International Journal of Medical Sciences; May 2023;6(2):28-35;
ISSNe 2522-7386; DOI: https://doi.org/10.32441/ijms.6.2.4

Comparison of the effect of ketamine and propofol on surgical operation patients

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Received: 27/2/2023 Accepted: 26/04/2023 Published: May 2023

Abstract
Background and objective: A prospective randomized controlled study was conducted to compare and evaluate the quality of anesthesia with ketamine or propofol.
Materials and methods: 80 patients, aged 18-50 years, who were scheduled to undergo minor surgeries of short duration (less than 1 hour of expected duration) were selected and divided in two groups. The patients were randomly assigned to the first group and the second group of 40 patients in each. Group I patients were given ketamine injection 0.5 mg/kg and group II received propofol injection (1.5 μg/kg) as a co-induction agent. After 2 minutes, induction of anesthesia was given with propofol (2.5 mg/kg) and an appropriately sized laryngeal mask was inserted. Anesthesia was maintained with 60% NO in O2 and an intermittent bolus of propofol injection (0.5 mg/kg) given after significant changes in heart rate, blood pressure, lacrimation, sweating, and abnormal movements were noted.
Results: There was a significant decrease ($P < 0.05$) in pulse rate, systolic and diastolic blood pressure at 1, 3 and 5 minutes in the group receiving propofol, while the change was insignificant ($P > 0.05$) at 10 minutes.
Conclusion: It was noted that ketamine as a starting material was better than propofol with regard to hemodynamic stability and caused fewer adverse effects during surgery and after surgery.
Keywords: Ketamine, propofol, anesthesia, elective surgery, short duration surgery.

Introduction

Sedation is an approach during surgery to achieve analgesia. This may be induced by receiving tranquilizers, however, the tranquilizers not resulted with analgesic effects [1]. Combination of analgesia and sedation lead to decrease consciousness levels which is essential for protection of patient's airway during surgery. They are used in emergency wards to manage and reduce painful procedures [2]. Propofol is one of the most common short-acting intravenous sedative drugs in the field of emergency medicine, which is used in children and adults. Also, for intubated or mechanically ventilated patients in intensive care units (ICUs) concerning induction and maintenance of general anesthesia, and in gastrointestinal endoscopic procedure propofol can be used.

It is suggested that ketofol combinations induce effective sedation in patients of all age groups when used in procedures such as spinal anesthesia or in gynecological, ophthalmological, and cardiovascular procedures. This drug is highly desirable because of its

favorable pharmacology. However, it is preferred to use with opioids because it not induced analgesic effects. Fentanyl and ketamine as an opioid induced analgesic effect when combined with propofol. The combination of propofol and ketamine (Ketofol) began in 1993. Its application was observed and is in line with decreased emergence reactions following the use of propofol before ketamine administration [3].

This combination has been used in different settings during burn dressing change, interventional radiology procedures, and procedural sedation in emergency departments [4-6]. It is important to mention that vomiting due to ketamine will be minimal; a shorter recovery time and agitation are the potential benefits of ketofol to ketamine in procedural sedation and analgesia [7,8]. Fentanyl is beneficial to pains which are intense and short in duration, and it can manage them effectively [9].

Among the opioid drugs, fentanyl can lead to a reduction in the dosage of propofol and decrease its complications [10], but there is a lack of enough evidence investigating the use of fentanyl and propofol combinations (also called fentofol) during emergency procedures. Although some studies have investigated the propofol combination, it seems that there is a need for comprehensive evidence about various procedures in emergency wards. Therefore, this research was conducted to compare the effectiveness, safety, and complications of intravenous infusion of ketofol with fentofol in painful emergency procedures.

On the premise of the available literature, we assume that the infusion of ketofol is more reasonable and has more favorable hemodynamic and provides better recovery in comparison with fentofol. Anesthesia drugs combination was an approach to reduce the complication. The drug combination led to use of lower doses as compared using of drug alone and this contributed to low occurrence of adverse effect [11]. Logically the adverse effects and complication in medical practice are related to the drug dosing. Thus, ketofol may be of better safe than using each drug alone. This mixture was named ketofol and was assessed as a sedative agent in several studies mainly as in emergency departments with encouraging results [12].

Ketamine is frequently used during outpatient anesthesia. N-Methyl-D-aspartate (NMDA) is classified as a receptor antagonist. However, its effectiveness mechanism has not been fully explained yet [13]. The half-life of ketamine is approximately 2 h, so it takes a long time for patients to regain consciousness [14]. Its side effects may include confusion, tension, or delirium [15]. The long half-life of ketamine and its dissociative anesthesia affect the awakening. Screaming, crying, and hallucinations can be witnessed during emergence. In our research, in order to reduce these effects, 0.1 mg/kg midazolam was administered to the patients in the induction stage. Midazolam is a sedative and hypnotic benzodiazepine and has a short half-life (2–3 h) [16].

Compared to ketamine, propofol has a shorter clearance (0.5–1.5 h) [17]. Propofol provides its hypnotic effects by activating the central inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [18]. It has also been demonstrated that Propofol selectively blocks acetylcholine release in the baso-cortical and septo-hippocampal pathways [19].

Aim of the study.

The primary objective of the study was to compare the adequacy of sedation and analgesia provided by two different ratios of ketamine and propofol combination on surgical operation patients The secondary objectives were to compare the hemodynamic variables, airway intervention if any, time for awakening, and the incidence of side effects between the two groups.

Patients and methods

Eighty patients, aged 18–50 years of both sexes, undergoing minor surgery (expected duration of surgery <1 hour) were randomized to this prospective double-blind

study in two groups. The study protocol was approved by the Al-Qalam Ethical Committee and informed consent was obtained from all patients. Patients with a history of high blood pressure, convulsions, mental disorders, liver or kidney disease, and any drug addiction were excluded from the study. Patients who were hypersensitive to propofol and ketamine were excluded from the study.

Patients were taken to the operating room and an 18-G intravenous cannula was inserted into the dorsal vein of the left hand and lactate started to ring. Intraoperative monitoring included ECG (continuous), pulse rate, noninvasive blood pressure, oxygen saturation and temperature (using a Datex AS5 Monitor®).All patients were asked to fast for 8 hours prior to the proposed time of surgery. All patients received glycopyrrolate 0.2 mg and ondansetron 0.1 mg/kg intravenously 15 minutes before induction. The patients were randomly divided into two groups according to the drug combination they received. The random numbers are written from random tables. Group I patients received an injection of intravenous ketamine 0.5 mg/kg and group II patients received an injection of propofol 1.5 μg/kg as a co-induction agent. After 2 minutes, anesthesia was induced. Propofol 2.5 mg/kg and patients were asked to count numbers during agitation. The drug was stopped once the patient could no longer count and this was confirmed by asking the patient to open his eyes. Immediately, an appropriately sized laryngeal airway mask (LMA) was inserted in classical technique by an experienced anesthesiologist and anesthesia was maintained at 60% N2O in O2. Patients, in whom the number of LMA insertion attempts increased to more than 2, were excluded from the study.

Additional doses of propofol (intermittent bolus 0.5 mg/kg) were given when there were more than 20% changes in baseline heart rate and blood pressure or there was tearing, sweating, or abnormal movements. The recorded parameters were systolic and diastolic blood pressure, pulse rate, respiratory rate, and arterial oxygen saturation at 1, 3, 5, and 10 minutes after induction. Intraoperative temperature monitoring was performed via the nasopharyngeal route (Datex AS 5®). Postoperatively, the incidence of apnea, incidence of laryngospasm, recovery time, adverse effects, (nausea, vomiting, dizziness, delirium) and awareness during the procedure were noted. Nausea, vomiting, dizziness, and delirium were monitored for 4 hours in the postoperative room and thereafter for the next 24 hours.

The LMA was removed and the patient was intubated upon completion of surgery and patients were given postoperative oxygenation by face mask. Statistically, mean age, mean weight, and intraoperative adverse events were compared using the Chi-square test, and Student's t-test was used to compare recovery time.

Result

In this study, data were collected for 80 patients who are going to undergo surgery. Among the 80 patients, 59 (73.75%) were males and 21 (26.25%) were females. Most patients were within the age of 18 to 28 years [47 (58.75%) patients]; 18 patients (22.50%) in the age group of 29-39 year, and 15 (18.75%) patients in age group of 40 to 50 years old. The standard of living for the patients was relatively good only 13 (16.25%) patients who were below the poverty line, 56 (70.00%)patients had surgery for the first time, 13 (16.25%) patients had problems with anesthesia, 12 (15.00%) patients had a positive family history of anesthesia problems, and this may increase the percentage of fear of anesthesia, as this study indicated that 21 (26.25%) patients had a fear of anesthesia.

Of the total, 30 (37.50%) patients were smokers, 9 (11.25%) of them were former smokers, 29 (36.25%) were non-smokers, while 7 (8.75%) patients were alcoholics and 23 (28.75%) patients had dental fillings. Personal data related to chronic diseases or that the patient might have before the operation were recorded. Of the total, 12 (15.00%) patients had high blood pressure, 6 (7.50%) patients had high sugar, 3 (3.75%) patients had a kidney

problem, and one (1.25%) of the patients had asthma, heart problems and thyroid gland disease. Additionally, 29 (36.25%) patients had influenza and 26 (32.50%) of them had vertebral problems. Out of a total 80 patients, 48 (60.00%) patients underwent spinal anesthesia, 11 (13.75%) patients had anemia and 24 (30.00%) patients had a positive family history for chronic diseases.

Forty patients received ketamine anesthesia, and the second group of 40 patients received propofol. Awakening time (spontaneous eye opening) was statistically higher (P=0.0001) in group I (8.4±2.7 min)than in group II (5.65±3.21 min). In addition, the recovery time (when patient was able to answer simple questions such as name, age, date of birth, time, and place) was significantly (P=0.000) higher in group I (14.1±3.2 min) than in group II (11.5±3.46 min). Also, the systolic and diastolic blood pressure was significantly (P=0.0001) higher in group I than in group II, Table.3. While, the HR was 94 ±20.6 in group I and 92±19.1 in group II, with none significant difference (P=0.65), and the PO2 was 97.5±2.8in group I and 98.2±2.6 in group II, with none significant difference (P=0.25), Table.3.

There was no complication observed in 77.5% patients in both groups. Ten percent patients of group II had felt nausea, 4 patients of group I and 1 patient of group II felt dizziness. Majority of patients of both groups had pleasant experience of anesthesia.

Table .1: Socio-demographic characteristics of the study sample

Variable		**Number [%]**
Age	**18 – 28**	**47[58.75]**
	29 -39	**18 [22.50]**
	40 -50	**15 [18.75]**
Gender	**Male**	**59 [73.75]**
	Female	**21 [26.25]**
Marital status	**Single**	**20 [25.00]**
	Married	**40 [50.00]**
	Divorced	**13 [16.25]**
	Widowed	**7 [8.75]**
Income	**Good**	**37 [46.25]**
	Poor	**13 [16.25]**
	Moderate	**30 [37.50]**
Is this a first anesthetic for you	**Yes**	**56 [70.00]**
	No	**24 [30.00]**
Have you ever experienced any anesthesia related problems	**Yes**	**13 [16.25]**
	No	**67 [83.75]**
Has anyone in your family experienced issues with anesthesia	**Yes**	**12 [15.00]**
	No	**68 [85.00]**
Do you have a fear of anesthesia	**Yes**	**21 [26.25]**
	May be	**37 [46.25]**
	No	**22 [27.50]**

Table .2.Patients' personal data.

	Variable	Number [%]
Are you a	**Smoker**	**30 [37.50]**
	Ex-smoker	**9 [11.25]**
	No-smoker	**29 [36.25]**
	Alcohol	**7 [8.75]**
Do you have dentures	**Yes**	**23 [28.75]**
	No	**57 [71.25]**
Do you have any health problems	**Hypertension**	**12 [15.00]**
	Hyperglycemia	**6 [7.50]**
	Asthma chronic or Emphysema	**1 [1.25]**
	Kidney disease	**3 [3.75]**
	Thyroid problems	**1 [1.25]**
Have you recently had a cold or the flu	**Yes**	**29 [36.25]**
	No	**51 [63.75]**
Do you have problems with your vertebrae or neck	**Yes**	**26 [32.50]**
	No	**54 [67.50]**
Do you prefer spinal or general anesthesia	**Spinal**	**48 [60.00]**
	General anesthesia	**32 [40.00]**
Do you have anemia	**Yes**	**11 [13.75]**
	No	**69 [86.25]**
Having family post history of chronic disease	**Yes**	**24 [30.00]**
	No	**56 [70.00]**

Discussion

Propofol has become an accepted standard for sedation during procedures performed under regional anesthesia, both central and peripheral [20]. However, it has some properties that limit its usefulness when used in conjunction with subarachnoid blockade. It causes a reduction in myocardial contractility and in peripheral vascular resistance, which results in a reduction of mean arterial pressure. The present study indicated that blood pressure was lower in patients receiving propofol. Recent work [21] has illustrated a continued hypotensive effect when a propofol infusion was used to sedate patients who were undergoing spinal anesthesia. In addition, the ketamine group shows higher blood pressure than in those receiving propofol. This finding was agreed to that reported by others who found in their meta-analysis study that ketamine bolus before spinal anesthesia had a higher blood pressure as compared to that receiving fentanyl [22]

Table .3.Recovery, awakening, time and postoperative complications

		Group I (n=40) Mean ±SD	Group II (n=40) Mean ±SD	P value
Awakening time [minute]		**8.4 ±2.71**	**5.65±3.21**	**0.0001**
Recovery time [minute]		**14.1 ±3.2**	**11.5 ± 3.45**	**0.0008**
Blood pressure		**132 ±2.81⁄88±0.81**	**125±1.7⁄82±0.69**	**0.0001**
Heart rate/min		**94±20.6**	**92±19.1**	**0.65**
PO2		**97.5±2.8**	**98.2±2.6**	**0.25**
Complication	**None**	**31**	**31**	
	Nausea	**4**	**1**	
	Vomiting	**0**	**4**	
	Delirium	**1**	**3**	
	Dizziness	**4**	**1**	

Ketamine is safe and produced increase in blood pressure in a dose dependent manner [23]. However, there is no increase in stroke index, and ketamine is a mild direct cardiac depressant. The previous study indicated ketamine and propofol combination with better respiratory and hemodynamic stability [24]. Heart rate and blood pressure were increased by ketamine without induction of hypertension [25]. Ketamine effect on blood pressure was suggested as an sympathetic nervous system effect [24]. Ketamine induce its pharmaceutical activity targeting voltage – sensitive Calcium channel, muscarinic channel, opioid receptors and NMDA receptors [2].Adding of ketamine to propofol influences the propofol cardio depressant [23,27].

When combinations of anesthetic agents are administered intravenously to patients, outcomes or adverse effects cannot be predicted by knowing the dose requirements of the individual agents [5]. In addition, ketamine anesthesia with propofol anesthesia alleviated hemodynamic depression without causing any significant apnea. After 10 minutes, no significant change in hemodynamic parameters was observed in the ketamine group. This may be due to the cardiac stimulant effect of ketamine which, in doses under anesthesia, may counteract the depressant cardiotonic effects of propofol.

PO2 was about similar in both groups and with none significant difference. Also, the heart rate was with none significant difference between the two groups and these finding indicated the addition of propofol not affected cardiac and respiratory function. The present study finding was consistent to that reported by others [6-9]. The wake time and recovery time were longer in first group and this finding indicated that combination of ketamine and propofol is better than ketamine alone. This finding agreed with previous reports [20,26]

In conclusion, ketamine, being a cardiac stimulant drug, is better regarding hemodynamic stability and adverse effects. The incidence of apnea and respiratory depression was also lower with ketamine, but recovery was faster where propofol was given.

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