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Comparison of low dose ketamine and butorphanol as an adjuvant to propofol for induction in patients undergoing laparoscopic cholecystectomy: A randomized clinical study

Authors
Rampal Singh[1], Sarfraz Ahmad[2], Ankur Garg[2], Pragati Saxena[3], Malti Agrawal[1], Gopal Krishan[4*], Ekta Singh[3]
[1]Professor, Department of Anaesthesiology, RMCH Bareilly
[2]Assistant Professor, Department of Anaesthesiology, RMCH Bareilly
[3]Junior Resident, Department of Anaesthesiology, RMCH Bareilly
[4]Associate Professor, Department of Anaesthesiology, RMCH Bareilly
*Corresponding Author
Gopal Krishan

Abstract
Introduction: *General anaesthesia is associated with marked cardiovascular changes. Induction with propofol is accompanied by decrease in mean blood pressure and heart rate. Ketamine and butorphenol provides stable perioperative hemodynamics during general anaesthesia.*
Aims and Objectives: *The aim of this study was to evaluate the efficacy of intravenous low dose ketamine with intravenous butorphanol on hemodynamic stability during laryngoscopy and intubation, intraoperative hemodynamics and postoperative pain.*
Methods and Materials: *It was a prospective randomised clinical study in which 100 ASA grade 1 or 2 patients who were posted for elective laparoscopic cholecystectomy under general anaesthesia, were enrolled into one of the two groups according to the agents to be given as an adjuvent for induction of general anaesthesia. Group A patients received 0.3mg/kg ketamine and group B patients received butorphanol 0.02mg/kg by intravenous route.*
Conclusion: *The present study observed excellent endotracheal intubation conditions with propofol and ketamine combination as compared to propofol and butorphanol combination. Analgesic effects of ketamine and butorphanol in the postoperative period were similar and helped painless shifting of patients.*
Keywords: *Butorphanol, Hemodynamic response, Endotracheal intubation, Ketamine, Laparoscopic cholecystectomy.*

Introduction

General anaesthesia is associated with marked cardiovascular changes, induction with propofol is accompanied with decrease in mean blood pressure and heart rate. Ketamine is well known for its effect in increasing mean blood pressure and heart rate, thus when used as an adjunct, it provides stable perioperative hemodynamics during general anaesthesia by counteracting the cardio depressant effects of propofol. The

sympatholytic effects of propofol are counteracted by ketamine, and stable perioperative hemodynamic conditions are achieved.[1]

Butorphanol like all other opioids produce antinociception through μ-receptor agonist activity, it also activates NMDA receptors, resulting in hyperalgesia and the development of tolerance. Antinociception produced by ketamine may be produced via different mechanisms of action: NMDA receptor antagonism, interaction with spinal μ receptors, and activation of the descending pain inhibitory monoaminergic pathways at the spinal level. The affinity of ketamine is higher for NMDA receptors than that for μ receptors or other non-NMDA receptors. Thus, even a small intravenous dose interacts more selectively with NMDA receptors and produces antinociception and the effect is not reversed by naloxone, suggesting that the μ-receptor agonistic activity is not involved in pain control. Thus, if given in subanesthetic dose before incision, ketamine might have role in evoking attenuation of sustained and severe postoperative pain and secondary hyperalgesia via central desensitization or antagonisation of NMDA activity.[2]

Various studies have also shown that patients receiving relatively large intraoperative dose of opioid complained more postoperative pain and consumed more analgesic, suggesting that administration of large doses of opioids causes hyperalgesia and acute opioid tolerance.[2]

Till date opioids along with adjuvant therapies, such as nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentin, and regional techniques are the mainstay for the management of acute pain. However, these therapeutic options may be associated with side effects, viz. opioid tolerance, organ failure, and various drug interactions, and thus are not desirable in all patients.[3] Intravenous subanesthetic ketamine when given as an adjunct to general anaesthesia, reduced postoperative pain and opioid requirements.[4]

We therefore tested this hypothesis that ketamine if given in subanesthetic dose as an adjuvant to propofol for induction is associated with improved hemodynamic stability during laryngoscopy and tracheal intubation, stable intraoperative hemodynamics and reduced postoperative pain in comparison to butorphanol.

Aims and Objectives

The aim of this study was to compare the efficacy of intravenous low dose ketamine with intravenous butorphanol on hemodynamic stability during laryngoscopy and intubation, intraoperative hemodynamics and postoperative pain.

Methods and Materials

After approval from the institutional ethical committee, the present one year study was conducted in the department of anaesthesiology, Rohilkhand Medical College and Hospital, Bareilly starting from November 2018 to October 2019.

The current study was carried out on 100 patients of American Society of anesthesiology classes I or II. Methodology of the study was according to ethical principles for medicine research involving human subjects outlined in the declaration of Helsinki.

Thorough pre-anesthetic check-up was done one day prior to surgery and informed written consent for participation in the study was taken. On the night before surgery, Tab. Ranitidine 150mg, Tab. Metaclopramide10 mg and Tab. Alprazolam 0.25 mg was given orally. Patients were advised to remain fasting for 8 hours before surgery.

On the day of surgery, after arrival in the operating room an 18-gauge IV catheter was placed in the forearm, and 15 mL/kg of Ringer's lactate solution was infused over a 20-min period followed by maintenance fluid according to Holliday-Segar formula.

In the operating room each patient was routinely monitored by pulseoximetry, noninvasive blood pressure (NIBP) and electrocardiography (ECG).

Measurements of pre-induction systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR), fingertip pulse-derived oxygen saturation (SpO_2) and VAS score were considered as baseline values**.**

Before surgery, patients were instructed to use a 10-point visual analogue scale (VAS) with 0 identifying no pain and 10 the worst imaginable pain.

Patients were randomly assigned, according to computer generated random number table, to one of the two groups according to the agents to be employed. Group A patients received 0.3 mg/kg ketamine while Group B patients received butorphanol 0.02 mg/kg, by intravenous route.

Inj. midazolam 0.02 mg/kg and inj. Glycopyrrolate 0.004mg/kg was given by intravenous route. Induction was done with 2 mg/kg propofol. Vecuronium 0.1 mg/kg was given as an intravenous bolus to assist tracheal intubation, which was carried out 3-4min subsequent to inj. Vecuronium. The patients were manually ventilated by bag and mask for 4 min with 100% oxygen just before oro-tracheal intubation. Direct laryngoscopy was performed using a Macintosh blade, and tracheal intubation was carried out. Patients were subsequently ventilated with a tidal volume of 8 ml/kg and a respiratory rate of 12/min. Anaesthesia was maintained with isoflurane 0.8 % and 65% nitrous oxide in oxygen and inj. vecuronium 1 mg i.v. every 20 minutes.

Hemodynamic parameters viz. SAP, DAP, MAP, HR and SPO_2 were monitored preoperatively, after intubation and there after every 15minutes till extubation.

Inj. Ondansetron 0.1 mg/kg i.v. was given 15 min prior to extubation. After completion of surgery and achieving complete hemostasis and placement of dressing, complete reversal of residual neuromuscular blockade was done by inj. Glycopyrrolate 0.004 mg/kg and inj. Neostigmine 0.05 mg/kg by iv route. Nitrous oxide was discontinued and 100% O2 administered. Patients were extubated after thorough oral and endotracheal suctioning.

Patients were transferred to the post anesthetic care unit (PACU), after tracheal extubation. They remained in the unit for at least 4 h and oxygen was given via a face mask at a rate of 6 L/min.

Pain intensity of the patient was assessed by VAS score at extubation and thereafter every 15-min interval during the first hour and then half hourly for 4 hours. Rescue analgesia was given when patient complained of VAS score ≥ 4. The time from giving of ketamine/ butorphanol until the first request for analgesic was recorded. Postoperative need for analgesic was considered as end point.

Patients with refusal for procedure, ASA grade III or more,age below 18 years or above 65 years, history of hypersensitivity to any of the drugs used ,anticipated difficult airway, emergency Surgery, pregnancy, history of hypertension/ hypotension, history of seizures and history of opioid addiction were excluded from the study.

Statistical Analysis: The data from the present study was systematically collected, compiled and statistically analyzed. Descriptive & inferential statistical analysis were derived from results on continuous measurements, presented as mean ± SD while results on categorical measurements were presented in numbers (%). Student t test was used to find the significance of the study parameters on a continuous scale between 2 groups (intergroup analysis).

The p value was determined to evaluate the level of significance, $p<0.05$ was considered as significant at 5% significance level, while $p<0.01$, significant at 1% was considered as highly significant. Chi Square/ Fisher's exact test was used to find the significance of the study parameters on the categorical scale where ever applicable between 2 groups.

The statistical data analysis was done by Microsoft Excel 2016 and Microsoft Word 2016 it was used to generate graphs, charts and tables.

The data were entered on a Microsoft Excel spread sheet and imported into Statistical Package for Social Sciences (SPSS) version 23 for statistical analysis. Data was presented in mean and standard deviation. Independent t-test was performed to find significant difference in different variables between two groups.

Observations and Results

In this study group A and group B were comparable in terms age, sex distribution, body weight, ASA grade and duration of surgery. There was no statistically significant difference between two groups (p>0.05). (Table no. 1)

In our study, the mean heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure after laryngoscopy, at 15 minutes, at 30 minutes, at 45 minutes, at 60 min, at 75 min, at 90 min, at 105 min, 120 min, before extubation and after extubation were significantly lower in group A (Ketamine) as compared to group B (Butorphanol). The hemodynamics were found to be more stable in the ketamine group compared to Butorphanol group with less variation reported with ketamine over different time intervals. (Table no. 2 and Graph no. 1, 2)

In current study, there was no significant difference in mean VAS score between group A and group B at different time interval (p>0.05). (Table no. 3)

During our study, no serious adverse effects like respiratory depression, sedation, postoperative nausea and vomiting, motor blockade, dysphoria or hallucinations were noted.

Table 1: Demographic Profile

Parameters	Group A (n=50)	Group B (n=50)	*p*-value
Age (Years)	39.16±9.47	38.8±11.28	0.863
Weight(Kg)	63.78±13.8	65.23±12.6	0.657
Gender (M/F)	11/39	10/40	0.486
ASA (I/II)	41/09	40/10	0.783
Duration of surgery(Min.)	71.64±26.8	72.86±27.6	0.823

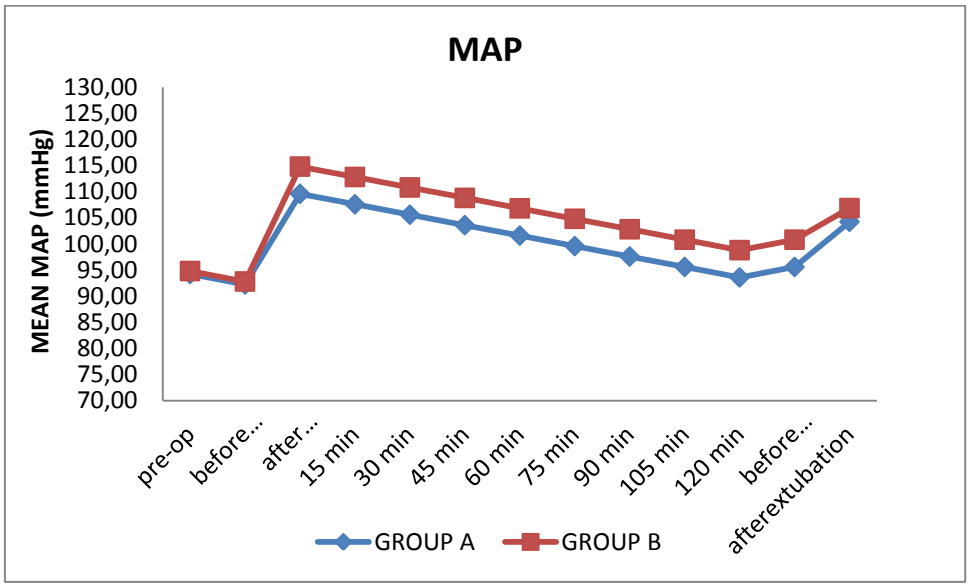
Table 2: Comparison of mean Heart Rate in Group A and Group B at Different Time Intervals

HEART RATE (beat per min)	**GROUP A(n=50)**	**GROUP B(n=50)**	***p*-value**
	(MEAN±SD)	**(MEAN±SD)**	
pre-op (Baseline)	(81.28±2.56)	(81.9±2.30)	0.206
before laryngoscopy	(80.96±2.68)	(81.68±2.31)	0.153
after laryngoscopy	(100.96±2.66)	(103.68±2.32)	<0.001
15 min	(96.96±2.68)	(99.68±2.31)	<0.001
30 min	(93.96±2.64)	(96.68±2.34)	<0.001
45 min	(91.96±2.62)	(94.68±2.31)	<0.001
60 min	(89.96±2.64)	(92.68±2.30)	<0.001
75 min	(87.96±2.66)	(90.68±2.32)	<0.001
90 min	(85.96±2.68)	(88.68±2.31)	<0.001
105 min	(81.96±2.68)	(86.68±2.34)	<0.001
120 min	(79.96±2.62)	(84.68±2.36)	<0.001
before extubation	(77.96±2.64)	(82.68±2.35)	<0.001
Afterextubation	(82.96±2.68)	(87.68±2.33)	<0.001

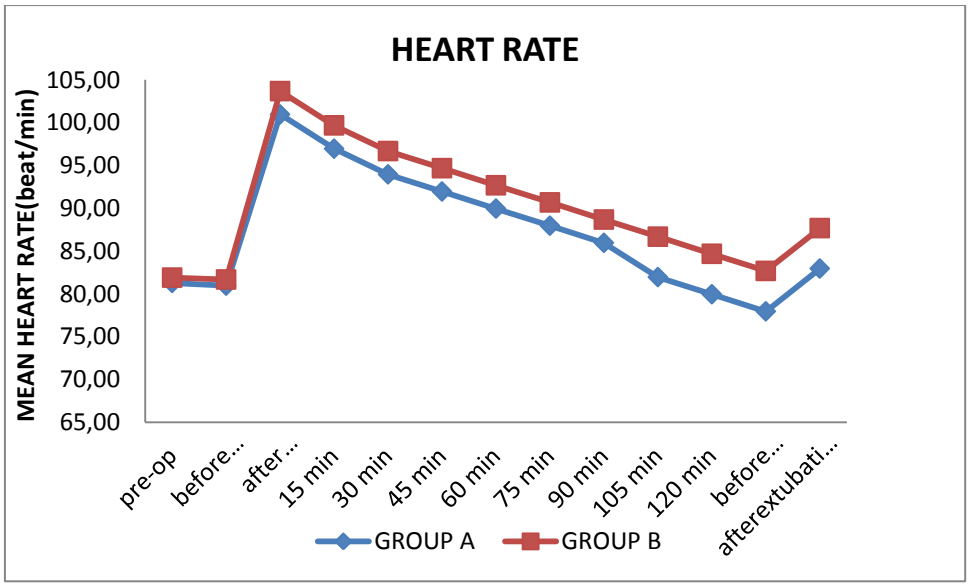
Table 3: Comparison of Mean Pain Score (Vas) in Between Group A and Group B at Different Time Intervals

VAS	GROUP A (n=50) (MEAN± SD)	GROUP B (n=50) (MEAN± SD)	*p*-value
Pre -op	(0.70±0.84)	(0.80±0.81)	0.545
After extubation	(1.40±0.97)	(1.54±0.91)	0.458
15 min	(2.44±1.07)	(2.52±0.95)	0.694
30 min	(2.72±1.05)	(2.76±0.98)	0.844
45 min	(3.04±0.95)	(3.11±0.91)	0.735
60 min	(3.29±1.2)	(3.40±1.1)	0.647
90 min	(3.8±0.83)	(3.98±0.78)	0.603
120 min	(4.26±0.78)	(4.34±0.64)	0.617
150 min	(4.29±0.79)	(4.34±0.68)	0.747
180 min	(4.30±0.84)	(4.37±0.72)	0.742
210 min	(4.35±0.89)	(4.42±0.76)	0.739
240 min	(4.58±0.9)	(4.73±0.53)	0.458

Graph 1: Comparison of mean arterial blood pressure between Group A and Group B



Graph 2: Comparison of mean heart rate between Group A and Group B



Discussion

Our study was a novel study in which we compared ketamine (0.3mg/kg) and butorphanol (0.02mg/kg) as an adjuvant to propofol for induction and effect on hemodynamic changes during laryngoscopy and intubation, intra-operative hemodynamics and postoperative pain.

Hemodynamic Profile

Due to opposing effects of propofol and ketamine on hemodynamic parameters, when given together at a lower dose, there is a decreased incidence of overall side effects and hemodynamic stability is maintained.

In our study the hemodynamics were found to be more stable in the ketamine group as compared to butorphanol group. Like our observations **Abbasivash *et al,*** [5] **Bajwa SJ *et al,*** [6] **Basagan-Mogo E *et al,*** [7] **Yang *et al,*** [8] **Aasim SA *et al*** [9] and **Baradari AG *et al*** [10] also concluded in their studies that propofol-ketamine co-induction provides more hemodynamic stability in comparison to propofol alone in patients scheduled for elective non-cardiac surgery.

Like our study **Kulkarni KR** and **Dalal NR** [11] stated that postinduction and post LMA insertion group, ketamine with propofol showed significantly lesser fall in systolic (SBP) and diastolic blood pressure (DBP) as compared to group butorphanol and ketamine. So, these studies have showed more stable hemodynamics with ketamine compared to butorphenol.

Saxena D *et al* [12] evaluated both preemptive and intra-operative effect of ketamine in a dose of 0.5 mg/kg/h, in patients undergoing laparoscopic surgery. Like our study they also found that ketamine provides good hemodynamic control during laryngoscopy and intubation and a stable hemodynamics during the surgery.

Rekhi BK *et al* [13] compared the effect of butorphanol, fentanyl and nalbuphine in obtundation of hemodynamic responses in laparoscopic cholecystectomy. In their study they found that fentanyl and nalbuphine when given intravenous five minutes prior to induction of anaesthesia provides better obtundation of hemodynamic responses to laparoscopic cholecystectomy as compared to butorphanol. This finding was in accordance to our study where butorphanol also provided lesser hemodynamic stability than ketamine.

Firoozabadi MD and Ebadi A [14] in a double blinded randomized, clinical trial examined the effect of the combination of Ketamine and thiopental on hemodynamic changes of patient during intubation in cesarean section under general anaesthesia. Like our study they found that combination of ketamine with thiopental can create better hemodynamic stability in patients after tracheal intubation.

In a randomised study **Rajan S *et al*** [15] evaluated effect of 0.25 mg/kg ketamine on hemodynamic responses during caesarean section under general anaesthesia as compared to normal saline. Their study was in accordance with our study as they found that IV ketamine 0.25 mg/kg can be safely used as an adjunct analgesic and amnesic to attenuate hemodynamic responses during caesarean section under general anaesthesia.

Honarmand A and **Safavi M** [16] compared the hemodynamic responses occurring during induction of anaesthesia by three methods: (a) thiopental added to fentanyl, (b) thiopental added to ketamine, and (c) thiopental added to fentanyl and ketamine. Unlike our studies they found that induction of anaesthesia with thiopental added to fentanyl and ketamine shows a superior degree of protection in preventing hemodynamic fluctuations than thiopental added to fentanyl, or thiopental added to ketamine.[2] The better hemodynamic stability in fentanyl with ketamine group in comparison to ketamine alone can be due to synergistic action of fentanyl.

Philip BK *et al* [17] compared effect of butorphanol (20 mcg/kg) vs fentanyl (1mcg/kg) on hemodynamic variables (viz. pulse rate and diastolic blood pressure) in 60 women undergoing ambulatory laparoscopic surgery. They observed a decrease in these parameters after intubation, with lower pulse rate and diastolic blood pressure with

reported with butorphanol, unlike our study, where we found a significant rise in these parameters with butorphanol. These differences may be attributed to different population group in our study.

Postoperative Pain

Postoperative analgesia is essential for normal functioning and early recovery, therefore reducing postoperative complications in patients after surgery. It also decreases length of hospital stay and cost of patient care.

Our results demonstrated that a single intravenous subanesthetic dose of ketamine or butorphanol administered before induction provides good postoperative analgesia and delays the first request for rescue analgesic.

Similar to our studies, **Laskowski K *et al,*** [18] **Singh H *et al***,[19] **Saxena D *et al***[12] and **Weilin Z *et al*** [20] also concluded that intravenous ketamine provides improved quality of pain control and also decreases opioid consumption, and thus can be used as an effective adjunct for postoperative analgesia.

In accordance with our study **Ye F *et al***[21] also conducted a meta analysis and concluded that ketamine appeared to significantly reduce postoperative pain and narcotic use in patients undergoing laparoscopic cholecystectomy.

Similar results were found in studies of **Schwesinger WH *et al***, [22] who confirmed that the even trans nasal administration of butorphanol in a 1- 2 mg dose is rapid, safe, and effective in controlling postsurgical pain.

Our results, however, are different with the results of **Darabi *et al***, [23] who could not demonstrate any reduction in analgesic consumption in the groups receiving ketamine. This could be due to both a smaller dose of ketamine used in their study along with simultaneous use of rectal diclofenac and intravenous paracetamol, which may be sufficient to take care of postoperative pain in inguinal herniorrhaphy which is a less painful procedure, thus masking any preemptive analgesic effects of ketamine.

Similarly, **Dullenkopf *et al,***[24] did not find any preemptive analgesic effects of ketamine. However, they had a heterogenous population of general surgical and orthopedic patients, and dose of ketamine used in the study may have been inadequate for the painful surgical procedures performed. It is proposed that adequate sensory blockade is necessary for preemptive effect of ketamine to be exhibited.

Conclusion

In the present study, we observed excellent endotracheal intubation conditions with propofol and ketamine combination as compared to propofol and butorphanol combination. Analgesic effects of ketamine and butorphanol in the postoperative period were similar and helped painless shifting of patients.

Thus, we conclude from our study that low dose ketamine is a better choice than butorphanol as co-induction agent for endotracheal intubation and providing stable hemodynamics under propofol anaesthesia for surgeries of short duration. It causes limited cardio-respiratory depression, thus provides better intubating conditions and lesser airway complications.

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