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A STUDY OF EFFECTS OF PERIOPERATIVE MAGNESIUM SULPHATE ON DESFLURANE REQUIREMENT, HEMODYNAMICS AND RECOVERY IN PATIENTS UNDERGOING ELECTIVE LAPAROSCOPIC SURGERY

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ABSTRACT **Background:** Balanced anaesthesia is the word coined to describe a balance of anaesthetic agents and techniques used to produce different components of anaesthesia i.e. analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance of homeostasis. The low blood: gas partition coefficient of desflurane, allows faster emergence from anaesthesia is compared to traditional inhalational anaesthetic agents. To reduce the requirement of desflurane and to attenuate the hemodynamic response various pharmacological agents have been used. Recently, the importance of magnesium in anaesthetic practice has been highlighted. Its inhibiting effects on release of catecholamines from adrenergic nerve endings and adrenal medulla, magnesium prevents intubation induced stress and resultant tachycardia and hypertension and therefore has been an option for minimizing adverse cardiovascular responses during laryngoscopy and intubation. So this study is planned to determine the effects of perioperative use of magnesium sulphate on MAC value of desflurane, hemodynamic parameters and recovery using BIS (bispectral index) monitoring in patients undergoing elective laparoscopic surgeries. **Methods:** The present comparative observational study was conducted during a period between September 2018 to October 2019 at the department of Anaesthesiology and Critical Care, Dr. S.N. Medical college and associated group of hospitals. Total 72 patients included in this study, divided in to two groups- Group D: [Desflurane i.v] and Group DM: [MgSO4+ Desflurane]. The data were collected and analyzed with the help of SPSS-22. **Results:** our study results in that magnesium can be used as an adjuvant to reduce the requirement of desflurane, maintain stable intra-operative hemodynamics as well as for a smooth recovery while causing a delay in recovery from anaesthesia.

KEYWORDS : Desflurane, Magnesium Sulphate, Elective Laparoscopic Surgery

INTRODUCTION

Balanced anaesthesia is the word coined to describe a balance of anaesthetic agents and techniques used to produce different components of anaesthesia i.e. analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance of homeostasis [1]. Achieving this state with a single agent (be it intravenous drugs or inhalational agent alone) can require doses that produce excessive hemodynamic depression. Thus it require a multidrug approach, to include the beneficial effects and minimize the undesirable qualities of each agent. Hence in present day scenario a combination of intravenous and inhalational agents is used to provide 'balanced anaesthesia'.

The low blood: gas partition coefficient of desflurane, allows faster emergence from anaesthesia is compared to traditional inhalational anaesthetic agents[2]. The higher vapour pressure of desflurane, better stability, low potency and solubility in blood or body tissues, more rapid uptake and wash out, precise control, rapid titration of depth of anaesthesia, and negligible metabolic properties make it a potentially favorable anaesthetic agent. Having a MAC of 6 vol.%, adding an adjuvant is beneficial to minimize its consumption and reduce adverse effects.

To reduce the requirement of desflurane and to attenuate the hemodynamic response various pharmacological agents have been used. Opioids are most commonly used to attenuate acute intraoperative hemodynamic responses but occurrence of typical opioid-related side effects have been reported in postoperative period[3]. Dexmedetomidine, a highly selective alpha-2 adrenergic receptor agonist has been reported to reduce desflurane consumption with attenuation of hemodynamic response to endotracheal intubation [4].

Parenteral magnesium sulphate (MgSO4) has been used for many years as an antiarrhythmic agent and for prophylaxis against seizures in pre-eclampsia. Recently, the importance of magnesium in anaesthetic practice has been highlighted.

Magnesium sulfate is a bivalent salt that produces vasodilatation and causes a drop in blood pressure by diminishing sympathetic excitability of muscle cells. Its positive effects on ischemia, infectious endocarditis and management of hemodynamic variables in patients with heart disease are being gradually recognized. Due to its inhibiting effects on release of catecholamines from adrenergic nerve endings and adrenal medulla, magnesium prevents intubation induced stress and resultant tachycardia and hypertension and therefore has been an option for minimizing adverse cardiovascular responses during laryngoscopy and intubation[5]. Magnesium has direct vasodilating properties on coronary arteries and inhibits catecholamine release, thus attenuates the hemodynamic responses during endotracheal intubation. Lack of magnesium increases the risk of perioperative arrhythmia [6].

Additionally perioperative addition of magnesium sulphate to total intra-venous anaesthesia (TIVA) has resulted in marked decrease in the amount of anaesthetic and analgesic requirement [7]. The anaesthetic effect of magnesium is thought to be related to several mechanisms, such as antagonism of NMDA receptors in the central nervous system, decrease of stress response to surgery by reducing catecholamine release and inhibition of acetylcholine release at motor nerve terminals [8,9]. A competitive antagonism in hippocampal calcium channel that regulate neurotransmitter release in the central nervous system has also been suggested. Perioperative analgesia, an important component of anaesthesia, is an effective factor for recovery and peri-operative morbidity. Inhibition of calcium influx, antagonism of NMDA receptors, and prevention of central sensitization after peripheral tissue injury or inflammation by inhibition of dorsal horn NMDA receptors have been suggested as the analgesic mechanisms of magnesium [10].

Effect of magnesium sulphate over MAC values of desflurane has been studied less, so this study is planned to determine the effects of perioperative use of magnesium sulphate on MAC value of desflurane, hemodynamic parameters and recovery using BIS (bispectral index) monitoring in patients undergoing elective laparoscopic surgeries.

Material and Methods

Study Design: It was a comparative observational study.

Study Setting: The present comparative observational study was conducted at the department of Anaesthesiology and Critical Care, Dr.

S.N. Medical college and associated group of hospitals after obtaining Institutional ethical committee approval and informed written consent from the patients.

Study Period: The present study was conducted during a period between September 2018 to October 2019.

Sample size:

Number of cases required in Group D: [Desflurane i.v]	36
Number of cases required in Group DM: [MgSO4+ Desflurane]	36
Total sample size (both groups together)	72

Statistical analysis:
All statistical analyses were performed by using SPSS 22.0 software package (SPSS Inc., Chicago, IL, USA). Yates continuity correction test *(Chi square test), Fisher's exact test and Fisher---Freeman---Halton test were used for comparison of qualitative data. All data were summarized as mean ± SD for continuous variables, numbers and percentages for categorical variables. A $p < 0.05$ was accepted as statistically significant.

Inclusion Criteria:
Patients with ASA Grade I and II, between 25 – 60 years of age, of either sex, posted for elective laparoscopic surgery (cholecystectomy) in reverse trendelenburg position under general anaesthesia lasting for more than 1 hour and willing to give an informed and written consent.

Exclusion Criteria:
Exclusion criteria included patients with Known hypersensitivity to local anesthetics, SBP<100 mmHg and HR<60/min on preoperative assessment, Patients with cardiac insufficiency, ischemia, arrhythmia, valvular heart disease, hypertension, renal failure, liver failure, electrolyte imbalance, myasthenia gravis, muscular dystrophy, untreated endocrine or metabolic disease, Patients with history of epilepsy/seizure disorder, Patients who are taking antihypertensive medications, Pregnant patients / breast feeding females, Morbid obesity (Body mass index >35), Patients on chronic opioids, tricyclic antidepressants, monoamine oxidase inhibitors. Any chronic systemic illness, Anatomical abnormality, Any infection at the regional site, Peripheral neuropathy or neurological deficits

METHODOLOGY

Premedication: All patients received tablet alprazolam 0.25 mg and pantoprazole 40 mg orally night before surgery.

Perioperative monitoring: Standard ASA monitoring with continuous 3-lead electrocardiogram (ECG), heart rate (HR), non invasive systolic, diastolic and mean arterial pressure (SBP, DBP,MAP), peripheral oxygen saturation (SPO_2), end tidal CO2 ($etCO_2$), bispectral index scoring (BIS), and end tidal desflurane concentration (etDes).

1. **Group D:** Patients received desflurane to achieve a BIS score of 45-55 during the surgery.
2. **Group DM:** Patients received desflurane with magnesium sulphate infusion to achieve a BIS Score of 45-55, using infusion pump with syringe containing 20 ml of magnesium sulphate (10000 mg) diluted to 50 ml using 0.9% normal saline, making a concentration of 200 mg/ml magnesium sulphate. In this group patients received a total dose of 30 mg/kg magnesium sulphate over a period of initial 15 min before intubation, followed by 10 mg/kg/hr infusion for entire intraoperative period.

Monitoring And Observation:-
The cardiovascular parameters noted are HR in beats per minute (bpm), SBP, DBP & MAP in mmHg baseline on arrival in OT then after 15 minute after giving magnesium sulphate, after induction, 1 minute, 5 minute, 10 minute after laryngeal intubation and then every 10 minute throughout surgery. After intubation, MAC and end tidal carbon dioxide ($etCO_2$) levels were additionally monitored and recorded throughout the operation every 10 minutes until extubation. Heart rate, MAP, SpO_2, BIS score were also recorded throughout the surgical procedure at an interval of 10 minutes.

Recovery time was measured by using Time to achieve BIS > 70, Time to tracheal extubation (BIS>80), Time to spontaneous eye opening, Time to follow verbal commands (being able to tell his/her name). The patient was observed for any adverse events or side effects during the postoperative period.

RESULTS

Table 1: Comparison of heart rate

Time	Heart Rate (bpm)		t value	p value
	Group D (Mean±SD)	Group DM (Mean±SD)		
Pre operative	82.97±7.00	83.47±5.68	0.332	0.74
After MgSO4 loading dose (15min)/Before induction	82.58±6.54 (Before induction)	82.69±9.45 (After loading dose of MgSO4)	0.057	0.953
After induction	77.76±7.29	73.11±8.03	2.519	0.014
1 min after intubation	86.08±9.97	81.27±9.47	2.095	0.039
5min	84.44±9.37	80.61±6.40	2.025	0.046
10min	80.27±8.88	75.27±10.50	2.181	0.032
20min	78.91±8.16	75.11±7.25	2.091	0.040
30min	78.44±7.36	72.80±4.98	3.805	0.0003
40min	77.8±7.26	70.86±6.40	4.353	<0.0001
50min	76.63±7.10	70.19±6.61	3.985	0.0002
60min	76.25±6.47	68.25±5.49	5.601	<0.0001
70min	77.36±5.46	70.15±5.27	3.283	0.003
80min	76.75±3.59	69.8±3.19	3.073	0.018
90min	70+0.00	68±0.00	NA	NA
Extubation	85.55±6.34	78.61±8.3	3.979	0.0002

Unpaired t test

Table 1 shows the variation in the heart rates of patients among the two groups, t-test showed that there was no significant difference in heart rate of the patients of the two groups at preoperative and before induction period (p>0.05). But the mean heart rate of group DM was significantly lower for all other time intervals when compared to group D (p<0.05).

Table 2: Comparison of diastolic blood pressure

Time	DBP (mmHg)		t value	p value
	Group D (Mean±SD)	Group DM (Mean±SD)		
Pre operative	79.16±6.72	77.22±6.80	1.22	0.226
After MgSO4 loading dose (15min)/Before induction	77.58±5.66 (Before induction)	75.41±6.07 (after loading dose of MgSO4)	1.565	0.122
After induction	73.75±4.77	71.80±6.71	1.417	0.160
1 min after intubation	80.52±8.42	75.05±5.93	3.185	0.002
5min	74.05±7.02	70.05±5.41	2.705	0.008
Extubation	70.47±10.11	64.94±10.13	2.316	0.023

Unpaired t test

Table 2 shows the variation of mean diastolic blood pressure (DBP) (in mm Hg) among the two groups from pre-operative period up to extubtion of the patient, t-test showed that there was a decrease in DBP at all times in group DM when compared to group D but the difference was statistically significant at 1 minute after intubation, 5 minutes after intubation and extubation (p<0.05).

Table 3: Comparison of mean arterial blood pressure

Time	MAP (mmHg)		t value	p value
	Group D (Mean±SD)	Group DM (Mean±SD)		
Pre operative	93.38±7.73	90.27±7.34	1.75	0.084
After MgSO4 loading dose (15min)/Before induction	91.83±5.92 (Before induction)	90.08±5.95 (After loading of MgSO4)	1.249	0.215
After induction	86.86±5.36	85.61±6.60	0.88	0.381
1 min after intubation	94.13±7.98	88.58±7.07	3.125	0.002
5min	88.80±7.00	84.36±5.25	2.99	0.003
Extubation	86.86±10.96	80.58±10.52	2.479	0.015

Unpaired t test

Table 3 shows the variation of mean arterial blood pressure (MAP) (in mm Hg) among the two groups from pre-operative period up to extubtion of the patient, t-test showed that there was a decrease in MAP at all times in group DM when compared to group D but the difference was statistically significant at 1 minute after intubation, 5 minutes after intubation and extubation ($p<0.05$).

Table 4: Comparison of minimum alveolar concentration of desflurane

Time	MAC		t value	p value
	Group D (Mean±SD)	Group DM (Mean±SD)		
5min	0.80±0.10	0.80±0.13	0.329	0.973
10min	0.80±0.06	0.66±0.06	10.35	<0.0001
20min	0.80±0.06	0.59±0.04	16.39	<0.0001
30min	0.78±0.07	0.58±0.05	14.18	<0.0001
40min	0.78±0.06	0.57±0.04	15.97	<0.0001
50min	0.78±0.05	0.56±0.05	17.3	<0.0001
60min	0.77±0.06	0.57±0.05	14.58	<0.0001
70min	0.73±0.07	0.61±0.08	2.445	0.037
80min	0.75±0.04	0.6±0.00	NA	NA

Unpaired t test

Table 4 shows the mean values of minimum alveolar concentration of desflurane between the two groups during the intra-operative period, t-test showed that the mean MAC of the patients of group DM was significantly lower than that of group D at different times after 5 minutes ($p<0.0001$).

Table 5: Comparison of time taken to reach BIS > 70

Interval between time zero and achieving BIS >70 (minutes)	Group D	Group DM	t value	p value
Median	4.07	5	5.925	<0.0001
Range	2.40-5.30	3.50-6.50		
Mean±SD	3.82±0.67	4.84±0.77		

Unpaired t test

Although There was no significant difference in the BIS score at all the times in both groups and were groups are comparable ($p>0.05$)

Table 5 and the bar diagram shows the difference in the duration of the two groups between the mean values to attain a BIS score of 70 (in minutes) after stopping the maintenance agents (Time-0). The value was 3.82±0.67 minutes in group D and 4.84±0.77 minutes in group DM, t-test showed that the mean time-0 to attain BIS 70 of the patients of group D was significantly lower than the group DM ($p<0.0001$).

Table 6: Comparison of time to extubation

Interval between time zero and Extubation (minutes)	Group D	Group DM	t value	p value
Median	4.52	6.05	7.401	<0.0001
Range	2.45-5.90	4.25-7.55		
Mean±SD	4.50±0.76	5.91±0.85		

Unpaired t test

Table 6 shows the comparison between the mean time taken for extubation (in minutes) after stopping the maintenance agents (Time-0) between the two groups. The value was 4.50±0.76 minutes in group D and 5.91±0.85 minutes in group DM, t-test showed that the mean time-0 to extubation of the patients of group D was significantly lower than the group DM ($p<0.0001$).

DISCUSSION

Desflurane is the most rapidly washed volatile anaesthetic agent allowing rapid recovery with minimal metabolism. The higher vapor pressure of desflurane, low blood:gas partition coefficient, better stability, low potency and solubility in blood or body tissues, more rapid uptake and washout, precise control, rapid titration of depth of anaesthesia and negligible metabolism properties make it a potentially favorable anaesthetic agent [11]. Having a MAC of 6 made it important to look for an adjunct that would minimize its consumption.

Magnesium is the second most important intracellular cation and is involved in energy metabolism, protein and nucleic acid synthesis and directly influences muscle contraction, neuronal activity, vasomotor tonus control, cardiac excitability and transmitter release. Magnesium decreases vascular resistance, pulmonary and systemic arterial pressures. It reduces catecholamine release and hence prevent intubation induced stress and resultant tachycardia and hypertension [5, 6].

The present study was aimed to evaluate the effect of perioperative magnesium sulphate on desflurane requirement, hemodynamic changes (HR, SBP, DBP and MAP) and recovery characteristics in patients undergoing elective laparoscopic surgery under general anaesthesia.

Intra-operative heart rate variations:

Magnesium decreases vascular resistance, pulmonary and systemic arterial pressures. It reduces catecholamine release and hence prevent intubation induced stress and resultant tachycardia and hypertension. In our study it was seen that the mean heart rate in the group DM was significantly lower than the group D at all points after induction upto extubation ($p<0.05$). Our observations were consistent with the result of some previous studies [12,13].

In a study, conducted by **Ryu J-H et al** [12], in 80 patients undergoing elective middle ear surgery to compare magnesium sulphate and remifentanil, they found significant reduction in the mean heart rate among the magnesium group as compared to the other group ($p<0.05$).

Another study conducted by **Kamble SP et al** [13], to evaluate effect of magnesium sulphate and clonidine in 90 patients undergoing elective laparoscopic cholecystectomy also found significant reduction in the intra-operative heart rate using magnesium ($p<0.05$).

Intra-operative variations in blood pressures (SBP, DBP and MAP):

Magnesium has direct vasodilating properties on coronary arteries and inhibits catecholamine release, thus attenuates the hemodynamic responses during endotracheal intubation and prevents intubation induced stress and resultant tachycardia and hypertension. In the present study it was observed that there was a decrease in SBP, DBP and MAP among the patients of the group DM at all points during intraoperative period when compared to the group D but the difference was significant statistically at 1 minute after intubation, 5 minutes after intubation and extubation ($p<0.05$). Our observations were consistent with the result of some previous studies [12,14].

In a study conducted by **Ryu J-H et al** [12], to evaluate the effects of magnesium sulphate in 50 patients undergoing elective gynaecological surgery under total intravenous anaesthesia, they found that there was significant reduction in MAP immediately after intubation ($p=0.014$), 5 minutes after intubation ($p=0.005$) and 30 minutes after operation ($p=0.008$).

A similar study was conducted by **Tomak et al** [14], it was found that there was a significant decrease in the MAP post intubation in the magnesium group. The decrease was not significant statistically at other times.

BIS score:

In our study, it was seen that there was no significant difference in the BIS score in the two groups at all times and the groups are comparable ($p>0.05$).

Intra-operative minimum alveolar concentration of desflurane:

In our study the minimum alveolar concentration of desflurane (MAC) intra-operatively was significantly lower in the group DM ($p<0.0001$). The percentage reduction in the requirement of desflurane was 21.51%, which was significant. Our observations were in agreement with the results of some previous studies [15,14,16,12].

Olgun B et al [15], conducted a similar study to evaluate the effects of magnesium sulphate on desflurane requirement and post-operative analgesia in sixty patients undergoing laparoscopic cholecystectomy and concluded that there was a significant reduction of 22% in the intra-operative requirement of desflurane using magnesium ($p<0.05$). A 19.6% reduction in the requirement of desflurane using magnesium ($p<0.05$) was seen in a similar study conducted by **Tomak et al** [26].

Norawat et al [16], conducted a study to evaluate the effect of magnesium on isoflurane and vecuronium requirement in patients undergoing laparoscopic cholecystectomy and found that there was 18-32% reduction in isoflurane requirement in magnesium groups (p<0.05). A significant reduction in the requirement of sevoflurane using magnesium (p<0.05) was found in a similar study conducted by **Ryu et al** [12].

Recovery parameters:

Magnesium has minimal postsynaptic effect at the neuromuscular junction but it potentiates the effect of nondepolarizing neuromuscular blockers by competing with calcium ions in the synaptic area and blocking acetylcholine release. Magnesium also shows competitive antagonism in hippocampal calcium channel that regulate neurotransmitter release in the central nervous system, hence is considered to delay the recovery. In our study, it was seen that there was a significant delay in recovery after stopping the maintenance agents with respect to time taken to reach BIS >70, time to extubation, time to spontaneous eye opening and time to follow verbal commands in magnesium group when compared to the other group.

Time to reach BIS >70: In our study, it was seen that time to reach BIS >70 was 3.82±0.67 minutes in group D and 4.84±0.77 minutes in group DM (p<0.0001).

Time to extubation: In our study, it was seen that time to extubation among the group D was 4.50±0.76 minutes whereas, among the group DM it was 5.91±0.85 minutes (p<0.0001).

Time to spontaneous eye opening: In the present study we found that the time to spontaneous eye opening in group D was 4.89±0.68 minutes while in group DM it was 6.63±0.79 minutes (p<0.0001).

Time to follow verbal command (Name Telling): Observations of our study shows that the the time to follow verbal commands (name telling) in group D was 6.51±0.93 minutes while in group DM it was 7.74±1.01 minutes (p<0.0001). The observations of our study were in agreement with some previous studies [14,17,13].

In a similar study conducted by **Tomak et al** [14], they found a significant delay in recovery in magnesium group, it was seen that time to extubation in magnesium group was 6.83±1.01 minutes when compared to 5.89±1.14 minutes in other group (p<0.001), time to spontaneous eye opening was 7.92±1.58 minutes and 6.95±1.30 minutes in the magnesium and other group respectively (p<0.001), time to cooperation (name telling) was 9.78±1.68 minutes and 8.24±1.34 minutes in the magnesium group and other group respectively (p<0.001).

Riaz et al [17], conducted a similar study and found a significant delay in recovery in magnesium group, it was seen that time to reach BIS >70 was 4.10±0.96 minutes in magnesium group and 3.75±1.11 minutes in the other group, time to spontaneous eye opening was 6.10±1.07 minutes and 5.0±-1.41 minutes in magnesium and other group respectively (p<0.05), time to respond to verbal commands was 7.50±1.0 minutes and 5.80±1.50 minutes in magnesium and other group respectively (p<0.05), time to extubate was 9.60±1.31 and 6.55±1.63 in magnesium and other group respectively (p<0.05).

In another study conducted by **Kamble et al** [13], it was found that the time to extubation was 8.12±1.59 minutes and 5.78±0.99 minutes in the magnesium and other group respectively and time to respond to verbal commands was 8.97±1.69 minutes and 7.07±1.00 minutes in the magnesium and other group respectively (p<0.001).

CONCLUSION

We conclude from our study that magnesium can be used as an adjuvant to reduce the requirement of desflurane, maintain stable intra-operative hemodynamics as well as for a smooth recovery while causing a delay in recovery from anaesthesia.

Conflict of interest:- There is no conflict of interest between authors.

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