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To Evaluate the Efficacy of Low Dose Ketamine in Attenuating Haemodynamic Stress Response Induced by Pneumoperitoneum in Laparoscopic Cholecystectomy Under General Anaesthesia: A Prospective Study

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Abstract

Background: Pneumoperitoneum required for laparoscopy causes cardiovascular and pulmonary stress responses. Various pharmacological interventions have been used to attenuate those sympathetic response. N-methyl-D-aspartate(NMDA) receptor antagonists like ketamine have received great attention. We used low dose of ketamine 0.3mg/kg for attenuation of pressor response. *Method*: Patients scheduled for laparoscopic cholecystectomy were divided in group K (ketamine0.3 mg/kg)and group N(normal saline).Ten minutes before creation of pneumoperitoneum, the (group K) received ketamine 0.3 mg/kg diluted in normal saline intravenously whereas group N received same amount of normal saline. Hemodynamicparameters were monitored and results observed. *Results*: Heart Rate,Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure were significantly attenuated in group K ($p<0.001$) as compared to group N. *Conclusion*: Low dose ketamine attenuates hemodynamic response in pneumoperitonium in laparoscopic cholecystectomy.

Keywords: Laparoscopic Cholecystectomy; Ketamine; Hemodynamic Response.

Introduction

Laparoscopic surgeries are known to cause lessmetabolic stressresulting in less postoperative pain. Pneumoperitoneum required for laparoscopy, affects homeostasis and leads to alterations in cardiovascular and respiratoryphysiology. Cardiovascular changes include increase in mean arterial pressure (MAP) with no significant change in heart rate (HR) [1], decrease incardiac output and increase in systemic vascular resistance. Various surgical methods like change in nature of insufflating gas [2], use of low intra-abdominal pressure [3,4] use of abdominal wall lift methods [5], have been tried to decrease the hemodynamic alterations associate with pneumoperitoneum, but has limitations. Use of various pharmacologic interventions like nitroglycerine [6], esmolol [7], have been used with varying degree of success. N-methyl-D-aspartate (NMDA) receptor antagonists have received attention because NMDA receptors have a role in central sensitization and neural modulation [8].

A low dose of preemptive ketamine,which could be insufficient for a major surgery may be adequate forminimally invasive surgery such as laparoscopic cholecystectomy, which causes less tissue trauma [9]. Conceivably, a smaller dose may have the benefit of minimal hemodynamic effects without additional psychotomimetic adverse effects [9]. The lower dose of 0.5 mg/kg being devoid of any adverse effects and hemodynamic changes is an optimal dose for preemptive analgesia in patients undergoing Laparoscopic cholecystectomy[10]. So we used 0.3mg/kg ketamine to evaluate whether any hemodynamic changes in laparoscopy surgery.

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Materials and Methods

After obtaining approval from hospital Ethical Committee, details of the procedure was explained to the patients and a written informed consent was taken. 20 ASA I or II patients undergoing laparoscopic cholecystectomy were enrolled into the study. Exclusion criteria included Patient refusal, ASA III or more, poor cardiovascular and respiratory reserve, known allergy or sensitivity to study drug and difficult airway (Mallampati grade 3 & 4). Patients were randomly divided into two groups. All patients received tab pantoprazole 40 mg and tab alprazolam 0.5 mg orally night before surgery and patients were kept nil by mouth overnight prior to surgery. In the morning the consent was checked; the preoperative assessment was reviewed. On arrival in operation theatre electrocardiogram (ECG),Non invasive Blood pressure (NIBP) and pulse oximeter were applied and baseline readings of parameters like HR (heart rate), SBP(systolic blood pressure), DBP (diastolic blood pressure), MAP (mean arterial pressure) and SpO_2 were noted. Capnometer ($ETCO_2$) was attached afterintubation. All patients received premedication inj.glycopyrrolate 4 μg/kg, inj ondansetron 0.08mg/kg, inj. midazolam 0.02 mg/kgand inj.diclofenac sodium 75mg intravenously . Patients were pre-oxygenated with 100% Oxygen for 5 minutes before induction and anaesthesia wasgiven with inj.thiopentone 5-7mg/kg intravenously followed by inj. suxamethonium 1.5-2mg/kg intravenously, to facilitate endotracheal intubation. $ETCO_2$ reading noted.Anaesthesia was maintained with oxygen,nitrous oxide, isoflurane and inj. atracurium. Pateints were randomly divided into two groups.10 minutes before establishment of pneumoperitonium, patients in Group K received inj.ketamine 0.3 mg/kg intravenously diluted in 10 ml in normal saline whereas Group N received 10ml inj normal saline. During surgery inj. ringer lactate was infused in accordance with deficit and maintenance. CO_2 pneumoperitoneum was created and intra-abdominal pressure was maintained between 12-14 mm Hg. Patients were ventilated mechanicallyusing pressure control mode of ventilation. Tidal volume and respiratory rate were adjusted to maintain end-tidal CO_2 between 35-45mm Hg. All parameter including of HR, SBP, DBP, MBP, SpO_2 and $ETCO_2$were monitored 1, 5, 10, 15, 20, 30, 45, 60, 75 minutes after inflation of pneumoperitonium.After completion of surgery neuromuscular blockage was reversed with inj.neostigmine 0.05 mg/kg and injglycopyrrolate 8μg/kg. All the patients were extubated uneventfully and were monitored for 30 minutes in recoveryroom following extubation. Monitoring and recording of parameters were done at following intervals and analyzed for study. Pre induction, 5 and 10 min after drug administration and 1, 5, 10, 15, 20, 30, 45, 60, 75 minutes after inflation of pneumoperitonium and after extubation.

Statistical Analysis

Numerical variables were presented as mean and standard deviation while categorical variables were presented as frequency and percent. For analysis, unpaired student – t test and chi- square test were used. P value <0.001 was considered statistically significant. All statistical analyses were done using SPSS version 16.

Results

The mean age of patients was 46.86 years in Group K and 43.33 years in Group N. There was no significant difference in both the groups in respect to age and weight of the patients. After 30 minutes of establishment of pneumoperitoneum, difference in pulse between group K (81±4.616) and Group N (86±0.83) and mean bloodpressure between group

Table 1: Baseline Comparison of the study groups according to Age

Groups	Group K	Group N	P value
Age in years (mean±SD)	46.866 ± 9.576	43.33 ± 7.470	0.1138 (non-significant)

Table 2: Baseline Comparison of the study groups according to Weight

Groups	Group K	Group N	P value
Weight in kg (mean ± SD)	53.3 ± 4.524	53.7 ± 5.923	0.844 (non-significant)

K (96.7±5.64) and Group N (103±1.22) was statistically significant (P<0.001).After 45 minutes of establishment of pneumoperitonium.Differencein pulse between group K (80.33± 4.56) and Group N (84.5±0.83) and Mean blood pressure between group K (98.3±6.52) and Group N (108.22±1.22) was statistically significant (P<0.001). After 60 minutes of establishment of pneumoperitonium difference in pulse between group K (82.67± 5.1) and Group N (84.5±1.83)and Mean blood pressure between group K (97.9±5.45) and Group N (107.5±0.84)was statistically significant (P < 0.001).The statistically significant difference in Pulse and Mean blood pressure were seen at time intervals from pre induction to 30, 45, 60 minutes after establishment of pneumoperitonum as shown in Figures 1 & 2.

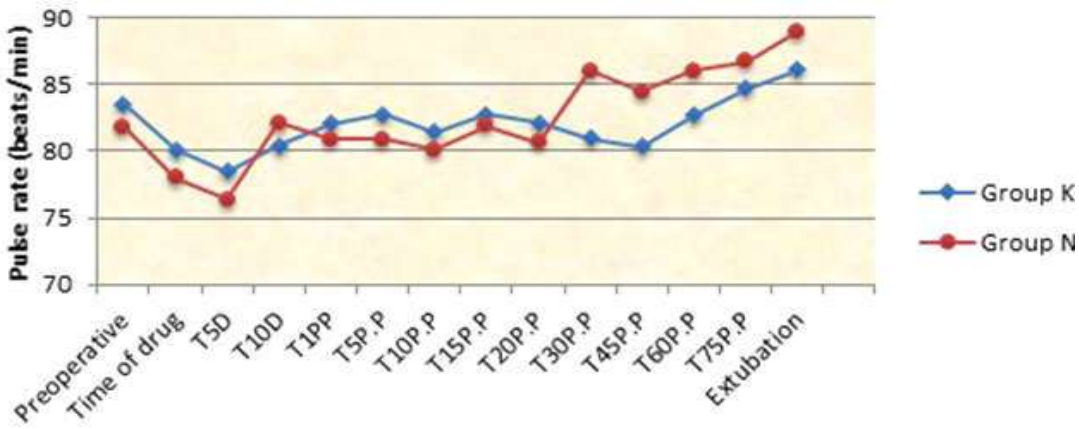

Fig. 1: Mean pulse rate (/min) at different time intervals in the study group

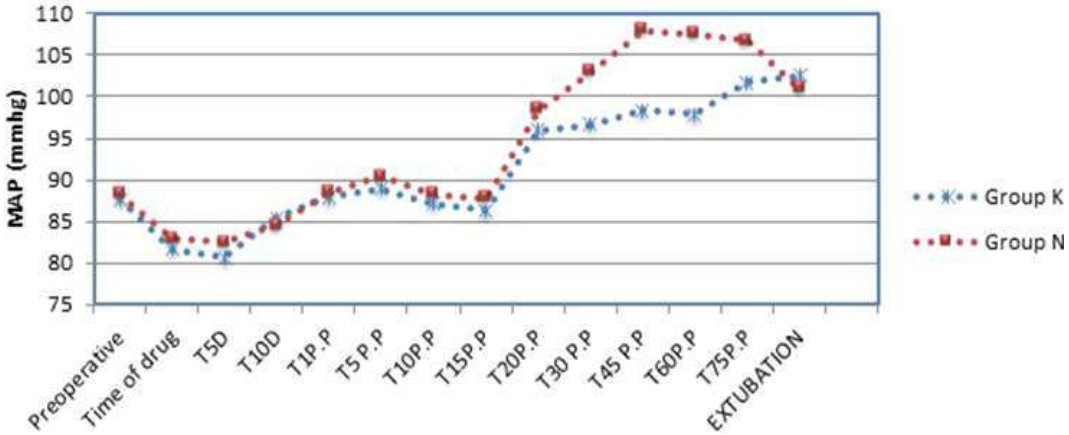

Fig. 2: Comparison of MAP (mmHg) in study and controlgroups at different time intervals

Discussion

This placebo controlled, double blind study was designed to assess the effects of ketamine on attenuation of hemodynamic stress responses during laparoscopic cholecystectomy. A study by Joris JL et al. concluded that vasopressin and catecholamines probably mediate the increase in systemic vascular resistance observed during pneumoperitoneum which causes elevation of hemodynamic parameters [13].

Prolonged intraoperative increase of 20 mm Hg or more in mean arterial pressure are known to significantly increase the incidence of myocardial ischaemia, infarction, and death [14]. It is demonstrated by D. Jee et al. that immediately after pneumoperitoneum, plasma levels of catecholamines and vasopressin increased significantly in the control group but not in the magnesium group. NMDA receptor antagonist are effective in blocking the release of catecholamines from both adrenergic nerve terminals and the adrenal gland. Because of the ability of magnesium sulphate an NMDA

receptor antagonist to attenuate adverse hemodynamic response, we have administered 0.3mg/kg ketamine (NMDA receptor Antagonist) 10 minutes before pneumoperitonum. The purpose of this study was to see the effect of ketamine, which is also potent NMDA receptor antagonist like magnesium sulphate, in attenuating the hemodynamic stress response to the effects of pneumoperitoneum, which is the key element in laparoscopic surgeries; and thus might be beneficial in patients with hypertension or cardiac diseases during laparoscopic procedures. In the present study, we observed that systolic and diastolic arterial pressures increased abruptly after pneumoperitoneum commencement, and increases in arterial pressure were sustained during the entire pneumoperitoneum period in the normal saline group as reported in previous observations [13,15].

However, in the ketamine group, haemodynamic responses to the onset of pneumoperitoneum were effectively blunted, and in particular, arterial pressures remained at a significantly lower level when compared with the normal saline group. Pneumoperitoneum using CO_2 causes a rapid and immediate increase in plasma catecholamines [16,17], possibly due to an increase in intraperitoneal pressure and stimulation of the peritoneum by CO_2 [16]. In addition to catecholamines, vasopressin is a major contributor to the haemodynamic changes induced by pneumoperitoneum. The high concentrations of vasopressin measured during pneumoperitoneum have been shown to be sufficient to have significant cardiovascular effects [15,18]. In addition, linear correlations have been reported between changes in arterial pressure and increases in the plasma concentrations of catecholamines [1] and vasopressin [15,18] during pneumoperitoneum. However, in the ketamine group, pneumoperitoneum was only associated with an initial insignificant increase in arterial pressure and no further increase, which could be because ketamine reduces catecholamine and vasopressin levels, and thus attenuates haemodynamic responses during pneumoperitoneum. Ishizaki et al. tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery [12]. They observed significant fall in cardiac output at 16 mm Hg of intra-abdominal pressure and hemodynamic alterations. So we kept intra-abdominal in our study between 12-14 mm Hg and decided to use ketamine to attenuate hemodynamic changes during laparoscopic surgeries. This attenuation of the effects is apparently related to the reduction in the release of catecholamine, vasopressin or both. NMDA receptors play a significant role in central sensitization in spinal cord. In previous studies conducted by D. Jee and D. Lee et al, they observed that magnesium sulphate an NMDA receptor antagonist effectively prevented sympathoadrenal hemodynamic stress responses during pneumoperitoneum. In similar scenario ketamine being an NMDA receptor antagonist was able to attenuate sympathoadrenal stress response following pneumoperitonium in our study. We therefore hypothesized that ketamine might attenuate the haemodynamic stress responses to pneumoperitoneum by changing neurohumoral responses as it is also a NMDA receptor antagonist.

Conclusion

Low dose of ketamine (0.3mg/kg) given before establishment of pneumoperitoneum, attenuates the hemodynamic stress responses during laparoscopic cholecystectomies without any adverse effect.

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Conflict of Interest: None

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