

Comparison of haemodynamic changes between propofol and ketofol as induction agents in patients undergoing laparoscopic surgeries under general anaesthesia

Vikasini Raman, Sivakumar Segaran, T. Ramyavel, Sagiev Koshy George, Mamie Zachariah

Department of Anaesthesiology and Critical Care, Pondicherry Institute of Medical Sciences, Puducherry, India

Abstract

Background and Aims: Laparoscopic surgeries are more commonly performed procedure nowadays because of its advantages however generation of pneumoperitoneum causes significant physiological changes. Propofol is the most commonly used induction agent but its use is limited by its side effects like dose-dependent hypotension and myocardial depression. So by combining propofol with ketamine to form ketofol may result in better hemodynamic stability. The aim of this study was to compare the haemodynamic changes in patients undergoing laparoscopic surgery under general anesthesia using propofol and ketofol as induction agents.

Material and Methods: In this prospective randomized double blind study, 80 patients of ASA I/II undergoing elective laparoscopic surgery were randomized into two Groups. Group A received 1 mg/kg of propofol + 1 mg/kg ketamine made up to a total volume of 20 ml with normal saline and Group B received 2 mg/kg propofol + normal saline to make up to an equal volume. Hemodynamic profiles like HR, SBP, DBP, and MAP were recorded at different time intervals until pneumoperitoneum. Postoperative recovery profile and complications were recorded. All data were entered in MS excel and analyzed using SPSS Version 20.0. Repeated measures ANOVA and Chi-square test were used to test the level of significance.

Results: Demographic character and duration of surgery were comparable. SBP, DBP, MAP and HR showed statistically significant difference in both groups in various time intervals with $P < 0.05$ with Group A (ketofol) having a better hemodynamic stability. Recovery profile in ketofol group took longer duration (4.95 min) compared to propofol group B (1.8 min). Postoperative nausea and vomiting were significant ($P = 0.004$) in ketofol group.

Conclusion: We concluded that ketofol had a better hemodynamic stability compared to propofol as an induction agent, however time for recovery in ketofol group took a longer period compared to propofol group, with no complication in either groups.

Keywords: Hemodynamic stability, ketofol, laparoscopic surgeries, postoperative recovery, propofol

Introduction

Laparoscopic surgery, also called as minimal invasive (MIS) or keyhole surgery, is a modern surgical technique performed worldwide, replacing many open surgeries for various surgical

conditions. The use of laparoscopy has revolutionized the surgical speciality with decrease in morbidity and mortality with reduced hospital stay.^[1] It minimizes the tissue trauma while achieving satisfactory therapeutic results. Laparoscopic surgery have been traditionally performed under general anesthesia after creating an artificial pneumoperitoneum by

Address for correspondence: Dr. Sivakumar Segaran, Associate Professor, Department of Anaesthesiology and Critical Care, Pondicherry Institute of Medical Sciences, Puducherry - 605 014, India. E-mail: siva85dr@gmail.com


This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Raman V, Segaran S, Ramyavel T, George SK, Zachariah M. Comparison of haemodynamic changes between propofol and ketofol as induction agents in patients undergoing laparoscopic surgeries under general anaesthesia. *J Anaesthesiol Clin Pharmacol* 2022;38:215-20.

Submitted: 14-May-2020 **Accepted:** 20-Jul-2020

Published: 13-Jan-2022

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/joacp
	DOI: 10.4103/joacp.JOACP_251_20

insufflation of carbon dioxide to provide adequate space for visualizing the abdominal contents clearly.^[2,3]

Creating artificial pneumoperitoneum causes significant physiological changes to various organ systems of the body due to increased intra-abdominal pressure and release of numerous neurohumeral factors which causes significant hemodynamic changes.^[3-5]

Propofol is a substituted isopropyl phenol^[6] (2,6 di-isopropylphenol) that is chemically distinct from all other induction agents. It is a non opioid, non barbiturate, sedative-hypnotic agent with rapid onset and short duration of action due to its lipid solubility. It produces general anaesthesia by facilitation of inhibitory neurotransmission mediated by GABA. It serves to reliably induce sedation, amnesia, and general anaesthesia. Although it is extremely effective and potent, propofol use is limited by a relatively high incidence of dose-dependent hypotension and respiratory depression.^[7,8]

Ketamine is a phencyclidine derivative that produces “dissociative anaesthesia,” which resembles a cataleptic state in which the eyes remain open with a slow nystagmic gaze.^[3] It is a non-competitive N-methyl-D-aspartate receptor antagonist with opioid receptor activity. It causes little or no respiratory and cardiovascular depression and has analgesic properties. Therefore, ketamine is widely used as a preventive analgesic for acute postoperative pain management.^[9-11] Ketamine as a single induction agent, however, is limited by its psychomimetic and sympathomimetic effects.^[12]

It has been postulated that combining ketamine and propofol (Ketofol) may potentially balance each other's hemodynamic adverse effects thus providing a stable hemodynamic profile at induction with added advantage of decrease in incidence of PONV, and postoperative shivering.^[13,14]

Hence, in this study we have aimed to compare the haemodynamic profile of patients undergoing laparoscopic surgeries under general anaesthesia following induction with propofol or ketofol.

Material and Methods

Following approval from institutional ethics committee (IEC: RC/17/62), CTRI No: CTRI/2019/10/021607 and written informed consent 80 patients with American society of Anesthesiologists (ASA) physical status I or II of either sex, aged 18–50 years requiring general anaesthesia with endotracheal intubation were enrolled in this study. The exclusion criteria were patients with uncontrolled hypertension

and diabetes mellitus, history of psychiatric illness, pregnant patients, BMI >30kg/m², and known allergy to study drugs. All enrolled patients were randomly divided into two groups Group A and Group B using computer generated random numbers.

This study is a prospective, randomized, double-blinded comparative study. The sample size was calculated based on a previous study,^[15] taking difference in the mean arterial pressure between the propofol (37%) and ketofol (7%) to be the effective size, a power analysis indicated that a minimum of 20 patient in each group would be needed with power of 80% and alpha error 5% to reject null hypothesis. To allow for lack of eligibility, dropouts and considering 25% chances for converting to open surgery, sample size was raised to 40 patients in each group.

All patients were kept fasting for 8 h and were premedicated with Ranitidine 150mg, Metoclopramide 10 mg, and Lorazepam 1 mg orally on night before surgery. On arrival of patient to the operation theatre standard ASA monitors like non-invasive blood pressure (NIBP), Pulse oximetry, Electrocardiogram (ECG) were attached and baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (SPO₂) were recorded. ETCO₂ was also kept available. An 18 G intravenous (IV) cannula was secured and Ringer Lactate was started with a bolus of 5 ml/kg over 15 min followed by a maintenance of 50 ml/h. Patients were pre-oxygenated with 100% oxygen for 3 min, glycopyrolate (0.2mg), midazolam (0.02 mg/kg), fentanyl (2 mcg/kg) were given intravenously followed by the study drug. The study drug was prepared and administered by the consultant who was not part of the study.

Group A received 1 mg/kg propofol plus 1 mg/kg ketamine (10 mg/ml dilution) diluted to 20 ml in a syringe and Group B received 2 mg/kg propofol diluted to 20 ml with normal saline in a syringe as induction agents.

After IV induction the feasibility of mask ventilation was checked and if the ventilation was adequate Vecuronium (0.1 mg/kg) was given. Once the patient was fully paralyzed he/she was intubated with an appropriate size endotracheal tube and position checked by capnography and bilateral air entry. The tube was then secured at the appropriate lip level and positive pressure ventilation was initiated with the ventilator. Anaesthesia was maintained by O₂:N₂O mixture (50:50), sevoflurane 1–1.5% and neuromuscular blockade was maintained with intermittent doses of Vecuronium as required throughout the surgery. Paracetamol 1 gram and Ondansetran 4 mg IV were given 30 min before the end of surgery.

At the completion of the surgery oropharyngeal suction was done, inhalation agent was stopped and patient was ventilated with 100% oxygen till recovery of spontaneous respiratory efforts, then residual neuromuscular blockade was reversed with IV neostigmine (50 mcg/kg) and glycopyrolate (10 mcg/kg). Endotracheal tube cuff was deflated and patients were extubated once the patient demonstrated resumption of regular spontaneous breathing, the ability to follow verbal commands or purposeful movements. The anesthetist blinded to the study recorded the following parameters SBP, DBP, MAP, HR, and SPO₂ before induction, 1 min after induction, 1 min after intubation and every 5 min after intubation until pneumoperitonium created. Postoperative nausea and vomiting (PONV) and shivering were graded using a four point scale [Tables 1 and 2].

Dexamthasone 8 mg and Tramadol 25 mg IV would have been given as rescue drugs for vomiting and shivering with grade >2. All postoperative parameters were recorded every 15 min till 2 h in the postoperative recovery room and ward.

Statistical analysis

Patients demographic data and clinical parameters were recorded and entered in the excel sheet. Mean ± SD was used to express the continuous variables. They were tested for the normality using the Kologrov–Smirnov test. Repeated measure ANOVA was used to compare the hemodynamic parameters (SBP, DBP, MAP, SPO₂, HR) over the various time intervals. The number of the patients who experienced PONV, pain, and shivering in each group were expressed as categorical variable and reported as percentages and compared using Chi-square test. All statistical analysis were carried out at 5% level of significance and *P* value <0.05 was considered as statistically significant. All statistical analysis were carried out using SPSS software 20.0.

Results

In this study 39 patients completed the study in group A, one patient was excluded because the surgery was converted to open surgery. In group B, 38 patients completed the study, two patients were excluded because in one patient surgery was converted to open surgery and another patient required additional drugs to maintain the hemodynamics [Figure 1].

The demographic profile of the study participants were comparable and they are not statistically significant [Tables 1 and 3]. The hemodynamic parameters were recorded at baseline (T1), 1 min after induction (T2), 1 min after intubaion (T3), 5 min after intubation (T4), and after pneumoperitoneum (T5).

The SBP in group A were 108.44 ± 14.10, 117.64 ± 17.19 and 110.49 ± 15.06 mm Hg at 1 min after induction (T2), 1 min after intubation (T3), and 5 min after intubation (T4), respectively . In group B, SBP were 90.84 ± 13.03, 104 ± 17.80, 102.42 ± 13.955 mm Hg at T2, T3, and T4 respectively and it was statistically significant with *P* < 0.05 [Figure 2].

The DBP in group A were 65.69 ± 8.60, 73.51 ± 11.46 and 70.62 ± 12.53 mmHg, respectively, at T2, T3, and T4. In group B, DBP were 61.29 ± 8.74, 68.53 ± 11.43, 67.47 ± 10.21 mm Hg at T2, T3, and T4, respectively, and it was statistically significant at T2 with *P* < 0.05 [Figure 3].

Table 1: Postoperative Nausea and Vomiting grading

Grade	Features
Grade 0	No nausea/vomiting
Grade 1	Nausea alone
Grade 2	Vomiting alone
Grade 3	Vomiting 2 times or more in 30 minutes interval

Table 2: Postoperative shivering grading

Grade	Features
Grade 0	No shivering
Grade 1	Mild - shivering localized to neck/thorax seen as artifact in ECG or felt by palpation
Grade 2	Moderate – intermittent involving of upper extremity ± thorax
Grade 3	Severe – generalized shivering / sustained upper extremity and lower limb shivering.

Table 3: Distribution of demographic data among the groups

Demographic data	Group A	Group B
Age (yrs) Mean±SD	33.95±7.84	33.47±8.97
Sex (M/F)	1/38	6/32
BMI (kg/m ²) Mean±SD	22.72±3.94	22.99±3.94
ASA (I/II)	35/4	36/2

SD - Standard deviation, BMI - Body mass index.

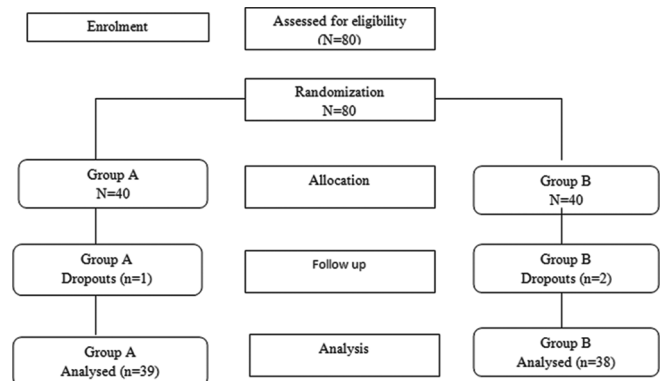


Figure 1: Consort flowchart

The MAP in group A were 79.92 ± 9.34 , 89.44 ± 12.12 and 83.15 ± 10.95 mm Hg at T2, T3, and T4, respectively. In group B, MAP were 72.58 ± 10.03 , 80.26 ± 13.44 and 78.95 ± 9.61 mm Hg at T2, T3, and T4, respectively, and it was statistically significant at T2, T3, and T4 with $P < 0.05$ [Figure 4]. The HR in group A were 90.13 ± 10.11 , 88.87 ± 11.22 and 85.59 ± 9.90 bpm at T2, T3, and T4, respectively. In group B, HR were 96.89 ± 16.78 , 87.05 ± 19.69 and 90.05 ± 13.65 bpm at T2, T3, and T4, respectively, and it was statistically significant at T2 with $P < 0.05$ [Figure 5]. The mean time for spontaneous eye opening were 4.95 ± 1.82 min and 1.82 ± 1.39 min in group A and B, respectively, with $P < 0.001$ which was statistically significant [Figure 6]. The mean time for obeying commands were 6.79 ± 2.33 min and 3.16 ± 1.48 min in group A and B, respectively, with $P < 0.001$ which was statistically significant [Figure 7].

In group A, 22 patients had postoperative vomiting and in group B, 2 patients had postoperative vomiting with $P < 0.004$ which was statistically significant [Figure 8]. No patients in either group had postoperative shivering.

Discussion

The use of laparoscopy has revolutionized the surgical procedure with its advantages of reduced morbidity with early

recovery, minimized incision size, and trauma with reduced postoperative discomfort and wound infections. However, laparoscopic surgery is not without its own specific risks, either due to the risks associated with individual laparoscopic techniques or due to the physiological changes associated with the creation of a pneumoperitoneum. The combined use of ketamine and propofol has been addressed with great success in anaesthesiology for many years. Both propofol and ketamine have a rapid onset, and are safe and effective for sedation and analgesia in minimally invasive procedures.^[16,17] Ketofol is a combination of ketamine and propofol in a single syringe and can be prepared in any desired concentration. Ketamine and propofol are physically compatible for 1 h at 23°C and have been combined in different proportions for different surgical procedures.^[18,19]

In our study we compared propofol and ketofol as an induction agents to achieve a stable hemodynamic profile during intubation and creation of pneumoperitoneum.

The results of this study demonstrated that ketofol (1:1 mixture) produced better haemodynamic stability when compared to propofol group. The HR, SBP, DBP, and MAP showed better stability at 1 min after induction, 1 min after intubation and after creation of pneumoperitoneum in ketofol group when compared to propofol group and it was statistically significant.

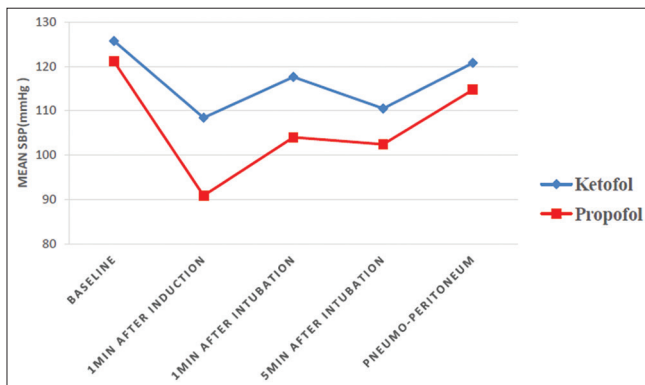


Figure 2: Distribution of mean SBP among the groups

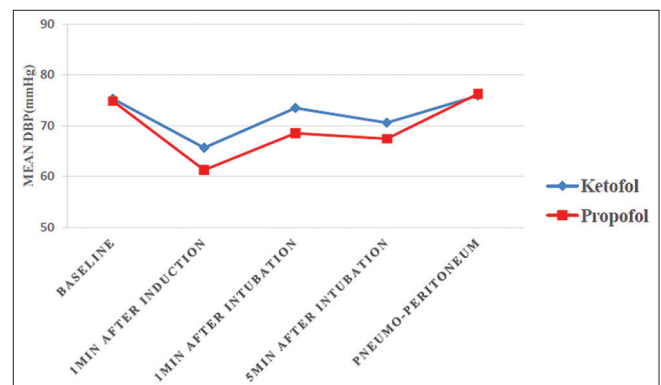


Figure 3: Distribution of DBP among the groups

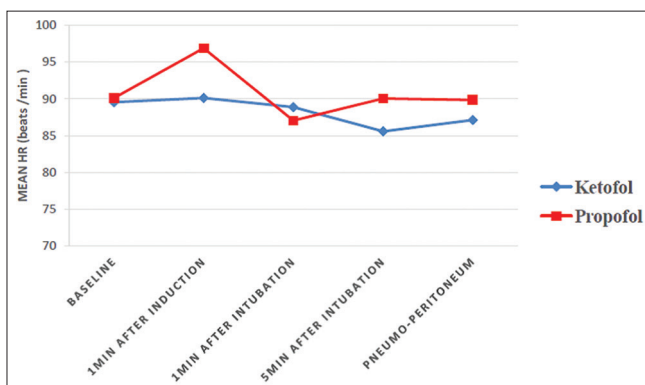


Figure 4: Distribution of MAP among the groups

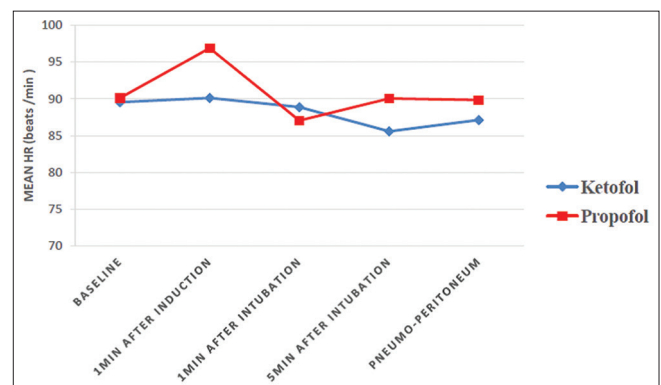


Figure 5: Distribution of HR among the groups

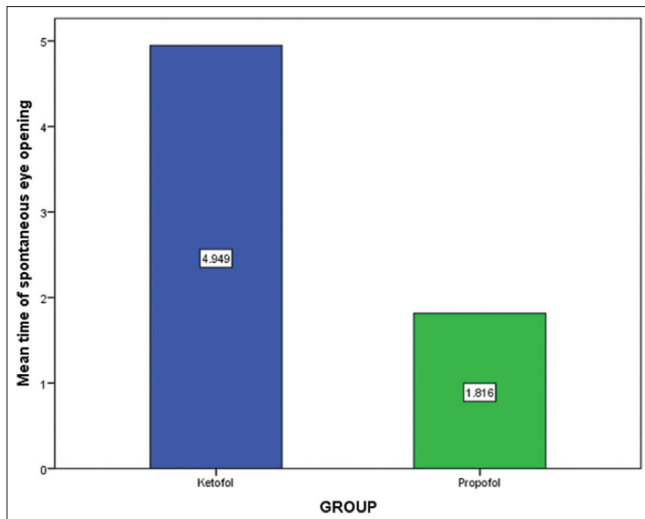


Figure 6: Mean time taken for spontaneous eye opening among the groups

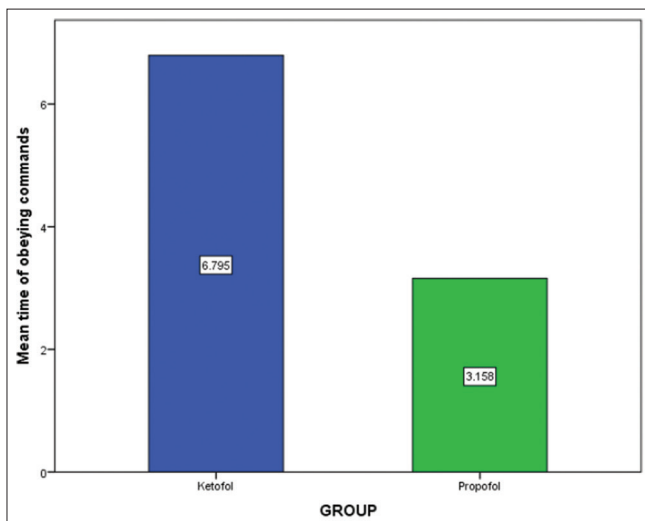


Figure 7: Mean time taken for obeying commands among the groups

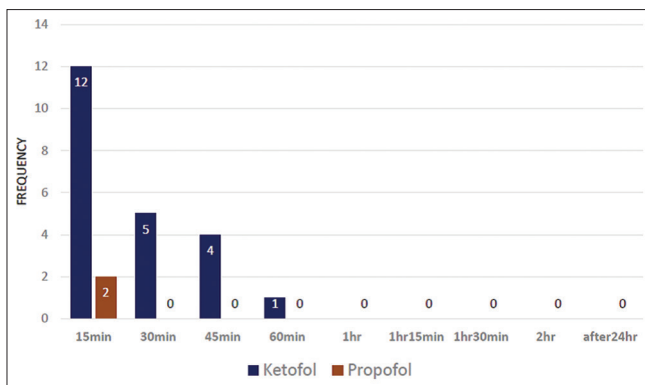


Figure 8: Distribution of PONV among the groups

Hamid Kayalha *et al.*^[20] conducted a similar study using ketofol and propofol as induction agents on hemodynamic stability in 96 ASA I and ASA II patients undergoing elective laparotomy surgery. Ketofol group received 1.5 mg/kg

ketofol (ketamine and propofol mixture was prepared 5 mg/ml ketamine & 5 mg/ml propofol mixture (1:1) in 20 ml syringe) and propofol group received 1.5 mg/kg as an induction dose. They found that heart rate, systolic, diastolic, and mean arterial blood pressure was significantly lower in propofol group after induction, 5 min and 10 min after intubation when compared to ketofol group. The results were similar to our study.

Atashkhoyi S *et al.*^[15] conducted a similar study in 60 patients undergoing diagnostic gynecological laparoscopic procedures under general anesthesia. Patients in the study group were anesthetized with ketamine 0.5 mg/kg and propofol 1–2.5 mg/kg, and patients in the placebo group were anesthetized with normal saline and propofol. They found that HR and MAP decreased during induction in placebo group when compared to study which is similar to our study.

In our study the mean duration of recovery was shorter in propofol group when compared to ketofol group. The mean duration of spontaneous eye opening was 1.82 min and 4.95 min in propofol and ketofol group, respectively. Similarly the mean time duration of recovery for obeying verbal commands were shorter in propofol group (3.16 min) when compared to ketofol group (6.79 min) and the difference was statistically significant.

A similar study was conducted by Ramakrishna *et al.*^[21] in 80 patients undergoing surgery under ambulatory anesthesia. They administered propofol slowly in one group till the end point of induction and another group received ketamine 0.5 mg/kg IV slowly followed by propofol till the end point of induction. They found there is decrease in MAP, mean systolic blood pressure, mean diastolic blood pressure in propofol group when compared with ketofol group. They also found that time to recovery was significantly delayed in ketofol group (9.8 min) when compared to propofol group (2.63 min) which is similar to our study.

Ketofol has its major impact on trend of blood pressure (SBP, DBP, and MAP) and heart rate. This trend follows a stable pattern after induction through intubation, post-intubation after creation of pneumoperitoneum. Such stable trend is probably due to decrease in sympathetic stimulation by somatic pain stimulatory input. This implies the fact that a major barrier to haemodynamic stability is the over-activation of sympathetic nervous system. This may be the reason for one patient in propofol group requiring additional drug for maintaining hemodynamic stability.

In our study we found that incidence of postoperative nausea and vomiting was higher in ketofol group than the propofol group. Similarly, Aboeldahab H *et al.*^[13] conducted a randomized study in 60 patients undergoing hernia repair under general anesthesia. Three groups, Group P, Group K, and Group KP received 2 mg/kg of propofol, 2 mg/kg ketamine and 1ml for every 5 kg (100 mg ketamine (10 mg/ml + 100 mg 1% propofol in 20 ml syringe) respectively as induction agents. They found that HR and MAP decreased in Group P after induction when compared to Group KP which is similar to our study. They also found that the incidence of postoperative nausea and vomiting were significantly less in propofol and ketofol groups when compared with ketamine group with *P* value <0.05 which is similar to our study. It was estimated that the incidence of postoperative nausea and vomiting (PONV) in patients who undergo surgeries under general anaesthesia was reported to range from 20–30%. Laparoscopic surgery is also known to increase the incidence of PONV. The PONV in the ketofol group is relatively high which may be due to the synergistic effect of laparoscopic surgery and ketamine which resulted in increased emesis.

There were no postoperative shivering and delirium in any of the patients in either group.

Conclusion

This study comparing the haemodynamic stability between propofol and ketofol in patients undergoing laparoscopic surgeries under general anesthesia has shown that ketofol offers a more stable haemodynamic stability without apparent side effects. However, the time to recovery for eye opening and obeying commands were longer in the ketofol group. The incidence of vomiting is also high in ketofol group.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Bajwa SJS, Kulshrestha A. Anaesthesia for laparoscopic surgery: General vs regional anaesthesia. *J Minimal Access Surg* 2016;12:4-9.
- Hatzinger M, Kwon St, Langbein S, Kamp S, Häcker A, Alken P, Hans Christian Jacobaeus: Inventor of human laparoscopy and thoracoscopy. *J Endourol* 2006;20:848-50.
- Barash PG, Cullen BF, Stoelting RK. *Clinical Anaesthesia*. 8th ed. Wolters Kluwer; 2017. p. 1261-72.
- McLaughlin JG, Scheeres DE, Dean RJ, Bonnell BW. The adverse hemodynamic effects of laparoscopic cholecystectomy. *Surg Endosc* 1995;9:121-4.
- Joris JL, Chiche J-D, Canivet J-LM, Jacquet NJ, Legros JJY, Lamy ML. Hemodynamic changes induced by laparoscopy and their endocrine correlates: Effects of clonidine. *J Am Coll Cardiol* 1998;32:1389-96.
- Hug CC Jr, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, *et al.* Hemodynamic effects of propofol: Data from over 25,000 patients. *Anesth Analg* 1993;77:S21-9.
- Bassett KE, Anderson JL, Pribble CG, Guenther E. Propofol for procedural sedation in children in the emergency department. *Ann Emerg Med* 2003;42:773-82.
- Sahinovic MM, Struys MMRF, Absalom, AR. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clin Pharmacokinet* 2018;57:1539-58.
- Hasanein R, El-Sayyed W, Nabil N, Elsayed G. The effect of combined remfentanil and low dose ketamine infusion in patients undergoing laparoscopic gastric bypass. *Egypt J Anesth* 2011;27:255-60.
- Bauchat JR, Higgins N, Wojciechowski KG, Mc Carthy RJ, Toledo P, Wong CA. Low-dose ketamine with multimodal postcesarean delivery analgesia: A randomized controlled trial. *Int J Obstet Anesth* 2011;20:3-9.
- Menkiti ID, Desalu I, Kushimo OT. Low-dose intravenous ketamine improves postoperative analgesia after cesarean delivery with spinal bupivacaine in African parturients. *Int J Obstet Anesth* 2012;21:217-21.
- White PF. Clinical pharmacology of intravenous induction agents. *Int Anesthesiol Clin* 1988;26:98-104.
- Aboeldahab H, Samir R, Hosny H, Omar A. Comparative study between propofol, ketamine and their combination (ketofol) as an induction agent. *Egypt J Anaesth* 2011;27:145-50.
- Akin A, Guler G, Esmoğlu A, Bedirli N, Boyacı A. A comparison of fentanyl-propofol with a ketamine-propofol combination for sedation during endometrial biopsy. *J Clin Anesth* 2005;17:187-90.
- Atashkhoyi S, Negargar S, Hatami-Marandi P. Effects of the addition of low-dose ketamine to propofol-fentanyl anaesthesia during diagnostic gynaecological laparoscopy. *Eur J Obstet Gynecol Reprod Biol* 2013;170:247-50.
- Akin A, Esmoğlu A, Tosun Z, Gulcu N, Aydoğan H, Boyacı A. Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. *Int J Pediatr Otorhinolaryngol* 2005;69:1541-5.
- Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2007;49:23-30.
- Saeed E. Ketofol infusion as a procedural sedation and analgesia modality for minor orthopedic surgeries: Evaluation of dose-outcome relation. *Ain Shams J Anaesthesiol* 2011;4:63-74.
- Erden IA, Pamuk AG, Akinci SB, Koseoglu A, Aypar U. Comparison of two ketamine-propofol dosing regimens for sedation during interventional radiology procedures. *Minerva Anesthesiol* 2010;76:260-5.
- Kayalha H, Kolahdoozha M, Yaghoobi S, Khezri MB, Mohajerani SA, Jahangirifard A. Effect of Ketofol instead of Propofol on hemodynamic stabilization for induction of Anesthesia in Laparotomy. *J Cell Mol Anesth* 2017;2:50-4.
- Rao AR, Kumar SV, Bindu AH. Comparative study between propofol and propofol with ketamine in ambulatory anaesthesia. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)* 2015;14:1-9.