



A comparative study of magnesium sulphate and clonidine in attenuating hemodynamic response to pneumoperitoneum in laparoscopic cholecystectomy

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Abstract

Introduction: Laparoscopic cholecystectomy is one of the most common laparoscopic surgeries performed worldwide. Pneumoperitoneum is commonly induced by carbon dioxide (CO₂). Pneumoperitoneum affects homeostasis and leads to alterations in cardiovascular, pulmonary physiology and stress response. Pneumoperitoneum, as well as hypercapnia due to CO₂, is responsible for the adverse cardiovascular effects. An abrupt elevation of mean arterial pressure, systemic vascular resistance and decreased cardiac output are commonly noted. This vasopressor responses are due to hypercarbia induced release of both catecholamines and vasopressin. Our aim was to evaluate and compare the effect of intravenously administered clonidine and magnesium sulfate for attenuating the hemodynamic responses to pneumoperitoneum during laparoscopic surgeries.

Material & Methodology: We conducted a prospective double blinded randomized control study in 90 patients belonging to ASA I and II undergoing elective laparoscopic surgeries in S. P. medical college, Bikaner after taking approval from Institutional Ethical committee and valid written informed consent from patients and their close relatives. Patients of both sexes ranging between 18 to 60 years of age were included.

Patients were divided randomly using computer-derived random number sequence into three groups of 30 each. Group-C received clonidine 1.0 µg/kg in 50 ml of normal saline. Group-M received magnesium 50mg/kg in 50 ml of normal saline. Group-NS received 50 ml normal saline.

The test drug solution was given after intubation and before pneumoperitoneum. The HR, SBP, DBP, MAP were noted.

Results: In both magnesium and clonidine groups, there was no statistically significant differences observed in SBP, DBP, MAP (*p*-value > 0.05) (statistically significant fall in HR between the group-M and group-C) but as compared to group-NS there was significant difference (*p*-value < 0.05) in hemodynamic parameters. In group-NS haemodynamic parameters were comparatively high as compared to other two groups.

Conclusion: Clonidine 1.0 µg/kg was equally effective as magnesium sulphate 50mg/kg in blunting the hemodynamic stress response during laparoscopic surgeries as compared to normal saline group where haemodynamic parameters were comparatively high.

Keywords: Magnesium sulphate, Clonidine, Laparoscopic cholecystectomy.

Introduction

Laparoscopic cholecystectomy is one of the most common laparoscopic surgeries performed worldwide¹. Advent of laparoscopic approach to cholecystectomy revolutionized the treatment of biliary tract disease. In 1985, Prof Dr Erich Muhe of Germany performed the first laparoscopic cholecystectomy². Laparoscopy results in multiple postoperative benefits including less surgical trauma, less pain, less pulmonary dysfunction, quicker recovery, and shorter hospital stay³. Pneumoperitoneum is commonly induced by carbon dioxide (CO₂). Pneumoperitoneum affects homeostasis and leads to alterations in cardiovascular, pulmonary physiology and stress response⁴. Pneumoperitoneum, as well as hypercapnia due to CO₂, is responsible for the adverse cardiovascular effects. An abrupt elevation of mean arterial pressure, systemic vascular resistance and decreased cardiac output are commonly noted⁵. This vasopressor responses are due to hypercarbia induced release of both catecholamines, vasopressin or both⁶. The cardiac output will be further decreased by the reverse trendelenburg position used in these surgeries. A number of strategies have been used to blunt these adverse hemodynamic changes associated with pneumoperitoneum and make laparoscopic cholecystectomy safer for the high risk patients. These include using drugs like Alpha2-adrenergic agonists⁷, beta-blocking agents⁸, opioids, vasodilators, or magnesium sulphate⁹ to avoid circulatory response to pneumoperitoneum, using low pressure pneumoperitoneum¹⁰, or alternatively not using pneumoperitoneum at all such as in abdominal wall lift (AWL) method.¹¹ Our aim was to evaluate and compare the effect of intravenously administered clonidine and magnesium sulfate for attenuating the hemodynamic responses to pneumoperitoneum during laparoscopic surgeries.

Material and Methodology

We conducted a prospective double blinded randomized control study in 90 patients belonging

to ASA I and II undergoing elective laparoscopic surgeries in S. P. medical college, Bikaner after taking approval from Institutional Ethical committee and valid written informed consent from patients and their close relatives. Patients of both sexes ranging between 18 to 60 years of age were included. Age below 18 years, above 60 year, patients with hypermagnesemia, known allergy to magnesium sulfate or clonidine, hypertension, morbid obesity, severe hepatic, renal, endocrine, and cardiac dysfunction and patients in whom laparoscopic cholecystectomy converted to open cholecystectomy were excluded from study.

Patients were divided randomly using computer-derived random number sequence into three groups of 30 each. Group-C received inj. clonidine 1.0µg/kg in 50 ml of normal saline over 10 min, prior to pneumoperitoneum. Group-M received inj. Magnesium sulphate 50mg/kg in 50 ml of normal saline over 10 min, prior to pneumoperitoneum. Group-NS received 50 ml normal saline over 10 min, prior to pneumoperitoneum.

On the day prior to surgery a thorough clinical examination of the patient were done including general physical examination and systemic examination. Routine investigations like CBC, BT, CT, urine analysis, fasting blood sugar, Liver function test, chest x-ray, Blood urea, serum creatinine, ECG, Viral markers were done. All patients were explained about the anaesthesia technique and written informed consent was taken from patients and their relatives. Patient was kept NBM for 8-10 hours.

Premedication with inj ranitidine 50 mg and inj ondansetron 4 mg was given 2 hours before surgery in preoperative room. On arrival in the operation theatre pulse oximeter, NIBP, ECG were connected to the patients and baseline vital parameters were recorded. Preoxygenation was done for 3 min and patients received 0.005mg/kg of inj glycopyrrolate and 2 µg/kg of fentanyl citrate intravenously. Propofol 2 mg/kg was used for induction and endotracheal intubation was

facilitated by a muscle relaxant, vecuronium bromide 0.1 mg/kg. The test drug was infused over 10 min before creating pneumoperitoneum. Systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and HR were recorded before induction (baseline values), at the end of magnesium sulfate/clonidine/saline administration and before pneumoperitoneum (P0), 5 min (P5), 10 min (P10), 20 min (P20), 30 min (P30), and 40 min (P40) so on every 10 min after pneumoperitoneum. Pneumoperitoneum inflation pressures was maintained at 14 mm Hg. Maintenance of anesthesia was with nitrous oxide (50%), oxygen (50%), and isoflurane and titrated doses of vecuronium 0.02 mg/kg. Intermittent positive pressure ventilation was used and end-tidal CO₂ (EtCO₂) was maintained between 35 and 40 mm Hg. Patients were positioned in head up tilt of 15° with right lateral tilt. During surgery, I.V. fluid ringer lactate was infused in accordance with maintenance volume requirements and blood loss. Hypotension (MAP <20% of baseline) was managed with fluid bolus or mephentermine 6 mg IV. Atropine 0.6 mg IV was given if HR < 50/min. Neuromuscular blockade was reversed with i.v. inj. neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg and extubation was done.

Data Analysis

A pre-structured pre-tested proforma was used for Data collection and for data analysis Microsoft excel was used. The sample size was calculated according to significant difference between drug group and placebo group and it was estimated that a sample size of 28 patients for each group would be sufficient to detect a difference of 15 mm hg between drug group and placebo group with a significant level of <0.05 and power of study as 80%. Continuous variable were expressed as mean (SD) and compared with student's t-test. Difference between proportion derived from categorical data were compared with chi square test. For all the p-values of less than 0.05 was considered significant.

Results

Table 1-4 shows the demographic variables of the patients in the three groups. All three groups were comparable in respect to age, body weight, sex, ASA status. The baseline vitals were comparable between all the groups.

In table-5 fall in SBP was statistically insignificant in group-M and group-C (p value > 0.05). Statistically significant fall in SBP from P5 till extubation noted in group-M & group-NS (p value < 0.05) and group-C & group-NS (p value < 0.05).

Table- 6 shows statistically insignificant fall in DBP in group-M and group-C (p value > 0.05). Significant fall in DBP from P5 till extubation noted in group-M & group-NS (p value <0.05) and in group-C & group-NS (p value <0.05).

Table-7 shows statistically insignificant fall in MAP noted between group-M & group-C (p value >0.05). Significant fall in MAP from P5 to P40 and at the time of extubation in group-M & group-NS and in group-C & group-NS (p value <0.05).

Table 8 shows statistically significant fall in heart rate between the group-M and group-C, group-M and group-NS, and group-C and group-NS (p value <0.05).

No significant episodes of hypotension or bradycardia were noted in any group.

Table: 1 Age wise distribution of study groups.

Age Group	Group-M	Group-C	Group-NS	P-value
21-30 years	9 (30%)	16 (53.3%)	10 (33.3%)	0.3267
31-40 years	12 (40%)	6 (20%)	6 (20%)	
41-50 years	6 (20%)	4 (13.3%)	6 (20%)	
51-60 years	3 (10%)	4 (13.4%)	8 (26.7%)	
Mean±SD	37±11.7	34.1±11.0	38.9±12.2	

Table: 2 Comparison of groups on basis of Mean body weight.

Weight (kg)	Mean±SD	P-value
Group-M	60.7±5.6	0.8910
Group-C	60.1±9.1	
Group-NS	63.2±8.3	

Table: 3 Gender wise distribution of patients.

Gender	Group-M	Group-C	Group-NS
Female	26 (86.7%)	25 (83.3%)	22 (73.3%)
Male	4 (13.3%)	5 (16.7%)	8 (26.7%)

Table: 4 Comparison of groups on the basis of ASA Status.

ASA Grade	ASA 1	ASA 2	P-value
Group-M	27 (90%)	3 (10%)	0.7841
Group-C	28 (93.3%)	2 (6.7%)	
Group-NS	30 (100%)	0 (0%)	

Table: 5 Comparison of groups on basis of Mean systolic blood pressure.

SBP (mmhg)	GROUP-M	GROUP-C	GROUP-NS	P-value		
	Mean±SD			Group M and C	Group M and NS	Group C and NS
Baseline	127.3±8.5	126.6±7.7	127.1±12.5	0.7394	0.6891	0.6514
After administration	124.3±9.6	123.3±8.1	125.3±12.9	0.6471	0.6521	0.7812
Before pneumoperitoneum	118±11.2	119.1±11.1	121.1±11.9	0.5147	0.3031	0.6214
5 min	122.6±11.8	122.1±13.4	134.6±11.1	0.8971	0.0002	0.0002
10 min	126.4±12.1	123.1±15.9	138.5±11.5	0.3694	0.0012	0.0001
20 min	122.9±12.2	117.5±17.4	136.9±12.7	0.1693	0.0031	0.0001
30 min	115.5±12	115.7±16.7	134.8±13.8	0.8125	0.0003	0.031
40 min	115.1±12.9	116.1±16.6	124.4±14.3	0.7815	0.0061	0.0424
Extubation	127.5±10.6	132.8±13.0	146.5±11.7	0.0888	0.0001	0.0001

Table: 6 Comparison of groups on basis of Mean diastolic blood pressure.

DBP (mmhg)	GROUP-M	GROUP-C	GROUP-NS	P-value		
	Mean±SD			Group M and C	Group M and NS	Group C and NS
Baseline	83.3±6.7	82.0±6.3	81.1±9.4	0.8214	0.702	0.0687
After administration	81.1±6.8	80.7±7.8	80.2±7.6	0.7394	0.6891	0.5147
Before pneumoperitoneum	76.7±9.0	79.7±8.8	75.7±9.0	0.6471	0.6521	0.1201
5 min	80.9±8.3	83.3±6.8	90.2±9.1	0.05211	0.0001	0.0015
10 min	85.1±7.8	83.0±9.7	89.9±9.2	0.5147	0.04	0.017
20 min	81.4±8.6	77.6±11.0	85.2±7.8	0.1415	0.051	0.0095
30 min	73.9±9.1	77.4±9.3	83.6±8.4	0.1461	0.0001	0.0001
40 min	71±9.5	72.1±12.3	79.5±4.6	0.214	0.0038	0.0035
Extubation	85.5±10.9	85.2±7.7	92.4±7.7	0.8125	0.0064	0.0071

Table: 7 Comparison of groups on basis of Mean arterial pressure.

MAP (mmhg)	GROUP-M	GROUP-C	GROUP-NS	P-value		
	Mean±SD			Group M and C	Group M and NS	Group C and NS
Baseline	96.4±6.7	96.8±5.7	96.1±7.3	0.8214	0.701	0.5147
After administration	93.0±7.3	94.7±7.5	96.2±9.6	0.5147	0.087	0.0687
Before pneumoperitoneum	89.7±8.7	92.3±8.4	91.3±10.5	0.1461	0.0614	0.7511
5 min	94.4±8.3	95.9±8.0	102.5±8.6	0.8125	0.0021	0.0095
10 min	98.5±9.6	95.3±10.8	104.5±10.4	0.6891	0.0071	0.0038
20 min	95.5±8.7	89.9±12.2	101.9±8.9	0.0818	0.0311	0.0001
30 min	88.3±8.2	89.5±12.1	102.1±9.7	0.6817	0.0001	0.0001
40 min	85.7±9.8	86.8±13.7	91.0±13.0	0.0871	0.014	0.017
Extubation	98.9±10.7	99.9±9.3	110.9±9.3	0.5061	0.0001	0.0006

Table: 8 Comparison of groups on basis of Heart Rate.

HR (beats/min)	GROUP-M	GROUP-C	GROUP-NS	P-value		
	Mean±SD			Group M and C	Group M and NS	Group C and NS
Baseline	90.1±11.3	95±13.9	90.1±8.4	0.5147	0.701	0.6151
After administration	81.9±7.7	92.5±13.5	98.1±7.1	0.0038	0.7511	0.0490
Before pneumoperitoneum	81.3±5.3	89.9±17.0	103.3±4.9	0.0001	0.1534	0.0001
5 min	82.1±7.4	93.1±12.3	104.1±5.1	0.0001	0.0001	0.0001
10 min	84.1±8.1	93.8±10.5	104.7±5.6	0.0001	0.0001	0.0001
20 min	84.3±6.3	91.4±8.5	103.4±4.1	0.0001	0.0001	0.0001
30 min	82.4±6.2	93.0±8.1	100.7±4.6	0.0006	0.0001	0.0001
40 min	84.1±6.9	79.7±6.2	98.9±1.7	0.0071	0.0001	0.0001
Extubation	94.9±7.8	98.9±12.3	101.2±5.9	0.0091	0.0021	0.041

Discussion

Laparoscopic surgeries are being performed more and more frequently now a days for various elective procedures. . So there is a need for the better control of hemodynamics intraoperatively in these types of surgeries. Various pharmacological agents have been studied in the recent past for attenuating the hemodynamic responses to the laparoscopy. Most of the studies have compared the effect of intravenous clonidine or magnesium with that of the control. Very few studies are available that compare intravenous clonidine with magnesium for attenuation of the hemodynamic responses to laparoscopy. We did a prospective, randomized, double blinded study to compare the effect of intravenous clonidine and magnesium on hemodynamic response to pneumoperitoneum in patients undergoing laparoscopic surgeries.

Kalra et al⁷ compared the attenuation of hemodynamic response during laparoscopic cholecystectomy due to pneumoperitoneum was infused with intravenous clonidine 1 µg/kg, clonidine 1.5 µg/kg, magnesium 50mg/kg and placebo and found that both clonidine doses and magnesium had significant attenuation on hemodynamic stress response when compared with placebo. The test drugs solution were infused after intubation for 15 minutes. Clonidine 1.5µg/kg showed statistically significant difference with magnesium 50mg/kg with no incidence of adverse events like bradycardia and hypotension.

Altan et al¹² used clonidine 3 µg/kg intravenously over a period of 15 minutes before induction and then 2µg/kg/min by continuous infusion intraoperatively. They observed significant incidences of bradycardia and hypotension in their study. Ray et al¹³ used 3 µg/kg of clonidine intravenously over a period of 15 min before induction and then 1 µg/kg/min by continuous infusion during surgery and observed significant incidences of bradycardia and hypotension in their study. We used clonidine 1µg/kg, given before pneumoperitoneum and we did not observe any

complications similar to study conducted by Kalra et al⁷.

Jee et al⁹ administered magnesium sulfate 50 mg/kg over 2-3 minutes, before pneumoperitoneum in patients undergoing laparoscopic cholecystectomy and observed that it effectively attenuated the hemodynamic stress response due to pneumoperitoneum without any episode of severe hypotension or bradycardia.

Kalra et al⁷ observed that statistically significant decrease in heart rate in patients who received clonidine 1.5µg/kg at the following intervals; 30 minutes after pneumoperitoneum (P <0.05) and 40 minutes after pneumoperitoneum (P <0.05) than magnesium 50mg/kg group. There was no statistically significant difference in heart rate between the clonidine 1µg/kg and magnesium 50mg/kg. This did not coincide with our study.

Altan et al¹² observed that there was no statistically significant difference in systolic blood pressure observed between the patients who received clonidine 3µg/kg bolus followed by 2µg/kg/hr infusion and magnesium sulphate 30mg/kg as a bolus followed by 10mg/kg/hr infusion. Jee et al⁹ conducted a study in which patients received magnesium sulphate 50mg/kg, infused immediately before pneumoperitoneum, showed statistically significant decrease in systolic blood pressure at 10 minutes (P <0.05), 20 minutes (P <0.05) and 30 minutes after pneumoperitoneum (P <0.05) than the placebo group. The observation of our study goes in concordance with above studies like Altan et al¹² and Jee et al⁹.

Altan et al¹² observed that there was no statistically significant difference in diastolic blood pressure observed between the patients who received clonidine 3µg/kg bolus followed by 2µg/kg/hr infusion, and magnesium sulphate 30mg/kg as a bolus followed by 10mg/kg/hr infusion. Jee et al⁹ conducted a study in which patients received magnesium sulphate 50mg/kg, infused immediately before pneumoperitoneum, showed statistically significant decrease in diastolic blood pressure at 10 minutes (P <0.05),

20 minutes ($P < 0.05$) and 30 minutes after pneumoperitoneum ($P < 0.05$) than the placebo group. The above studies were in favour our study.

In our study, there was no statistically significant fall in diastolic blood pressure is noted between the group-M and group-C. There was significant fall in diastolic blood pressure from P5 till extubation in group-M and group-NS. Similarly, in group-C and group-NS significant fall in diastolic blood pressure was also found from P5 till extubation.

Mishra et al¹⁴ observed that the patient who received clonidine 1.5µg/kg showed a statistically significant difference in mean arterial pressure at the following intervals; 5 minutes after pneumoperitoneum ($P = 0.037$), 10 minutes after pneumoperitoneum ($P < 0.001$), 15 minutes after pneumoperitoneum ($P = 0.006$) and 20 minutes, 25 minutes, 30 minutes, 35 minutes and 40 minutes pneumoperitoneum ($P < 0.01$).

Conclusion

Intravenous administration of clonidine 1.0µg/kg before pneumoperitoneum is as effective as intravenous magnesium sulfate 50mg/kg before pneumoperitoneum in blunting the haemodynamic stress responses during laparoscopic surgeries.

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