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Research Article

Comparison of Magnesium Sulphate and Dexmedetomidine for Attenuation of Stress Response in Patients Undergoing Laparoscopic Cholecystectomy under General Anaesthesia by Measuring Biochemical Markers of Stress Response: A Prospective Randomized Study

Shivam Jaisawal[1], Vijay Kumar Nagpal[1], Amlendu Yadav[2], Sandeep Kumar[1]*, Rupesh Yadav[1]

[1]*Department of Anesthesiology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr RML Hospital, New Delhi, India.*

[2]*Department of Critical Care Medicine, Atal Bihari Vajpayee Institute of Medical Sciences and Dr RML Hospital, New Delhi, India.*

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ABSTRACT

Background: Laryngoscopy, endotracheal intubation, pneumoperitoneum creation and extubation is stressful event marked by hemodynamic changes during laparoscopic procedures. This increases secretion of many biochemical stress markers for example, cortisol levels, TNF-alpha levels, CRP levels, blood Sugar levels. Aim of the study was to compare magnesium sulphate and dexmedetomidine for attenuation of stress response in patients undergoing laparoscopic cholecystectomy under general anaesthesia by measuring biochemical markers of stress response.

Methods: 60 patients, age between 18 to 60 years of either sex, who were undergoing Laparoscopic cholecystectomy randomized into two groups of 30 patients each by computer generated random number. Group M- received magnesium sulphate 50 mg/kg and group D - received dexmedetomidine 1 µg/kg.

Results: The demographic data were comparable in both groups. Cortisol levels rise in both the groups but significantly more in group M than group D at 30 minute (p-value < 0.001) and 4 hours (p-value < 0.001). CRP levels rise in both the groups but significantly more in group M than group D at 30 min (p-value 0.013) and 4 hours (p-value 0.020). Blood sugar levels rise in both the groups but significantly more in group M than group D at 30 min, 4 hours and 24 hours (p-value <0.001). TNF-alpha levels rise in both the groups but significantly more in group M than group D at 30 min (p-value 0.005) and 4 hours (p-value 0.007).

Conclusion: We conclude that biochemical stress marker levels (Cortisol levels, TNF-alpha, levels, CRP levels, Blood Sugar levels) were more increased in the magnesium sulphate group compared with the dexmedetomidine group. Heart rate and Mean arterial pressure were higher in the Magnesium sulphate group than the Dexmedetomidine group. Dexmedetomidine is better than magnesium sulphate in attenuating the stress of surgery in patients undergoing laparoscopic cholecystectomy.

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: sandeepvmmc@gmail.com

Introduction

In 1987, Philipe Mouret performed the first laparoscopic cholecystectomy [1]. It became popular because of the shorter time for surgery and less pain. Laryngoscopy, tracheal intubation and extubation, the surgery itself, creating pneumoperitoneum, all excite a stress response leading to endocrinological changes [2]. Endotracheal intubation is considered as, to be one of the stress inducing stimuli in anesthesia [3], Laryngoscopy, endotracheal intubation, and extubation may cause hemodynamic changes [4]. Direct laryngoscopy and tracheal intubation in patients with normal protective airway reflexes result in stimulation of the sympathetic nervous system. It causes increased levels of catecholamines leading to tachycardia and hypertension [5].

Apart from endotracheal intubation, pneumoperitoneum creation is another stressful event marked by hemodynamic changes during laparoscopic procedures [6]. This increases secretion of many catabolic and anabolic hormones resulting in increased metabolic rate, for example, cortisol, catecholamines, glucagon, aldosterone, antidiuretic hormone, thyroid hormone, and growth hormone [1,7-8]. Plasma levels of catecholamines and vasopressin are increased immediately after pneumoperitoneum. The renin-angiotensin-aldosterone–system (RAAS) is activated by increased levels of catecholamines leading to some of the characteristic hemodynamic changes like elevated arterial pressure and increased systemic/pulmonary vascular resistance [9-10].

Despite laparoscopy being minimally invasive, the classical stress responses (catecholamines, cortisol, and glucose) are not greatly changed in comparison to open cholecystectomy [11-12]. Hence, stress attenuation is also of high relevance to patients and anaesthesiologists. Various pharmacological agents like opioids, dexmedetomidine, magnesium sulphate, clonidine, and deep anaesthetics are used to achieve this goal [13].

Magnesium sulphate decrease the stress response by blocking the discharge of catecholamines from the adrenal gland and causes vasodilatation [14]. Magnesium sulphate also produces the vasodilator effect, and high-dose Magnesium diminishes vasopressin-stimulated vasoconstriction [15-17]. Dexmedetomidine is a well-known alfa-2 adrenergic agonist, and It has analgesic properties and sedative effects without respiratory depression, thus it decreases the stress response to surgery [13]. Dexmedetomidine decrease sympathetic, and cardiovascular response to laryngoscopy if given as preanesthetic medication [18-19].

So we proposed this study to compare the detailed biochemical response of magnesium sulphate and dexmedetomidine in patients undergoing laparoscopic cholecystectomy under general anaesthesia by measuring biochemical marker levels. Aim of the study was to compare magnesium sulphate and dexmedetomidine for attenuation of stress response in patients undergoing laparoscopic cholecystectomy under general anaesthesia by measuring biochemical markers of stress response.

Methods

This prospective Randomised Study was conducted after approval from institutional ethics committee (IEC/ABVIMS/RMLH/668/19) and registration with clinical trial registry of India (CTRI/2020/09/027772). 60 patients age between 18 to 60 years of either sex, ASA class I and II, BMI up to 30 kg/m2, posted for elective laparoscopic cholecystectomy were included for the study. Patients with hypermagnesaemia, a known allergy to magnesium sulphate, a known allergy to dexmedetomidine, hemodynamically unstable patients, Pregnancy were excluded.

The sample size calculation was based on a study conducted by Chandrasekaran V et al, observed that mean values of blood glucose intraoperative after 30 minutes was 100.17 mg/dl, 110.27 mg/dl in dexmedetomidine and magnesium sulphate respectively [1]. These values taken as a reference and assuming a standard deviation of 10 mg/dl, the minimum required sample size with 95% power of study and 5% level of significance is 26 patients in each study group. The total sample size taken is 60 (30 patients each group), to decrease the margin of error.

After written and informed consent, all the patients. After a full pre-operative evaluation, and investigation, patients meeting the inclusion criteria were taken for the study. 60 patients were randomly divided into two group of 30 patients each by computer generated random number. Group D - Patient Received Dexmedetomidine 1 µg/kg. and Group M – Patient Received Magnesium sulphate 50mg/kg. Patients were premedicated with Tab Ranitidine 150 mg night prior to surgery. After shifting the patient to the operating table standard monitoring in the form of ECG, heart rate, non-invasive BP, Pulse oximetry were attached. Baseline vitals were recorded. A wide bore intravenous cannula was secured and IV fluids infusion was started. Patients in group M received magnesium sulphate 50 mg/kg diluted to make 50 ml with normal saline and group D received dexmedetomidine 1 µg/kg (2 ml diluted in 48 ml normal saline and make a total of 50 ml). Both these groups received drugs over 15 minutes through an infusion pump. After 15 minutes of test drug injection general anaesthesia was induced by using fentanyl 2 mcg/kg and propofol 2mg/kg. Vecuronium bromide (0.1mg/kg) was used to facilitate laryngoscopy and tracheal intubation. Laryngoscopy and intubation was done after 3 minutes of Vecuronium bromide administration by using cuffed endotracheal tube. General anesthesia was maintained with 50:50 oxygen and nitrous oxide and Vecuronium bromide and Sevoflurane throughout the surgery. At the

end of the surgery, patients were assessed for extubation and extubated after giving reversal agents, Neostigmine 0.05mg/kg + Glycopyrrolate 0.01 mg/kg.

Samples for biochemical measurement was taken as follows, baseline sample at 8 AM, intra operative- 20 minutes after pneumoperitoneum ,4 hours after reversal of anaesthesia, 24 hours after induction of anaesthesia. Sample collection was done by doing venepuncture each time from different limbs and 5 ml of blood was sampled at each time.

Primary objective of the study was to compare magnesium sulphate and dexmedetomidine for attenuation of stress response in patients undergoing laparoscopic cholecystectomy under general anaesthesia by measuring biochemical markers of stress response. Secondary objective of the study was to compare hemodynamic responses with magnesium sulphate and dexmedetomidine preoperatively, 1 minute, 5 minutes and 20 minutes after creating pneumoperitoneum.

Statistical Analysis

In statistical analysis was performed by the SPSS program for Windows, version 21.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t-test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi-square test or Fisher's exact test. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference

Results

60 patients were included in the study. No significant difference was seen in age(years) between group M (Mean ± SD 39.67 ± 8.71) and group D (Mean ± SD 38.67 ± 9.59) (p value 0.674). No significant difference was seen in Weight (kg) between group M (Mean ± SD 62.63 ± 5.42) and group D (Mean ± SD 64.80 ± 6.84) (p value 0.518). No significant difference was seen in height (cm) between group M (Mean ± SD 158.77 ± 5.34) and group D (Mean ± SD 161.67 ± 7.43) (p value 0.088). No significant difference was seen in BMI(kg) between group M (Mean ± SD 24.85 ± 1.91) and group D (Mean ± SD 24.92 ± 3.21) (p value 0.916) (Table 1).

Baseline cortisol levels were comparable in both group (p-value 0.801). Cortisol levels rise in both the groups but significantly more in group M than group D at 30 minute (p-value < 0.001) and 4 hours. (p-value < 0.001). Baseline TNF- alpha levels were comparable in both groups. TNF - alpha levels rise in both the groups but significantly more in group M than group D at 30 min (p-value 0.005) and 4 hours (p-value 0.007). The TNF- alpha level fell back to initial values in both groups at 24 hrs. Baseline CRP levels were comparable in both groups. CRP levels rise in both the groups but significantly more in group M than group D at 30 min (p-value 0.013) and 4 hours (p-value 0.020). The CRP levels fell back to initial values in both groups at 24 hrs. Baseline Blood sugar levels were comparable in both groups. Blood sugar levels rise in both the groups but significantly more in group M than group D at 30 min, 4 hours and 24 hours. (p-value <0.001) (Table 2).

Baseline heart rate was comparable in both groups. Heart rate increases in both the groups but significantly more in group M than group D at 0 minute (p-value 0.039), 1 minute (p-value 0.008) and returned back to baseline at 20 minutes. Baseline mean arterial pressure was comparable in both groups. Mean arterial pressure increases in both the groups but significantly more in group M than group D at 1 minute (p-value <0.001), 5 minutes (p-value 0.002), and 20 minutes (p-value 0.008) (Table 3).

Table 1- Demographic details

	Group M Mean ± SD	Group D Mean ± SD	P value
Age (years)	39.67 ± 8.71	38.67 ± 9.59	0.674
Weight (kg)	62.63 ± 5.42	64.80 ± 6.84	0.518
Height (cm)	158.77 ± 5.34	161.67 ± 7.43	0.088
BMI (kg/m2)	24.85 ± 1.91	24.92 ± 3.21	0.916

Table 2- Comparison of Cortisol levels, TNF-alpha levels, CRP levels, Blood Sugar levels between two groups

	TIME	Group M Mean ± SD	Group D Mean ± SD	P value
Cortisol levels	Baseline	321.77±84.06	327.07±35.67	0.801
	30 minutes	463.97±107.1	376.63±36.09	<0.001
	4 hours	563.53±100.25	408.07±28.82	<0.001
	24 hours	332.57±73.24	325.67±30.63	0.387
TNF-alpha levels	Baseline	18.58±5.85	17.02±4.41	0.395
	30 minutes	31.92±10.61	24.42±5.7	0.005
	4 hours	25.29±7.78	20.21±4.51	0.007
	24 hours	17.34±5.04	16.03±4.24	0.351

CRP levels,	Baseline	0.51 ± 0.08	0.52 ± 0.04	0.435
	30 minutes	0.64 ± 0.11	0.57 ± 0.07	0.013
	4 hours	0.61 ± 0.1	0.55 ± 0.06	0.020
	24 hours	0.53 ± 0.07	0.53 ± 0.05	0.713
Blood Sugar levels	Baseline	101.23 ± 7.89	101.23 ± 5.37	1.000
	30 minutes	110.93 ± 7.41	103.83 ± 5.62	<0.001
	4 hours	118.63 ± 7.12	106.7 ± 5.62	<0.001*
	24 hours	109.79 ± 7.78	100.9 ± 4.46	<0.001

Table 3- Comparison of Heart rate, Mean arterial pressure between the two groups

	Time in minutes	**Group M Mean ± SD**	**Group D Mean ± SD**	**P value**
Heart Rate	0	76.4 ± 6.34	77 ± 4.39	0.671
	1	81.93 ± 6.42	78.97 ± 4.24	0.039
	5	84.17 ± 6.21	80.33 ± 4.4	0.008
	20	76.07 ± 5.63	75.97 ± 4.35	0.939
Mean arterial pressure	0	83.77 ± 3.21	82.97 ± 4.15	0.407
	1	87.33 ± 3.23	82.53 ± 4.79	<0.001
	5	86.9 ± 3.27	83.4 ± 4.95	0.002
	20	83.57 ± 3.98	80.73 ± 3.95	0.008

Discussion

Laparoscopic cholecystectomies are performed under general anaesthesia during which surgery itself, laryngoscopy, tracheal intubation, and extubation, and other critical events like pneumoperitoneum increase surgical stress response leading to endocrinological and other inflammatory responses.

In our study, serum cortisol levels rise in both the groups at 30 minutes after pneumoperitoneum and 4 hours after the procedure, and came back to near baseline values at 24 hours in both groups. The rise in cortisol levels was significantly higher in the magnesium group as compared to the dexmedetomidine group at 30 minutes (p-value < 0.001) and 4 hours after the procedure (p-value < 0.001). Yacout A et al [20], observed in their study that intravenous infusion of dexmedetomidine causes a reduction in stress response to major surgery. They found less increased cortisol levels in the dexmedetomidine group as compared with the normal saline group postoperatively (p-value< 0.000). Their results were similar to our study. Sari R et a [21], observed in their study found a significant increase in cortisol levels postoperatively (6 hours) in comparison to preoperative levels (p-value= 0.02). Their results are matching our study. Desborough J [12], found in their article that cortisol levels increase rapidly following the start of surgery and peak at about 4-6 hrs of surgery. We found a similar change in the cortisol levels in our study.

In our study serum TNF-alpha levels rise in both the groups at 30 minutes after pneumoperitoneum and 4 hours after the procedure and came back to near baseline values at 24 hours in both the groups. The rise in TNF-alpha levels was significantly higher in the magnesium group as compared to the dexmedetomidine group at 30 minutes after pneumoperitoneum (p-value < 0.005) and 4 hours after the procedure (p-value< 0.007), signifying better suppression of inflammatory response by dexmedetomidine. Sari R et al [21], in their study found a significant increase in TNF-alpha levels postoperatively (6 hours) in comparison to preoperative levels (p-value = 0.003). Their results are matching our study.

In our study serum CRP levels rise in both the groups at 30 minutes after pneumoperitoneum and 4 hours after the procedure and came back to near baseline values at 24 hours in both groups. The rise in CRP levels were significantly higher in the magnesium group as compared to the dexmedetomidine group at 30 minutes after pneumoperitoneum (p-value < 0.013) and 4 hours after the procedure (p-value < 0.020), signifying better suppression of inflammatory response by dexmedetomidine. Sari R et al [21], in their study found that there was no significant increase in CRP levels in postoperative than preoperative (P-value= 0.14).

In our study blood sugar levels rise in both groups. The rise was more in the magnesium sulphate group than the dexmedetomidine group at 30 minutes, 4 hours, and 24 hours after the procedure (p-value < 0.001). Harsoor S et al [22], studied the effect of dexmedetomidine on blood sugar levels in general anaesthesia. They found a less increase (P< 0.01) in blood glucose levels in dexmedetomidine (118.2 ± 16.24 mg/dL) as compared to the placebo group (136.95 ± 19.76 mg/dL) 1 hour postoperatively and returning to near baseline levels by 6 hours postoperatively in both the groups. Chandrasekaran V et al [1], found an increase in blood sugar levels from baseline value at 60 minutes after induction of surgery in all three groups (167.17 in control, 101.73 in dexmedetomidine, and 117.67 in magnesium). Dexmedetomidine had better control of blood sugar than magnesium sulphate in their study. Our study results are

similar to this study. Gupta K, et al [13], used blood sugar measurement to compare dexmedetomidine with fentanyl premedication for stress attenuation in laparoscopic cholecystectomy surgery. Dexmedetomidine had better control of blood sugar than fentanyl in their study. Our study found similar result.

In our study, both heart rate and mean arterial pressure increased at 1 minute and 5 minutes after creating pneumoperitoneum, and returned back to baseline levels at 20 minutes after pneumoperitoneum. The increase in heart rate and MAP were more in the magnesium sulphate group than the dexmedetomidine group. This suggests that dexmedetomidine achieved better hemodynamic control than magnesium sulphate in our study. Chandrasekaran V et al [1], compared Dexmedetomidine and Magnesium Sulphate to assess neuroendocrine response and found significantly lower heart rate and MAP throughout pneumoperitoneum and after the release of pneumoperitoneum in dexmedetomidine group compared with magnesium sulphate. This correlates with our study results. Gupta K et al [13], compared dexmedetomidine with fentanyl for stress attenuation in laparoscopic cholecystectomy surgery. They found less hemodynamic changes in the dexmedetomidine group in perioperative period as compared with the fentanyl group. We had similar changes in HR and MAP in our study.

Our study has certain limitations; the study had a small sample size. The study was conducted in a single center. A multi-centered study may be more informative.

Conclusion

We conclude that biochemical stress marker levels (Cortisol levels, TNF-alpha levels, CRP levels, Blood Sugar levels) were more increased in the magnesium sulphate group compared with the dexmedetomidine group. Heart rate and Mean arterial pressure were higher in the Magnesium sulphate group than the Dexmedetomidine group. Dexmedetomidine is better than magnesium sulphate in attenuating the stress of surgery in patients undergoing laparoscopic cholecystectomy.

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