Original Article

Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy

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Abstract

Background: Both magnesium and clonidine are known to inhibit catecholamine and vasopressin release and attenuate hemodynamic response to pneumoperitoneum. This randomized, double blinded, placebo controlled study has been designed to assess which agent attenuates hemodynamic stress response to pneumoperitoneum better.

Materials and Methods: 120 patients undergoing elective laparoscopic cholecystectomy were randomized into 4 groups of 30 each. Group K patients received 50 ml normal saline over a period of 15 min after induction and before pneumoperitoneum, group M patients received 50 mg/kg of magnesium sulfate in normal saline (total volume 50 ml) over same time duration. Similarly group C1 patients received 1 μg/kg clonidine and group C2 1.5 μg/kg clonidine respectively in normal saline (total volume 50 ml). Blood pressure and heart rate were recorded before induction (baseline value), at the end of infusions and every 5 min after pneumoperitoneum.

Statistical Analysis: Paired *t* test was used for intra-group comparison and ANOVA for inter-group comparison.

Results: Systolic blood pressure was significantly higher in control group as compared to all other groups during pneumoperitoneum. On comparing patients in group M and group C1, no significant difference in systolic BP was found at any time interval. Patients in group C2 showed best control of systolic BP. As compared to group M and group C1, BP was significantly lower at 10, 30 and 40 min post pneumoperitoneum. No significant episodes of hypotension were found in any of the groups. Extubation time and time to response to verbal command like eye opening was significantly longer in group M as compared to other groups.

Conclusion: Administration of magnesium sulfate or clonidine attenuates hemodynamic response to pneumoperitoneum. Although magnesium sulfate 50 mg/kg produces hemodynamic stability comparable to clonidine 1 μg/kg, clonidine in doses of 1.5μg/kg blunts the hemodynamic response to pneumoperitoneum more effectively.

Key words: Clonidine, laparoscopic cholecystectomy, magnesium sulfate, pneumoperitoneum

Introduction

Pneumoperitoneum affects homeostasis and leads to alterations in cardiovascular, pulmonary physiology and stress response. Cardiovascular changes include increase in mean arterial pressure (MAP) with no significant change in heart rate,[1-3] decrease in cardiac output and increase in systemic vascular resistance (SVR). These vasopressor responses are consequent to hypercarbia-induced release of catecholamines,[4-6] vasopressin, or both.[1,7,8]

Magnesium blocks release of catecholamines from both adrenergic nerve terminals and adrenal gland. Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intubation. Magnesium also produces vasodilation by acting directly on blood vessels and in high doses, attenuates vasopressin-mediated vasoconstriction. Clonidine, a selective alpha 2 adrenergic agonist, causes a fall in the heart rate and blood pressure along with decreased SVR and cardiac output. We hypothesized that both magnesium and clonidine might also attenuate hemodynamic stress response to pneumoperitoneum.

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Materials and Methods

After approval from ethical committee and written informed consent of the patients, this study was conducted in a tertiary care medical college hospital. 120 patients, of American Society of Anesthesiologists (ASA) physical status I, undergoing elective laparoscopic cholecystectomy with CO_2 pneumoperitoneum, were enrolled in this study. Power calculations suggested that a minimum of 17 subjects per group were required to detect 10% difference in arterial pressure between groups (a = 0.05, b = 0.80). Patients in whom surgery could not be completed laparoscopically and open cholecystectomy done were excluded from the study. Patients who showed exaggerated hypertensive response (taken as systolic BP >180mmHg or diastolic BP >110 mmHg) during surgery and administered nitroglycerine infusion, were excluded from the study. Patients were randomly divided into four groups using sealed envelopes chosen by the patients and the randomization was done immediately before pneumoperitoneum. The four groups were:

- Control group (group K) – received 50 ml normal saline over a period of 15 min before pneumoperitoneum.
- Magnesium group (group M) – received 50 mg/kg of magnesium sulfate in normal saline (total volume 50 ml) over a period of 15 min before pneumoperitoneum.
- Clonidine group 1 (group C1) – received 1 μg/kg clonidine in normal saline (total volume 50 ml) over a period of 15 min before pneumoperitoneum.
- Clonidine group 2 (group C2) – received 1.5 μg/kg clonidine in normal saline (total volume 50 ml) over a period of 15 min before pneumoperitoneum.

Patients were premedicated with intravenous ranitidine 0.25 mg/kg, metoclopramide 0.15 mg/kg and glycopyrrolate 0.02 mg/kg in preoperative room. On arrival in the operation theater, monitors were attached (heart rate, NIBP, oxygen saturation, ECG) and baseline vital parameters like heart rate, systolic and diastolic blood pressure, and oxygen saturation were recorded. Butorphanol 0.05 mg/kg intravenous was given for analgesia.

Anesthesia was induced with intravenous propofol 2.5 mg/ kg and vecuronium bromide 0.1mg/kg was used to facilitate tracheal intubation. Syringes were prefilled with test drug and were given to the anesthesiologist conducting the case for blinding, immediately after induction and before pneumoperitoneum. Patients received normal saline 50 ml (group K), or magnesium 50 mg/kg in normal saline (group M), or clonidine 1 μg/kg (group C1) in normal saline or clonidine 1.5 μg/kg (group C2) in normal saline over a duration of 15 min. Anesthesia was maintained with oxygen-nitrous oxide mixture (50:50), propofol infusion at the rate of 100 μg/kg/min and vecuronium bromide 0.02mg/kg intermittent boluses. During surgery, Ringer's lactate was infused in accordance with maintenance volume requirements and blood loss. All patients were operated with head-up tilt of 15°. CO_2 pneumoperitoneum was created and intra-abdominal pressure maintained at 14 mm Hg. Intermittent positive pressure ventilation (IPPV) was delivered, with tidal volume and respiratory rate adjusted to maintain end tidal carbon dioxide between 35 and 45 mm Hg. The surgical technique used was identical in all the groups.

Blood pressure and heart rate were recorded before induction (baseline value), at the end of saline, magnesium or clonidine infusions and before pneumoperitoneum (P0), 5 min (P5), 10 min (P10), 20 min (P20), 30 min (P30) and 40 min (P40) after pneumoperitoneum.

As the pneumoperitoneum was released, propofol infusion was stopped. Neuromuscular block was reversed with i.v neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/ kg and tracheal tubes were removed. Time to extubation was taken as time from stopping of propofol infusion to endotracheal tube removal. After tube removal, time to response to verbal commands (spontaneous eye opening) was also recorded.

Comparison of post-pneumoperitoneum blood pressure and heart rate with baseline values was done using paired-T test amongst the same group while inter-group comparisons were done using ANOVA. Categorical data was compared using Chi-square test. *P* value <0.05 was considered as statistically 'significant.' Statistical analysis was done using Graphpad software (San Deigo, USA)

Results

The distribution of patients in the groups is shown as Table 1. All groups were comparable in respect to age, sex, body weight, height and duration of surgery. Baseline arterial pressures and heart rate were similar in all groups. Four subjects (three in group K and one in group M) were excluded from study: One patient in group K and one in group M had to be converted to open cholecystectomy; and two patients in group K developed exaggerated hypertensive response during pneumoperitoneum needing administration of nitroglycerine infusion.

Systolic blood pressure (SBP) was significantly higher in group K as compared to all other groups from P5 to P40 ($P < 0.0001$). On comparing patients in group

Table 1: Demographic characteristics and baseline vitals of patients

	K $n = 27$	M $n = 29$	C1 $n = 30$	C2 $n = 30$	*P* value
Age	38.3 ± 9.1	40.2 ± 8.5	42.7 ± 09.3	38.8 ± 8.9	0.23
Sex	11/16	15/14	16/14	14/16	0.77
Weight	60.7 ± 9.4	61.2 ± 9.6	63.3 ± 8.9	63.6 ± 9.7	0.53
Height (cm)	155.1 ± 8.9	157.7 ± 9.1	152.2 ± 7.9	156.3 ± 9	0.10
Duration of surgery (min)	50 ± 6.4	47.3 ± 7.8	48.9 ± 7.2	50.4 ± 8.3	0.39
Baseline vitals Systolic BP	120.2 ± 9.8	122.4 ± 10.1	123.2 ± 11.1	120.7 ± 10.5	0.66
Diastolic BP	79.1 ± 9.8	81.4 ± 9.7	78.4 ± 10.4	79.9 ± 9.5	0.68
Heart rate	73.3 ± 8.7	72.6 ± 8.7	73.6 ± 9.1	74 ± 9.2	0.94

Table 2: Recovery time following discontinuation of propofol infusion

	K	M	C1	C2	*P* value
Extubation time (min)	7 ± 2.1	8.7 ± 2.8	6.5 ± 1.9	6.2 ± 1.8	<0.0001
Response to verbal commands	8.8 ± 1.7	10.7 ± 2	9.1 ± 1.9	9.8 ± 2.3	0.0023

M and group C1, no significant difference in SBP was found at any time interval. Patients in group C2 showed best control of SBP. As compared to group M patients, SBP of group C2 patients was significantly lower at P10 ($P < 0.05$) and P30 ($P < 0.01$) and on comparison to C1 patients, it was significantly lower at P10 ($P < 0.05$), P30 ($P < 0.05$) and P40 ($P < 0.05$). No significant episode of hypotension was found in any of the groups post pneumoperitoneum.

Diastolic BP (DBP) of patients in group K was raised significantly at P30 ($P < 0.01$) and P40 ($P < 0.05$) as compared to group M and at P5 ($P < 0.05$), P30 ($P < 0.001$) and P40 ($P < 0.001$) as compared to group C1. No significant difference was found in DBP between group M and group C1 at any time interval during pneumoperitoneum. In comparison to C2, DBP was significantly higher in patients of group M at P30 ($P < 0.05$) and P40 ($P < 0.001$), while patients of group C1 showed significantly higher DBP at P40 ($P < 0.05$) when compared to C2.[Figure 1]

On comparing heart rate of patients in group K with groups M and C1, no significant difference was found. However, heart rate in group K patients was significantly higher as compared to group C2 at P0, P20 ($P < 0.01$), P30 ($P < 0.05$) and P40 ($P < 0.01$). On comparing group M with group C1, no significant difference was found at any time interval. Heart rate was significantly higher at P30 ($P < 0.05$) and P40 ($P < 0.05$) in group M as compared to group C2. On comparing patients in group C1 to group C2, no significant difference was found at any time interval.[Figure 2]

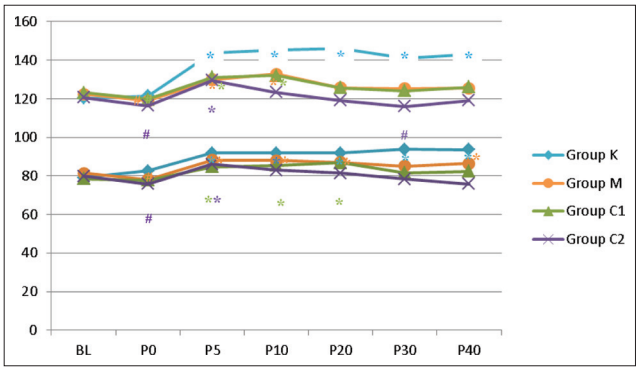

Figure 1: Variations in systolic and diastolic BP in all groups during pneumoperitoneum (* shows significant increase and # shows significant decrease when compared to baseline)

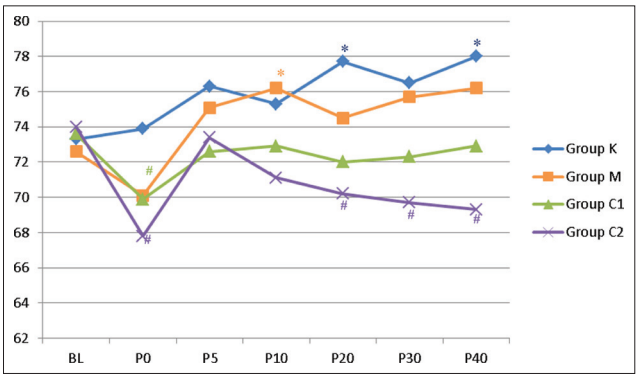

Figure 2: Variations in heart rate of patients under all groups after pneumoperitoneum (* shows significant increase and # shows significant decrease when compared to baseline)

Table 2 shows the extubation time and time to respond to verbal commands. Extubation time in group M was significantly prolonged when compared to group K ($P < 0.05$), group C1 ($P < 0.01$) and group C2 ($P < 0.001$). No significant difference was found in extubation time between group K, group C1 and group C2 when compared to each other. Time to response to verbal command like eye opening was significantly longer in group M as compared to group K ($P < 0.01$) and group C1 ($P < 0.05$) while no significant difference was found between group M and C2. No significant difference in time to response to verbal commands was found amongst other intergroup comparisons.

Discussion

Cardiovascular changes in pneumoperitoneum include increase in MAP with no significant change in heart rate.[1-3] Studies to investigate the role of magnesium in laparoscopic surgeries have been conducted earlier.[9] Our study is the first randomized, double blinded, placebo controlled study to compare the role of magnesium sulfate and clonidine in attenuating stress response to pneumoperitoneum.

Jee *et al.*,[9] administered magnesium sulfate 50 mg/kg over 2-3 min, before pneumoperitoneum in patients undergoing laparoscopic cholecysyectomy and found that it effectively attenuated the effects of pneumoperitoneum without any episode of severe hypotension or bradycardia. We used same dose of magnesium sulfate in our study to compare it with clonidine. Our results show that in group K, both SBP and DBP increased abruptly after pneumoperitoneum and this increase was sustained throughout the procedure. In comparison to group K, response to pneumoperitoneum in patients of group M was attenuated as shown by significant reduction of SBP and DBP. Plasma catecholamine and vasopressin concentrations are significantly lowered by magnesium[9] and hence magnesium sulfate effectively blunted the sympathoadrenal hemodynamic stress responses to pneumoperitoneum. The reduction in blood pressure could be attributed to vasodilatory effect of magnesium sulfate.[10]

Studies have suggested that magnesium can inhibit catecholamine release *in vitro*[11] and *in vivo*.[12,13] Serum magnesium concentrations of 2-4 mmol/l are required to exert these effects.[14,15] Jee *et al.* found that magnesium sulfate bolus of 50 mg/kg before pneumoperitoneum increased serum magnesium concentrations to this range.[9] Like catecholamines, vasopressin also contributes to hemodynamic changes induced by pneumoperitoneum. Vasopressin concentration increases when intra-abdominal pressure compresses abdominal capacitance vessels and this reduces intra-thoracic blood volume due to a decrease in venous return.[16,17] Vasodilatory effects of magnesium sulfate lead to dilatation of abdominal vessels which might prevent vasopressin release. Further studies are however needed to determine precise mechanism by which magnesium reduces vasopressin concentration.

Our results also show no significant difference in heart rate amongst group K, group M and group C1. Clonidine inhibits the release of catecholamine and vasopressin and thus modulates the hemodynamic changes induced by pneumoperitoneum.[18] Aho *et al.*,[19] used clonidine for prevention of hemodynamic responses associated with laparoscopic surgery. Yu *et al.*,[20] used 150 μg of oral clonidine as premedication for maintenance of hemodynamic stability during pneumoperitoneum and recommended its routine use as premedication in laparoscopic surgeries. Altan and Turgut[21] used clonidine 3 μg/kg intravenously over a period of 15 min before induction and 2 μg/kg/min by continuous infusion intraoperatively. They observed significant incidences of bradycardia and hypotension in their study. Ray *et al.*[22] used 3 μg/kg of clonidine intravenously over a period of 15 min before induction and 1 μg/kg/min by continuous infusion during surgery and observed significant incidences of bradycardia and hypotension in their study. We reduced the dose of clonidine, given before pneumoperitoneum, to 1.5 and 1 μg/kg and gave no intraoperative infusion. We did not witness any episodes of significant bradycardia or hypotension in any of the groups.

Patients receiving 1 μg/kg clonidine showed significantly better hemodynamic control than group K patients. Interestingly, no significant differences were found in hemodynamics of these patients when compared to group M but patients receiving 1.5 μg/kg clonidine showed better hemodynamic control than all other groups, possibly because the higher dose of clonidine in group C2 attenuated hemodynamic response to pneumoperitoneum more effectively. Extubation time in group M was significantly increased as compared to other groups. No significant difference between group M and C2 could be explained as C2 group received larger dose of clonidine, which also causes sedation.

Magnesium sulfate potentiates neuromuscular blockade induced by non-depolarizing neuromuscular blocking agents and this possibly was the cause of the prolongation.[23-25] Time to response to verbal commands was significantly prolonged in patients receiving magnesium sulfate in comparison to group K and C1. This delay could be due to CNS depressant effects of magnesium sulfate. Peck and Meltzer[26] attempted anesthesia by magnesium sulfate infusion in patients for herniorrhaphy and achieved a narcotic state. Depressant effect of magnesium sulfate on CNS of animals too has been reported.[27] Magnesium is also to antagonize NMDA receptors in CNS.

To conclude, administration of magnesium sulfate or clonidine before commencement of pneumoperitoneum effectively attenuates hemodynamic response to pneumoperitoneum. Although, clonidine 1 μg/kg produces hemodynamic stability comparable to magnesium sulfate 50 mg/kg in patients undergoing laparoscopic surgery, clonidine 1.5 μg/kg blunts the hemodynamic response to pneumoperitoneum more effectively.

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