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A Prospective Randomized Comparative Study of Intravenous Dexmedetomidine versus Magnesium Sulphate as an Adjunct during Anesthesia for Laparoscopic Cholecystectomy

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Abstract

Introduction: The hemodynamic response to endotracheal intubation, pneumoperitoneum and extubation can increase perioperative morbidity and mortality. Dexmedetomidine is a highly selective alpha 2 adrenoreceptor agonist, routinely used to attenuate hemodynamic stress response. Magnesium Sulphate also inhibits catecholamine release from adrenal glands. It can modulate the neurohumoral responses observed during laparoscopic surgeries.

Aim and objectives: To compare the effectiveness of intravenous Dexmedetomidine and Magnesium Sulphate as an adjunct during anesthesia for laparoscopic cholecystectomy.

Materials and method: After taking permission from institutional ethical committee, patients of 18-60 years of either sex and American society of anesthesia grade I and II were divided into two groups of 35 each. In Group D, Dexmedetomidine 1 µg/kg and Group M, Magnesium Sulphate 40 mg/kg over 15 min in 20 ml NS were given intravenously before induction of general anesthesia. Peri operative hemodynamic parameters were noted as well as postoperative analgesia and sedation were assessed.

Results: There was fall in mean arterial pressure and heart rate after giving Magnesium Sulphate and Dexmedetomidine infusion, which further decreased after giving propofol in both the groups. There was rise in both the parameters after intubation and pneumoperitoneum but remained lower than the baseline throughout the intraoperative period in both the groups. The fall in mean arterial pressure and heart rate was more in Magnesium Sulphate group than in Dexmedetomidine group ($p<0.001$). Postoperative analgesia and sedation were comparable in both the groups.

Conclusion: Both, Dexmedetomidine 1 µg/kg and Magnesium Sulphate 40 mg/kg were able to attenuate hemodynamic response to anesthesia and surgical manipulation during laparoscopic cholecystectomy. However, Magnesium Sulphate produced better hemodynamic stability compared to Dexmedetomidine.

Keywords: Magnesium Sulphate; Dexmedetomidine; Laparoscopic cholecystectomy; Hemodynamic response

Introduction

Nowadays, laparoscopic surgery is the first choice for surgical management of various indications because of its benefits. However, it is associated with increase in serum catecholamine and nor epinephrine levels during pneumoperitoneum and carbon dioxide insufflation. All leads to significant alterations in hemodynamics which is harmful to the patients with compromised cardiac function in whom this may predispose the myocardium to ischemia [1-3]. Perioperative ischemia is associated with a significant increase in postoperative morbidity and mortality. Modern anesthesia practices therefore aim to prevent sympathetic discharge and provide hemodynamic stability perioperatively. Dexmedetomidine, being a more selective α2 receptor agonist, decreases catecholamine by 90% and causes fall in the heart rate and blood pressure along with decreased systemic vascular resistance and cardiac output. It increases the hemodynamic stability, and decreases anesthetic requirements and postoperative analgesic requirements. Magnesium Sulphate ($MgSO_4$) is well known to block the release of catecholamine from both adrenergic nerve terminals and the adrenal gland. Moreover, Magnesium produces vasodilator effect by acting directly on blood vessels, and high-dose Magnesium attenuates vasopressin-stimulated vasoconstriction. Magnesium also exerts its analgesic action as a non-competitive NMDA receptor antagonist, blocking ion channels in a voltage dependent manner. Several studies like Karla et al. and Shruthi et al. used intravenous Magnesium sulphate to suppress pressure responses to anesthetic and surgical manipulation during laparoscopic cholecystectomy [4,5]. So, we decided to carry out this study to compare the effectiveness of intravenous Dexmedetomidine and Magnesium Sulphate as an adjunct during anesthesia on hemodynamic response to critical incidences like laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. We hypothesized that $MgSO_4$ will be more effective in this regard than Dexmedetomidine. Our secondary aims were to compare the effect of both the drugs on postoperative sedation level, time to first rescue

analgesia, total analgesic requirement in 24 hours post operatively and occurrence of any adverse effects like hypotension, hypertension, bradycardia, tachycardia, arrhythmias or excessive sedation.

Material and Methods

It was a prospective randomized comparative study of total 70 patients, approved by our hospital ethics committee (CTRI/2018/07/0140901). Patients of 18-60 years of age group, ASA status I and II of either sex, posted for elective laparoscopic cholecystectomy were included in the study. Sample size per group was calculated using the t-test (Designing Clinical Research, Third edition, chapter 6; 65-84, Stephen B Hulley, Steven R Cummings, Warren S Browner, Deborah R Grady, Thomas B Newman) By taking the parameter mean arterial pressure from the reference study, sample size of 32 patients in each group was required to obtain study power of 80%, significance level 5% with confidence interval 95% [6]. After considering the dropouts, we have taken 35 patients in each group. Patients having anticipated difficult airway, morbid obesity, allergy to study drug, heart rate <60 beats/min, pregnant or lactating females and patients who refused to give consent were excluded from the study. Randomization was done by computer generated random numbers and they were randomly allotted to two groups by sealed envelope method. In group D inj. Dexmedetomidine 1 μg/kg slow infusion over 15 minutes in 20 ml normal saline and in group M, inj. $MgSO_4$, 40 mg/kg slow infusion over 15 minutes in 20 ml normal saline was given before induction. All patients underwent a thorough pre-anesthetic check-up and routine investigations were done. They were explained in detail about the objectives of the study, advantages and likely complications. Informed written consent was taken from those willing to participate in the study. All the patients were kept nil by mouth from 10 p.m. a day before surgery. Tab. Ranitidine (150 mg) was given orally on the previous night of operation. On the day of surgery, intravenous line was secured and a multipara monitor was attached and the baseline parameters Heart Rate (HR), systolic and diastolic blood pressure, mean arterial pressure (MAP) and oxygen saturation, were recorded.

Premedication was given just before study drug infusion to all the patients in the form of inj. Glycopyrrolate 5 μg/kg, inj. Ondansetron 0.08 mg/kg and inj. Fentanyl 2 μg/kg intravenously. Inj Dexmedetomidine (inj DEXEM, Themis Medicare) 100 μg in a 20 ml syringe diluted with normal saline up to 20 ml (5 μg/ml). Magnesium Sulphate used in study was inj Magnesium sulphate (Arco Life sciences), 2 gm of $MgSO_4$ diluted with normal saline up to 20 ml (100 mg/ml). Both the infusions, Inj Dexmedetomidine in a dose of 1 μg/kg and $MgSO_4$ 40 mg/kg, were given through the INFUSA 101-P syringe infusion pump over 15 minutes just after premedication. Preoxygenation was done for 3 minutes after completion of the study drug infusion. Patients were induced with inj Propofol 2 mg/kg and amount of drug needed for induction was noted down. Once jaw was relaxed after giving inj Succinyl Choline, laryngoscopy and tracheal intubation was done. Close circuit with $ETCO_2$ monitor was attached and confirmed. Anesthesia was maintained with controlled ventilation through closed circuit with O_2:N_2O (50:50) in fresh gas flow of 2 litres/min, Sevoflurane and intermittent inj Vecuronium. All patients were operated with head-up tilt of 150. CO_2 pneumoperitoneum was created and intraabdominal pressure maintained at 14 mm Hg. Intermittent positive pressure ventilation 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. During surgery, Ringer's lactate solution was administered in accordance with fasting volumes, maintenance volumes, and blood losses. Arterial pressures, heart rate, SPO_2, $EtCO_2$ and ECG were measured before induction (baseline); after intubation; before pneumoperitoneum; at 1, 5, 15, 30, 45, 60, 90 and 120 minutes after pneumoperitoneum, post-pneumoperitoneum; and after extubation. At the end of operation, nitrous oxide and Sevoflurane were stopped. The residual neuromuscular blockade was reversed by intravenous inj. Neostigmine and Glycopyrrolate. Postoperatively, sedation was assessed at 1 min, 15 min, 30 min, 60 min and 120 min with the help of Ramsay sedation score as follows:

(1) Patient is anxious and agitated or restless or both,

(2) Patient is cooperative, oriented and tranquil,

(3) Patient responds to commands only,

(4) Patient exhibits brisk response to light glabellar tap or loud auditory stimulus,

(5) Patient exhibits sluggish response to light glabellar tap or loud auditory stimulus,

(6) Patient exhibits no response.

Postoperative pain intensity was assessed using a 10 point visual analogue scale (VAS) on which 0 indicates no pain and 10 indicates the worst pain imaginable. Inj Tramadol 50 mg intravenously was given if VAS ≥ 4 as a rescue analgesic and was repeated when required. Time for first rescue analgesia and total number of analgesic doses required in first 24 hours were noted. Perioperative adverse events like hypotension, hypertension, bradycardia, arrhythmias and excessive sedation were noted and treated accordingly. All the data obtained were properly tabulated in excel sheet and statistical analysis for various parameters was done using MedCalc software, version 12.5.0.0. Student's paired t-test was used for intra-group comparison and unpaired t-test for intergroup comparison of categorical data. Chi-square test was used for qualitative (demographic) data like ASA grading and gender. Results were expressed as Mean ± SD and p value<0.05 was considered significant.

Results

All the demographic variables were comparable between both the groups (Table 1).

Parameters	Group D	Group M
Age (years) (Mean ± SD)	39.25 ± 12.51	37.45 ± 12.72
Sex : male	5 (14.28%)	4 (11.42%)
female	30 (85.71%)	31(88.57%)
ASA grade:1	18 (51.42%)	20 (57.14%)
2	17 (48.57%)	15 (42.85%)
Weight (kg) (Mean ± SD)	59.63 ± 9.01	59.03 ± 7.44
Duration of anesthesia (Minutes)	99.05 ± 10.01	98.05 ± 12.08

Table 1: Demorgraphic data.

The mean HR and MAP before starting the infusion were comparable in both the groups. After starting the infusion, the mean heart rate in group D and group M, there was a highly significant decrease in HR and MAP following the drug infusion.

Laryngoscopy and intubation raised the HR and MAP, but this rise was short and then again it became less than the pre-infusion value and remained so after creation of pneumoperitoneum and release of pneumoperitoneum. Extubation caused rise in mean HR and MAP but values were not higher than pre-infusion value and remained highly significantly lower than preinfusion value for 10 min after extubation.

The values remained highly significantly lower in Group M compared to Group D at every point of time like laryngoscopy, intubation, pneumoperitoneum and extubation (Figures 1 and 2).

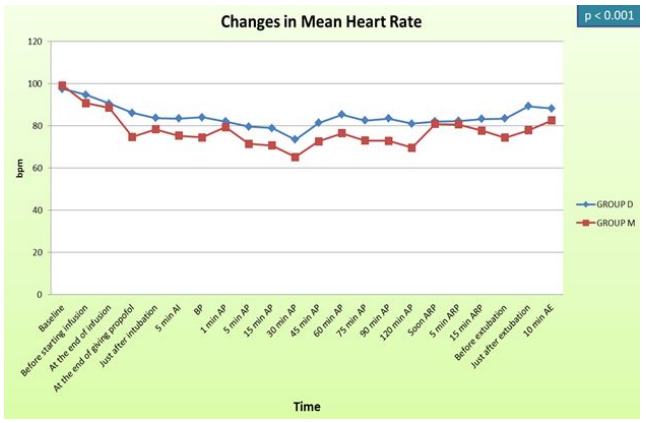

Figure 1: Changes in mean heart rate.

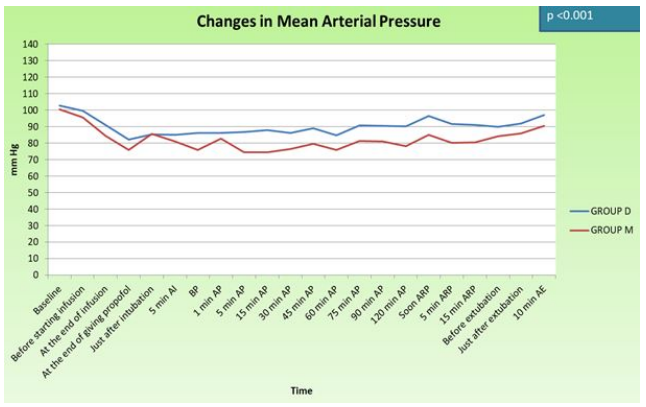

Figure 2: Changes in mean arterial pressure.

The mean HR decreased by 6.92% in group D and by 10.52% in group M after drug infusion. While, MAP decreased by 11.75% in group D and by 15.89% in group M after drug infusion.

Laryngoscopy and intubation caused a rise in mean HR and MAP but the values were still less than pre-infusion values. Pneumoperitoneum and extubation both caused a rise in mean HR and MAP but the values were still less than pre-infusion values. The control over mean HR and MAP was better in group M compared to group D (Tables 2 and 3).

Time	Group D	Group M
After drug infusion	6.92% ↓	10.52% ↓
After laryngoscopy and intubation	↑ but still values 6.41% less than pre infusion value	↑ but still values 9.3% less than pre infusion value
After pneumoperitoneum	15.5% ↓	19.66% ↓
After extubation	9.33% ↓	16.75% ↓

Table 2: Changes in heart rate % wise from pre infusion values.

Time	Group D	Group M
After drug infusion	11.75% ↓	15.89% ↓
After laryngoscopy and intubation	↑ but still values 10.33% ↓ than pre infusion value	↑ but still values 14.74% ↓ than pre infusion value
After pneumoperitoneum	16.42% ↓	17.78% ↓
After extubation	5.58% ↓	9.88% ↓

Table 3: Changes in mean arterial pressure % wise from pre infusion values.

Majority of the patients remained sleepy but responded to verbal commands in both the groups at 1 minute post extubation. None of the patients in two groups were heavily sedated (score 4, 5, 6).

Post operatively, up to 2 hours the sedation score was 2 in majority patients in both the groups (Figure 3). The mean time for first rescue analgesic requirement in group D was 110 ± 32.7 minutes and in group M was 120 ± 25.6 minutes.

The cumulative analgesic dose requirement was 115 ± 24.8 mg in group D and 102 ± 38.3 mg in group M in 24 hours post operatively. Both the groups were comparable in this regard (Table 4). No incidence of any perioperative adverse events observed in our study.

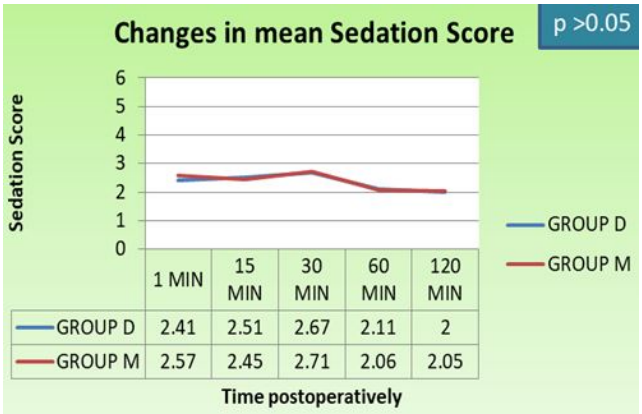

Figure 3: Changes in mean sedation score.

Parameter	Group D	Group M	p value
Time for first rescue analgesic requirement (Minutes)	110 ± 32.7	120 ± 25.6	0.158
Cumulative analgesic dose required in 24 hours (Mg)	115 ± 24.8	102 ± 38.3	0.096

Table 4: Time for first rescue analgesia and total analgesic requirement in 24 hrs.

Discussion

Dexmedetomidine infusion in the dose of 1 μg/kg and $MgSO_4$ infusion in the dose of 40 mg/kg not only significantly reduced the mean HR and MAP before induction of anaesthesia but also controlled their rise following laryngoscopy, tracheal intubation, pneumoperitoneum as well as extubation. Their values remained significantly lower than baseline at every point of time. The mean values of the HR and MAP were highly significantly less than the baseline value with $MgSO_4$ compared to Dexmedetomidine at each critical juncture of surgery.

Dexmedetomidine and Magnesium sulphate significantly reduced the release of catecholamines, especially nor epinephrine release, thereby attenuating the increase in systemic vascular resistance. So, both drugs improve intra and postoperative haemodynamic stability by stabilizing the changes in arterial pressure, heart rate and cardiac output.

Activation of α2 adrenergic receptors by Dexmedetomidine in the brain and spinal cord inhibits neuronal firing, thereby causing hypotension, bradycardia, sedation and analgesia. Generally presynaptic activation of α2 adrenergic receptors inhibits the release of nor epinephrine. Post synaptic activation of α2 adrenergic receptors in the central nervous system inhibits sympathetic activity and therefore decreases blood pressure and heart rate.

Thus, effects on hemodynamic are mediated by inhibition of central sympathetic outflow. Dexmedetomidine produces its effects on haemodynamic variables by acting on α2 subtype of receptors located in CNS and in peripheral smooth muscle cells. Bhana et al. and Kallio et al. reported completely blocked nor epinephrine secretion of sympathetic nerves by single dose of intravenous Dexmedetomidine and 92% decrease in plasma norepinephrine levels leading to decrease in MAP and HR [7,8].

The effect of $MgSO_4$ on hemodynamics is due to its interaction and activation of membrane Ca-ATPase and Na-K-ATPase which are involved in trans-membrane ion exchange during depolarization and repolarisation phases, thus acting as a cell membrane stabilizer. This calcium inhibitory effect of $MgSO_4$ and attenuates vasopressin-stimulated vasoconstriction causes central arteriolar vasodilatation and acts against vasospasm. Another mechanism could involve the reduction of catecholamine release with sympathetic stimulation, thereby decreasing the stress response to surgery.

Various authors like James MF et al. and D Jee et al. used $MgSO_4$ in a dose of 60 mg/kg and 50 mg/kg respectively and confirmed the efficacy of intravenous $MgSO_4$ in controlling the hemodynamic response to various critical incidences like laryngoscopy, intubation, pneumoperitoneum and extubation [9,10]. Shruthi P Kamble et al. compared Magnesium sulphate 50 mg/kg with Clonidine 1 mcg/kg in attenuating hemodynamic response to pneumoperitoneum during laparoscopic cholecystectomy and concluded that the response was better with Magnesium 50 mg/kg [6].

James MF et al. and Pichard Ja reported that 2-4 mmol/l concentration of $MgSO_4$ is required to inhibit the release of catecholamine and vasopressin or both [9,11]. D Jee et al. 2009 recommended bolus dose of 40-50 mg/kg before pneumoperitoneum to exert this beneficial effect during laparoscopy. This justifies the preoperative intravenous infusion of $MgSO_4$ in dose of 40 mg/kg in our study [10].

As a further support for efficacy of both drugs, Bryskin and Weldon used a combination of Dexmedetomidine and Magnesium sulphate for hemodynamic control during laparoscopic resection of pheochromocytoma and reported that cardiovascular stability was achieved [12].

Postoperatively, majority of the patients had sedation score 3, means they were sleepy but responded well to verbal commands in both the groups. This result correlated well with Zarauza R et al. who found that patients receiving $MgSO_4$ were not sedated in spite of using it as bolus and/or infusion [13]. Peck and Meltzer attempted anesthesia by $MgSO_4$ infusion in patients for herniorrhaphy and achieved a narcotic state [14]. Depressant effect of $MgSO_4$ on central nervous system of animals too has been reported [15].

Dexmedetomidine has specificity for α2 a subtype that has been detected in locus coeruleus, a key source of noradrenergic innervations of the fore brain and an important modulator of vigilance. The α2 adrenoceptor activation has been attributed to inhibition of this nucleus which is responsible for this sedative effect of Dexmedetomidine. Moreover it has strong synergistic effect with other sedatives and opioids and produces 50 to 70% reduction in Propofol, Midazolam and opioids requirement [16,17].

We used inj. Fentanyl in the premedication to provide intraoperative analgesia and inj Tramadol as rescue analgesic in the postoperative period. No difference found on comparing the effect of Dexmedetomidine and $MgSO_4$ in the mean time for first rescue analgesic requirement and the cumulative rescue analgesic dose requirement in 24 hours postoperatively.

The effective use of $MgSO_4$ on postoperative analgesia was reported by Mentes et al. in patients undergoing laparoscopic cholecystectomy [18]. $MgSO_4$ exerts its analgesic action as a non-competitive NMDA receptor antagonist, blocking ion channels in a voltage dependent manner. It abolishes hyper sensitization by blocking NMDA receptor activation in the dorsal horn by excitatory amino-acid transmitter. Zarauza R et al. suggested that NMDA blocking drugs should be given before beginning of nociceptive stimulus to inhibit process of central sensitization [14].

Dexmedetomidine produces analgesic effect by an action on α2 receptors within the locus cerouleus and spinal cord. Stimulation of α2 adrenergic receptors at this site reduces central sympathetic output, resulting in increased firing of inhibitory neurons. The presence of Dexmedetomidine at α2 adrenergic receptors in dorsal horn of spinal cord modulates the release of substance P to produce analgesic effect.

Conclusion

Dexmedetomidine 1 μg/kg or $MgSO_4$ 40 mg/kg before pneumoperitoneum can ameliorate the pressure responses to anesthetic and surgical manipulations during laparoscopic

cholecystectomy without producing any significant adverse effects. Although, $MgSO_4$ blunts this response better compared to Dexmedetomidine.

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