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Perioperative infusion of magnesium sulfate versus dexmedetomidine on the hemodynamic responses in patients undergoing laparoscopic cholecystectomy: A randomized controlled trial

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ABSTRACT

Background: Laparoscopic cholecystectomy is associated with less post-operative pain, shorter hospitalization, and a faster functional recovery as compared to the open procedure. However, like any other surgery, a stress response is induced. Anesthesia interventions such as direct laryngoscopy, tracheal intubation, and extubation involve severe sympathetic stimulation. Magnesium can block the release of catecholamines from both the adrenal gland and adrenergic nerve terminals by inhibiting of activation of membrane Ca^{2+}-ATPase and Na^{+}-K^{+}-ATPase. **Aims and Objectives:** Both magnesium sulfate and dexmedetomidine decrease the release of catecholamines and attenuate pressor responses to anesthesia and surgery. **Materials and Methods**: Eighty-four ASA I/II patients were randomly allocated to two groups. Group D received dexmedetomidine 1 µg/kg followed by 0.4 µg/kg/h and Group M received 2 g $MgSO_4$ followed by 15 mg/kg/h. hemodynamic variables were recorded as T0 (after loading dose of study drug), just before (T1) and 1, 2, and 3 min after ProSeal laryngeal mask airway (PLMA) insertion (T2 [i] [ii] [iii]), before and after peritoneal insufflation (T3 and T4), before and after table tilt (T5 and T6), after resuming flat position (T7), peritoneal deflation (T8), PLMA removal (T9), and on post-anesthesia care unit admission (T10). Data were collected and analyzed using SPSS 17 statistical software. **Results:** The demographic profile was comparable. After the study drug administration, there was a fall in mean arterial pressure (MAP) in both groups (Group D > Group M) and no pressor response to PLMA insertion. At peritoneal insufflation, the MAP increase was significantly more in Group M at T6, T7, and T8 (31.9%, 27.9%, and 35.6% above baseline, respectively). Although there was a fall in systolic blood pressure (SBP) from the baseline throughout the procedure in both groups, SBP was significantly higher at most times in Group M as compared to Group D ($P<0.05$). In both groups, there was a similar rise in diastolic blood pressure after peritoneal insufflation. The mean heart rate was significantly lower in Group D at all time points. **Conclusion:** Dexmedetomidine seemed to be superior to $MgSO_4$ for ameliorating hemodynamic responses in patients undergoing laparoscopic cholecystectomy.

Key words: Laparoscopic cholecystectomy; Magnesium sulfate; Dexmedetomidine

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INTRODUCTION

Laparoscopic cholecystectomy is associated with less post-operative pain, shorter hospitalization, and a faster functional recovery as compared to the open procedure. However, like any other surgery, a stress response is induced. Anesthesia interventions such as direct laryngoscopy, tracheal intubation, and extubation involve severe sympathetic stimulation. Carbon dioxide insufflation and the subsequent pneumoperitoneum lead to an increase in plasma catecholamine, renin, and vasopressin levels with increases in blood pressure (BP), systemic and pulmonary

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vascular resistances, and a fall in the cardiac output (CO).[1] Furthermore, the reverse Trendelenburg position leads to diminished venous return with a further reduction in CO.

Magnesium can block the release of catecholamines from both the adrenal gland and adrenergic nerve terminals by inhibiting of activation of membrane Ca^{2+}-ATPase and Na^{+}-K^{+}-ATPase. It produces vasodilatation by direct action on blood vessels and, in high doses, can attenuate vasopressin-induced vasoconstriction. Magnesium has a calcium inhibitory effect causing arteriolar vasodilatation and causes analgesia by blocking N-methyl-D-aspartate receptors.[2]

Dexmedetomidine has also been used to attenuate adverse hemodynamic responses in laparoscopic surgery. It is an alpha-2 adrenergic agonist and provides analgesia, sympatholysis, and sedation without causing respiratory depression and decreases opioid requirements and the stress response to surgery.[3]

Zarif et al. compared the use of loading doses of dexmedetomidine and $MgSO_4$ followed by intraoperative infusions on hemodynamics in patients undergoing laparoscopic colectomy.[4] The present study was conducted to evaluate the effects of perioperative infusions of $MgSO_4$ and dexmedetomidine on attenuation of the hemodynamic responses in patients undergoing laparoscopic cholecystectomy.

Aims and objectives

To evaluate the effects of the perioperative infusion of magnesium sulphate versus dexmedetomidine on the hemodynamic responses in patients undergoing laparoscopic cholecystectomy with regard to:

1. Blood Pressure (SBP, DBP, MAP)
2. Heart rate (HR).

MATERIALS AND METHODS

After Institutional Ethics Committee approval, this double-blind randomized controlled trial was conducted on patients scheduled for laparoscopic cholecystectomy under general anesthesia in the Department of Anaesthesiology in MAMC and associated Lok Nayak Hospital, New Delhi, over a period of 12 months. Patients of ASA I/II, aged 18–50 years were included in the study after the informed consent was obtained. Patients with a history of allergy to study drugs, diabetes mellitus, chronic hypertension, cardiac disease, neuromuscular disorders, and renal or hepatic insufficiency were excluded as were obese or pregnant patients and patients with an anticipated difficult airway. Based on results of a previous study,[4] for achieving a power of study equal to 80% and P=0.05, with mean arterial pressure (MAP) being the primary outcome, a sample size of 42 patients in each group was calculated.

A complete pre-anesthetic checkup was done and written informed consent was taken. Randomization was done by computer-generated random number tables, and group assignments were sealed in sequentially numbered opaque envelopes, which were opened immediately before surgery. Patients were blinded to their group allocation. On the morning of surgery, patients were randomly allocated into one of the two groups: Group M (Magnesium) or Group D (Dexmedetomidine).

On arrival in the operation theater, intravenous access and standard non-invasive monitoring were established and pre-operative vital signs were recorded. All patients were pre-medicated with 1 mg intravenous midazolam and pre-loaded with ringer lactate at 5 mL/kg and 5 min later, the loading dose of the study drug in 20 mL was administered over 10 min followed by infusion. Patients in Group M received intravenous $MgSO_4$ 2 g followed by an infusion at 15 mg/kg/h and in Group D received 1 μg/kg dexmedetomidine followed by an infusion at 0.4 μg/kg/h.

General anesthesia was then induced with intravenous fentanyl 1.5 μg/kg and propofol 1–2 mg/kg followed by atracurium 0.5 mg/kg and the airway was secured with an appropriate-sized ProSeal laryngeal mask airway (PLMA) with intracuff pressure maintained <60 cmH_2O using cuff pressure manometer intermittently. If the PLMA was not placed within the first attempt (i.e., PLMA removed and re-inserted) or placement time >30 s, that case was excluded from the statistical analysis. PLMA insertion time was considered from the time of introduction of the device into the oral cavity until the appearance of the first square wave capnograph on the monitor. If the PLMA was not placed within the first attempt or PLMA insertion time >30 s, the case was excluded from further statistical analysis. Maintenance of anesthesia in both groups was with 50% N_2O in O_2 and 1% isoflurane. The patient's lungs were mechanically ventilated with minute ventilation adjusted to maintain normocarbia. After the creation of the pneumoperitoneum, the intra-abdominal pressure was maintained ≤12 mmHg. Fifteen min before the expected end of the surgery, all patients received intravenous diclofenac 75 mg and ondansetron 4 mg. Infusion of the study drug was discontinued on removal of trocars. Residual neuromuscular blockade was reversed with intravenous neostigmine and glycopyrrolate and patients were shifted to the post-anesthesia care unit (PACU).

Hemodynamic variables including systolic BP (SBP), diastolic BP (DBP), MAP, and heart rate (HR) were recorded as T0 (baseline – after loading dose of study

drug), T1 (just before PLMA insertion), T2(i), T2(ii), T2(iii) (1, 2, and 3 min after PLMA insertion), T3 (at peritoneal insufflation), T4 (5 min after starting peritoneal insufflation), T5 (before making 30° RTP), T6 (5 min after 30° RTP), T7 (5 min after positioning flat), T8 (5 min after peritoneal deflation), T9 (after PLMA removal), and T10 (at admission to PACU). The sedation score was recorded on arrival in the PACU as 1 – awake, 2 – sleepy but arousable, and 3 – sleepy difficult to awake. The data were collected and analyzed using SPSS version 17 statistical software. Quantitative data were expressed as mean (±SD) or numbers as appropriate and analyzed using unpaired Student's t-test or univariate two-group repeated measures analysis of variance with *post hoc* Dunnett's test as appropriate. Nominal and non-normally distributed variables were analyzed using the Mann–Whitney test. A $P<0.05$ was considered statistically significant.

Sample size calculation

$$n = \frac{2\sigma^2\left(z_{\alpha/2} + z_{\beta}\right)^2}{\Delta^2}$$

n = sample size
Δ = the expected difference and
σ = standard deviation of the difference
$z_{\alpha/2} = 1.96$
$z_{\beta} = 0.842$.

Clinical trial registration number

CTRI/2018/06/014453.

RESULTS

In our study, out of 84 patients who entered the study pool, four patients were not included in the statistical analysis as in Group M, three patients developed a MAP >110 mmHg at peritoneal insufflation, 5 min after starting peritoneal insufflation, and before making surgical position, respectively, for which injection labetalol was given and in Group D, one patient developed bradycardia (HR <50 bpm) before peritoneal insufflation and was given intravenous atropine. Our study comprised two groups (M and D), each of which consisted of 39 and 41 subjects, respectively. The demographic profile of the patients was similar in both groups (Table 1).

The MAP was significantly lower just before PLMA insertion and 1 and 2 min after PLMA insertion and after positioning for surgery with the onset of surgical manipulation in Group D as compared to Group M (Figure 1). In Group M, there was no MAP response to PLMA insertion and MAP remained at baseline values.

Table 1: Demographic characteristics

Parameters	Group D	Group M	P-value
	Mean±SD	Mean±SD	
Age (years)	36.05±12.01	38.10±12.12	0.594
Gender (Male/Female)	10%/90%	5%/95%	1.00
Weight (kg)	62.05±8.10	58.85±8.28	0.224
Height (cm)	157.22±5.44	153.17±7.31	0.054
BMI (kg/m²)	25.05±2.64	25.042±2.8	0.996

BMI: Body mass index

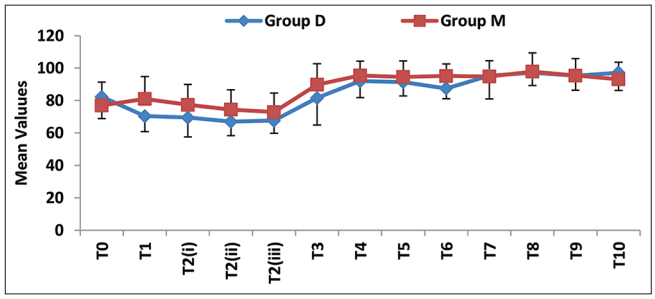

Figure 1: Comparison of mean arterial pressure in both groups

Whereas in Group D, the MAP continued to fall and was 15.6% below baseline 3 min after PLMA insertion. In both groups, the MAP continued to rise with the onset of peritoneal insufflation. The MAP remained significantly higher in Group M during surgical manipulation from T6 up to T8, that is, 5 min after peritoneal deflation with a maximum rise in MAP of 35.6±26.13% above baseline at T8. The SBP was significantly higher after PLMA insertion, at peritoneal insufflation, and during surgical manipulation in Group M as compared to Group D. The DBP was significantly lower after the bolus drug and after PLMA insertion in Group D as compared to Group M. The mean HR was significantly lower in Group D as compared to Group M at all studied times, that is, T0–T10 (Figure 2). On computing the mean hemodynamic data from the data collected at various time points, it was found that values of all hemodynamic parameters were significantly lower in Group D, ($P<0.05$) (Table 2). On arrival in the PACU, nine patients in Group D and 21 in Group M were fully awake, 32 patients in Group D were sleepy but arousable as compared to 18 in Group M. No patient in any of the two groups was sleepy and difficult to awake. The mean sedation score was 1.79±0.42 in Group D and 1.47±0.51 in Group M ($P=0.048$).

DISCUSSION

The hemodynamic changes observed during laparoscopic surgery are due to the combined effects of pneumoperitoneum, patient position, type of anesthesia, and hypercapnia from absorbed carbon dioxide. The increase in systemic vascular resistance is the main

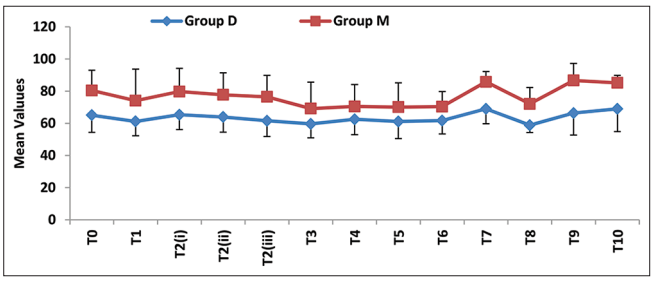

Figure 2: Comparison of heart rate in both groups

Table 2: Comparison of mean hemodynamic parameters between two groups

Mean	Group D (Mean±SD) mmHg	Group M (Mean±SD) mmHg	P-value
SBP	104.77±6.12	111.29±7.49	0.005
DBP	70.22±5.48	75.56±5.77	0.008
MAP	80.28±5.13	87.33±5.97	<0.001
HR	64.24±8.53	79.59±12.48	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, MAP: Mean arterial pressure

reason why the BP increases, despite a fall in the CO.[5] In laparoscopic cholecystectomy, the use of the RTP leads to diminished venous return and a further decrease in CO. Various pharmacological agents have been used to attenuate these adverse hemodynamic effects. In the present study, we studied the effects of intravenous $MgSO_4$ and dexmedetomidine in attenuating the increases in arterial pressure which occur during laparoscopic cholecystectomy. Intravenous dexmedetomidine, 1 μg/kg followed by an infusion of 0.4 μg/kg/h, was found to be more effective than $MgSO_4$, 2 g followed by an infusion of 15 mg/kg/h, in attenuating the hemodynamic responses during laparoscopic cholecystectomy.

In the dexmedetomidine group, there was a fall in MAP after induction and up to 3 min after PLMA insertion, and after peritoneal insufflation, the maximum rise in MAP during pneumoperitoneum was only 16.1%, above baseline. Whereas, in the magnesium group, there was no fall in MAP after induction, and after peritoneal insufflation, there was a significant rise in MAP from the baseline with the MAP increasing by 22.3%, 30.6%, and 28.9% at T3, T4, and T5, respectively. At T6, that is, after surgical positioning and after the onset of surgical manipulation, the rise in MAP from baseline was only 9.8±19.85% in Group D, whereas it was 31.9±24.11% in Group M. During surgical manipulation from T6 to T8, that is, up to 5 min after desufflation of the pneumoperitoneum, the MAP remained significantly higher in Group M when compared to Group D. The MAP in Group M increased to 35.6% after deflation of the pneumoperitoneum and remained elevated 28.7% above the baseline on the transfer of patients to the PACU. In three patients in Group M, the MAP increased to above 110 mmHg requiring administration of labetalol.

At most of the measured time points, there was a fall in SBP in both groups and the SBP returned to almost baseline levels by the end of the procedure. There was a minimal SBP response to PLMA insertion, but the SBP rose steadily after peritoneal insufflation and during surgical manipulation. There was no significant rise in SBP during the surgery in either group, and both drugs seemed to be effective in attenuating rises in SBP during laparoscopic cholecystectomy.

In both groups, there was a fall in DBP during induction and PLMA placement, but the DBP was significantly lower after the bolus drug and after PLMA insertion in Group D as compared to Group M. The fall in DBP from baseline values after the loading dose of the drug was higher in Group D and this fall in DBP remained significantly greater in Group D during PLMA insertion. There was a marked rise in DBP at peritoneal insufflation in both groups. This rise was significantly higher in Group M as compared to Group D. The maximum rise in DBP from the baseline was highest 5 min after assuming the flat position in both groups, being 42.9±22.34% in Group M and 30.6±35.03% in Group D.

During the procedure, the HR was significantly higher in Group M as compared to Group D at all studied times. The percentage change in HR from baseline during induction and creation of the pneumoperitoneum was <20% in both groups at all times. This is similar to previous studies which report no significant increase in HR during laparoscopic cholecystectomy.[6]

Dexmedetomidine is known to cause cardiovascular depression. The administration of 1 μg/kg dexmedetomidine initially results in a transient increase in BP and a reflex decrease in HR, especially in younger, healthy patients. The initial reaction is due to peripheral α-2B adrenoceptor stimulation of vascular smooth muscle and can be attenuated by administering the drug slowly.[7] This increase in MAP over the first 10 min has been shown to be about 7%, and is followed by a decrease in BP of approximately 10–20% below the baseline and a fall in HR of 16–18%.[6] The HR tends to stabilize below baseline values due to the inhibition of central sympathetic outflow overriding the direct stimulating effects and stimulation of the pre-synaptic α-2 adrenoceptors leading to a decreased norepinephrine release. One patient in Group D developed bradycardia before peritoneal insufflation and was given an injection atropine 0.6 mg intravenously.

Dexmedetomidine also causes reversible sedation without any respiratory depression. Although 32 patients in

Group D had a sedation score of 2 versus 18 patients in Group M, this difference was not statistically significant. No patient in either group had a sedation score of 3. Earlier reports also suggest that the sedation caused by dexmedetomidine is reversible.[8]

Rabie and Abdelfattah showed that perioperative intravenous infusion of dexmedetomidine 0.4 μg/kg/h and 0.6 μg/kg/h attenuated hemodynamic stress response during intubation, with the start of surgical manipulation, pneumoperitoneal insufflation and extubation in patients undergoing laparoscopic cholecystectomy.[9]

Srivastava et al. compared 1 μg/kg dexmedetomidine over 15 min followed by an infusion of 0.5 μg/kg/h with esmolol 1 mg/kg followed by 0.5 mg/kg/h in attenuating the hemodynamic response to pneumoperitoneum in elective laparoscopic cholecystectomy and found that HR, SBP, and DBP were significantly lower after induction, intubation and all times during pneumoperitoneum in the dexmedetomidine group as compared with the saline and esmolol groups.[10] In the present study, after starting insufflation, there was a rise in MAP in both groups, but the rise in Group M was significantly higher as compared to the rise in Group D. The rise in MAP during pneumoperitoneum was clinically insignificant (maximum 16.1%) in the dexmedetomidine group.

$MgSO_4$ has also been used to attenuate hemodynamic responses to stress. It is likely that its vasodilatory effects may contribute to hemodynamic stability during pneumoperitoneum.[11] Jee et al. found that administration of 50 mg/kg $MgSO_4$ before the creation of pneumoperitoneum attenuated the arterial BP rises and led to a significant reduction in the HR during the period of pneumoperitoneum. They suggested that plasma Mg levels of 2–4 mmol/L are required to obtain hemodynamic responses in laparoscopic cholecystectomy which is achieved with a bolus dose of 50 mg/kg.[12] In another study, Goral et al. found that toxic levels of serum magnesium are not reached after 50 mg/kg $MgSO_4$ as loading dose and continuous infusion of 20 mg/kg/h.[13] In the present study, we used a dose of 2 g intravenous $MgSO_4$ as a loading dose followed by an infusion of 15 mg/kg/h.

In the present study, there was a significant rise in MAP (>20% from baseline) in the magnesium group at all times after the creation of the pneumoperitoneum and this was significantly higher as compared to the dexmedetomidine group during positioning for surgery and surgical manipulation. While both dexmedetomidine and $MgSO_4$ have been shown to attenuate the hemodynamic response caused by pneumoperitoneum and position changes in laparoscopic surgeries independently, only a few studies have compared the use of dexmedetomidine with magnesium sulfate for blunting the hemodynamic responses in laparoscopic cholecystectomy.

Zarif et al. compared the effect of dexmedetomidine and magnesium sulfate on hemodynamic parameters in patients undergoing laparoscopic colectomy. Both drugs were comparable in ameliorating the pressor responses to anesthetic and surgical manipulations during laparoscopic colectomy. This difference is difficult to explain in the absence of more invasive hemodynamic monitoring data. As laparoscopic colectomy is conducted in the Tredelenburg position, the venous return may be augmented and may maintain the CO, unlike laparoscopic cholecystectomy which is conducted in the RTP. While the hemodynamic effects of magnesium can be attributed predominantly to its action on smooth muscle, dexmedetomidine reduces sympathetic activity, and provides analgesia. This may explain why dexmedetomidine was better able to attenuate the hemodynamic responses to surgical stimulation as compare to magnesium.

Limitations of the study

There were some limitations in the present study:

As only ASA 1 patients were included in the study, the results of this study cannot be extrapolated to patients with systemic diseases like diabetes, chronic hypertension, cardiac disease, obesity etc.

No invasive hemodynamic monitoring was done. Plasma catecholamines, vasopressin levels and serum magnesium levels were not monitored prior to and during the surgery.

CONCLUSION

Based on our results, dexmedetomidine seemed to be superior to $MgSO_4$ in attenuating the pressor response during induction of anesthesia and creation and maintenance of pneumoperitoneum and surgical manipulation. Further studies are required to assess the efficacy of $MgSO_4$ in attenuating these responses.

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Author's Contribution:
SS- Concept and design of the study, results interpretation, review of the literature, and preparing the first draft of the manuscript. Statistical analysis and interpretation, revision of the manuscript; **ARB-** Concept and design of the study, results interpretation, review of the literature and preparing the first draft of the manuscript, revision of the manuscript.

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