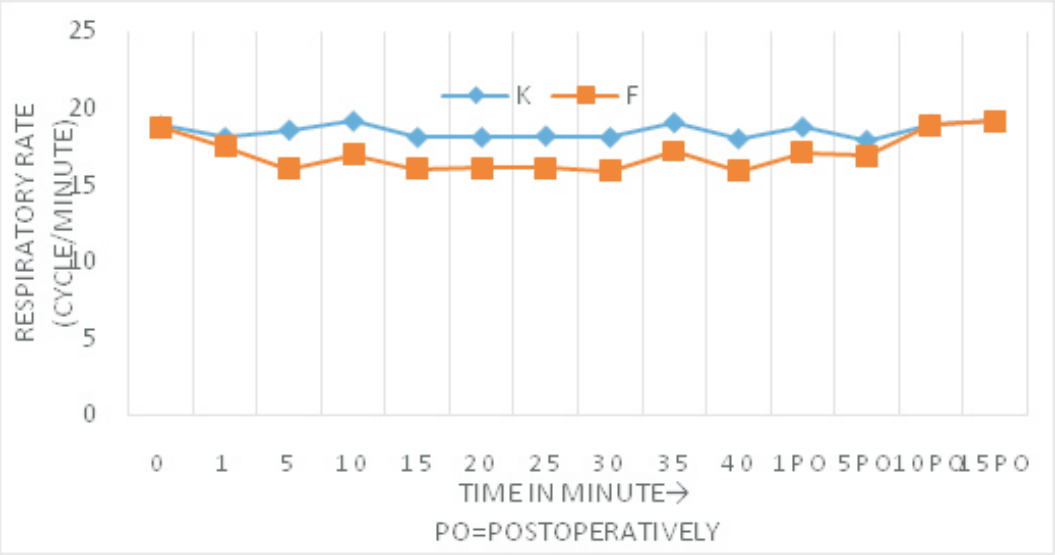

Figure 1: Comparison of Perioperative Mean Respiratory Rate

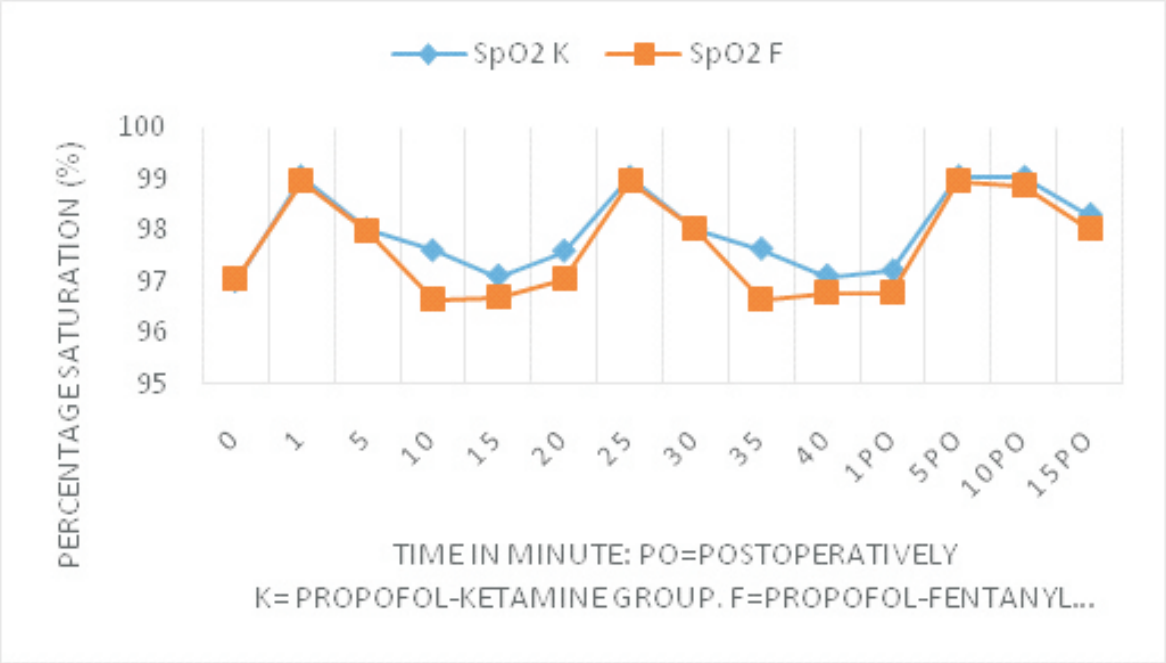

Figure 2: comparison of perioperative mean oxygen saturation (spo_2).

DISCUSSION

This study showed that propofol-fentanyl and propofol-ketamine combinations provide safe and effective anaesthesia in adults undergoing short surgical procedures.

In this study respiratory rate and pulse rate were observed to be lower in propofol-fentanyl group than propofol-ketamine group. With reduction in RR of two to three cycles per minute among group F. A similar study by Brajesh *et al*[6] dealing with propofol-ketamine vs propofol-fentanyl combinations showed results comparable with this study. This study finding is in contrast with that of Zeynep *et al,*[7] who observed that there was no statistically significant difference in RR during the procedure in the two groups. This could be attributed to the short duration of the procedures (10.9min vs 10.7min) in that study and the drugs were administered as boluses, incremental doses were only given in few patients that showed signs of discomfort. Maintenance dose in form of continuous infusion was not administered. However, similar to what was observed in this study, RR observed after induction of anaesthesia by Zeynep *et al*[7] was significantly lower in Propofol-fentanyl group compared to Propofol-ketamine group ($p<0.05$). The fall in respiratory rate with propofol and fentanyl combination could be attributed to the respiratory depressant effects of propofol and fentanyl.

In this study Propofol-fentanyl combination showed a significant increase in apnoea, as ten (19%) patients developed apnoea compared to six (11%) patients in propofol-ketamine group ($p=0.41$). This finding is similar to that of Brajesh *et al*[6] who reported the incidence of apnoea after induction in propofol-fentanyl group to be 20% compared to 16% in propofol-ketamine group. Previous studies[8,9,] have reported contrasting results when compared with this study. Bajwa *et al*[10]reported no incidence of apnoea with the use of propofol-ketamine and propofol-fentanyl. Nalini *et al*[8] also reported no incidence of apnoea among propofol-ketamine and propofol-fentanyl groups. This study and the study of Brajesh *et al*[6] employed the use of continued infusion of the anaesthetic agent throughout the period of anaesthesia. However, Brajesh *et al*[6] administered their

induction agents separately, ketamine was first administered in patients in group I, followed by propofol two minutes later and patients in group II received fentanyl first, followed by propofol two minutes later, however, this study combined the two drugs in the same syringes and the drugs were administered at once. Although Bajwa *et al*[10] also used similar agents for continuous infusion as was used in this study, all their patients were paralyzed with succinylcholine and intubated following induction of anaesthesia. This would have masked any incidence of apnoea that could have occurred on induction of anaesthesia, unlike this study and the study of Brajesh *et al*[6] where all the patients were allowed to breathe spontaneously during induction, maintenance and recovery phase of anaesthesia. Apnoea was managed with bag and mask ventilation with 100% oxygen. No patient required endotracheal intubation and no patient was allowed to developed desaturate below SpO_2<93%. None of the patient developed laryngospasm.

CONCLUSION

This study confirms that both propofol-fentanyl and propofol-ketamine combinations are safe techniques for TIVA in patients undergoing short surgical procedures. Propofol-fentanyl has a respiratory depressant effect. Propofol-ketamine combination provided better respiratory effect.

It may be recommended that either propofol–ketamine or propofol–fentanyl can be used as an excellent combination in TIVA for elective short surgical procedures. Where respiratory compromise is anticipated, propofol-ketamine will be advantageous.

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