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A comparative study of two different doses of magnesium sulfate on pneumoperitoneum-related hemodynamics and on the recovery in patients undergoing laparoscopic gynecological surgeries: A double-blind, randomized, clinical study

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ABSTRACT

Background: Pneumoperitoneum (PP) with carbon dioxide (CO_2) induces hemodynamic response due to the release of catecholamines and vasopressin. Magnesium Sulfate ($MgSo_4$) inhibits the release of these mediators and attenuates the hemodynamic responses to carbon dioxide PP. **Aims and Objectives:** This study aimed to compare two different doses of intravenous Magnesium Sulfate on attenuating PP-related hemodynamic responses. We also evaluated recovery time, the time interval between administration of the reversal agent and extubation. **Materials and Methods:** Seventy female patients undergoing laparoscopic surgeries were randomized into two groups. Group I received 30 mg/kg of $MgSo_4$ and Group II received 50 mg/kg of $MgSo_4$ intravenous infusion prior to PP, respectively. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were measured at regular intervals. The secondary outcome, Train of four ratio (TOF%), at reversal and extubation was recorded. Recovery time was noted. **Results:** Demographic data, HR, SBP, DBP, and MAP were comparable between groups I and II, with no clinical and statistical significance in the 'P' value. The mean TOF ratio (%) at reversal was lower in group II (58.47 ± 5.40) versus group I (66.93 ± 3.43), with a $P<0.001$. The mean TOF ratio (%) at extubation was lower in group II (93.70 ± 2.39) versus group I (97.47 ± 1.59), with a $P<0.001$. Recovery time in minutes was higher in group II (17.80 ± 1.19) versus group I (13.87 ± 0.67), with a $P<0.001$. **Conclusion:** Magnesium Sulfate 30 mg/kg and 50 mg/kg intravenous infusions prior to CO_2 PP showed comparable hemodynamics in laparoscopic gynecological surgery. However, Magnesium Sulfate 50 mg/kg resulted in prolonged recovery from non-depolarizing muscle relaxants, necessitating neuromuscular monitoring for safer use.

Key words: Magnesium sulfate; Laparoscopy; Pneumoperitoneum; Hemodynamics response; Recovery time

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INTRODUCTION

Laparoscopic surgery aims to achieve a satisfactory therapeutic result while minimizing the traumatic and metabolic stress of the intervention.[1] Carbon dioxide pneumoperitoneum (PP) leads to alteration in the cardiovascular, pulmonary physiology and stress responses. Cardiovascular changes include elevation of arterial

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pressure,[2] systemic vascular resistance, and decreased cardiac output, leading to hypertension and tachycardia[3] are mainly due to the release of catecholamines, vasopressin, or both.[4,5] Pharmacological agents such as opioids,[6] alpha-2 adrenergic agonists,[7] beta-blocking agents,[8] vasodilators[9] are often used to attenuate these circulatory responses to carbon dioxide PP.

Magnesium is known to block the release of catecholamines from adrenergic nerve terminals and adrenal glands.[10] It produces vasodilatation by directly acting on blood vessels, and in high doses, it is capable of attenuating vasopressin-stimulated vasoconstriction.[11] Magnesium acts as a calcium channel blocker at presynaptic nerve terminals and reduces acetylcholine release at the motor endplate, diminishing muscle fiber excitability, thereby reducing the amplitude of endplate potential, resulting in the potentiation of neuromuscular blockade produced by non-depolarizing muscle relaxants.[12] It is an N-Methyl-D-aspartate receptor antagonist with antinociceptive effects.[13] Magnesium has been administered in different routes to attenuate the PP-associated hemodynamic response and reduce postoperative pain. Therefore, we hypothesized that Magnesium Sulfate might attenuate the hemodynamic stress responses to PP by changing neurohumoral responses in patients undergoing laparoscopic gynecological surgeries.

Aims and objectives

The primary aim of the study was to compare Magnesium 30mg/kg and 50mg/kg intravenous infusion prior PP on attenuation of the hemodynamic response in laparoscopic gynecological surgeries. The secondary endpoint was to assess recovery time and to evaluate any side effects.

MATERIALS AND METHODS

This prospective, double-blinded, randomized clinical trial was performed after obtaining written informed consent and approval from the institutional ethics committee, Kidwai Memorial Institute of Oncology, Bengaluru (KMIO/MEC/015/January 05, 2018) from February to September 2018. The study was conducted in accordance with the Declaration of Helsinki throughout the project.

Seventy American Society of Anesthesiologists (ASA) I and II patients, aged 18–60 years, undergoing laparoscopic gynecological surgeries who provided consent were recruited.

Patients with hypermagnesemia, a known allergy to Magnesium Sulfate, hypertension, cardiac dysfunction, morbid obesity, and severe hepatic, renal, or endocrine dysfunction were excluded from the study.

All eligible patients underwent pre-anesthetic workup and completed all the necessary investigations. The study patients received standardized pre-anesthetic counseling about the nature of the study, the anesthetic procedure, possible complications, and their management. Patients were premedicated with tablet pantoprozole 40 mg and tablet Alprazolam 0.5 mg orally at bedtime before surgery and kept nil by mouth on the night before the surgery.

Patients were randomly allocated to one of the two groups based on computer-generated random numbers, and the numbers were entered in sequentially numbered, sealed, opaque envelopes. The drugs were prepared and administered by an anesthesiologist who was not involved with data collection or patient management.

On arrival in the operating room, routine noninvasive monitors (ECG, noninvasive blood pressure, and Pulse oximetry (SpO_2) were connected, and baseline readings of parameters were noted. A capnometer was attached during induction of anesthesia. The Organon Train of Four (TOF)–Watch S portable neuromuscular transmission monitor was connected, and the ulnar nerve was stimulated by placing the electrode on the volar aspect of the wrist using a separate portable monitor.

Patients were premedicated with injections of glycopyrrolate 0.2 mg, Midazolam 0.02 mg/kg, and fentanyl 1.5 ug/kg. Patients were preoxygenated with 100% oxygen for 3 min and induced with injections of propofol (titrated to loss of verbal response to command) and rocuronium 0.8 mg/kg to facilitate endotracheal intubation.

- Group I $MgSo_4$ 30 mg/kg (n=30): received Magnesium Sulfate 30 mg/kg diluted in 20 mL normal saline over 5 min prior to PP
- Group II $MgSo_4$ 50 mg/kg (n=30): received Magnesium Sulfate 50 mg/kg diluted in 20 mL normal saline over 5 min before PP.

The study drug was infused using an infusion pump over 5 min after intubation, prior to CO_2 PP. Carbon dioxide PP was created, and intraabdominal pressure was maintained between 12 and 14 mmHg. Intermittent positive pressure ventilation was used, and end-tidal CO_2 ($EtCO_2$) was maintained between 35 and 40 mmHg. Anesthesia was maintained with a mixture of oxygen and nitrous oxide, isoflurane, and Rocuronium 0.5 mg/kg. Hemodynamic parameters such as Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded every 10 min after PP until extubation and every 15 min post-extubation. Neuromuscular blockade was reversed using Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.01 mg/kg at the end of surgery, when the TOF ratio

CONSORT FLOW DIAGRAM

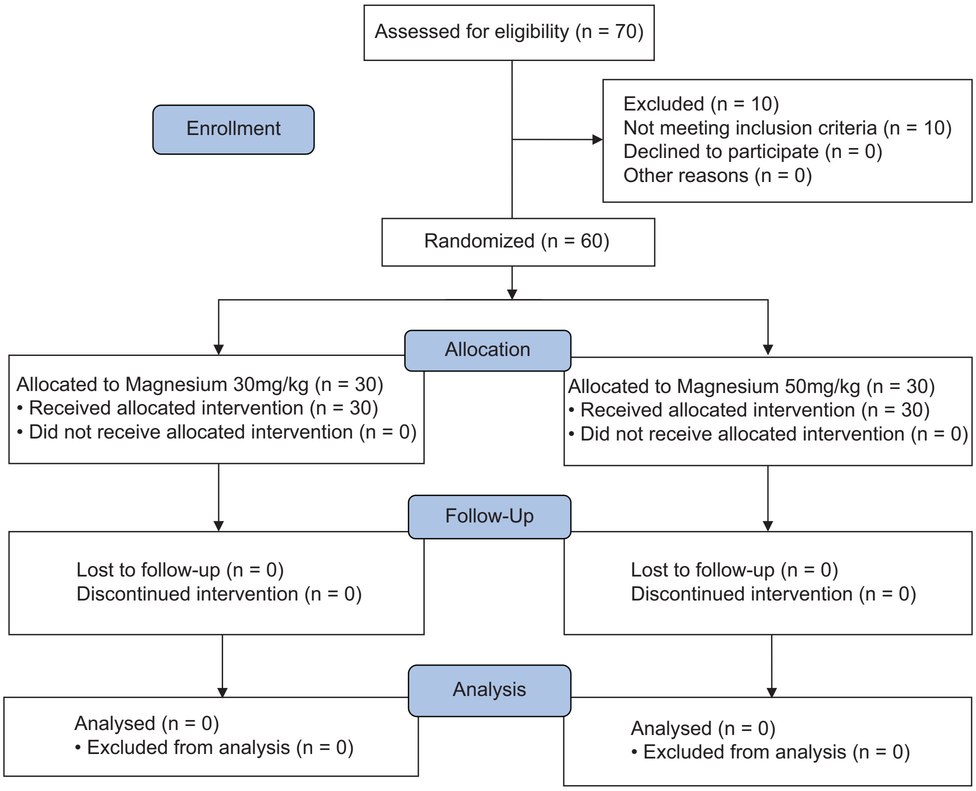


Table 1: Patient characteristics

Patient characteristics	Group I $MgSo_4$ (30 mg/kg)	Group II $MgSo_4$ (50 mg/kg)	P-value
Age (years)	44.17±13.14	43.73±11.41	0.892
Height, (cm)	151.07±3.07	149.37±3.78	0.061+
Weight, (kg)	53.37±12.47	50.37±8.75	0.285
ASA grade (I/II)	18:12	21:9	0.417
Duration of surgery (min)	79.67±33.37	87.70±40.59	0.406
PP Duration (min)	72.57±32.66	79.90±39.00	0.433

ASA: American Society of Anesthesiologists, PP: Pneumoperitoneum

was ≥40% (≥0.4). The TOF ratio at administration of the reversal agent and at extubation was noted. Recovery time was defined as the time interval between administration of the reversal agent and extubation and was noted. Patients were extubated once the TOF ratio was between 90% and 100% (0.9–1). After surgery, patients were shifted to the post-anesthesia care unit, where hemodynamic parameters were recorded. Any adverse or side effects were also noted. Data collection was performed by one of the authors blinded to the interventions.

Statistical analysis

The sample size was calculated based on previous studies.[16] To find the difference between both groups regarding hemodynamics, with the power of the study at 80% and the alpha error at 5%, 30 patients were needed in each group. 35 patients were included in each group to compensate for dropouts (15%). Data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) version 18.0 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) and R environment Version 3.2.2.

All parameters followed a normal distribution. An independent t-test was used to compare the baseline characteristics between the groups. The chi-square test was used for the association of qualitative variables (ASA class). Continuous variables (HR and blood pressure) were compared between the two groups using an unpaired t-test. Intra-group differences were evaluated by two-way analysis of variance (ANOVA), and inter-group differences were evaluated using the unpaired

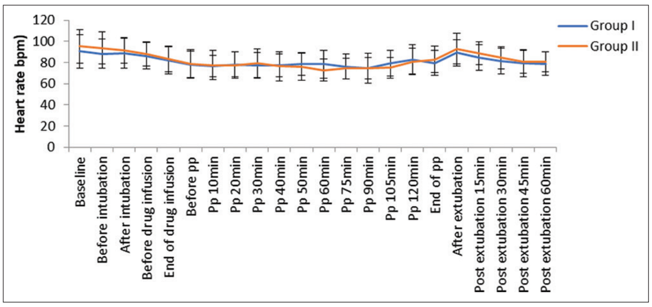


Figure 1: Comparison of heart rate in both the groups

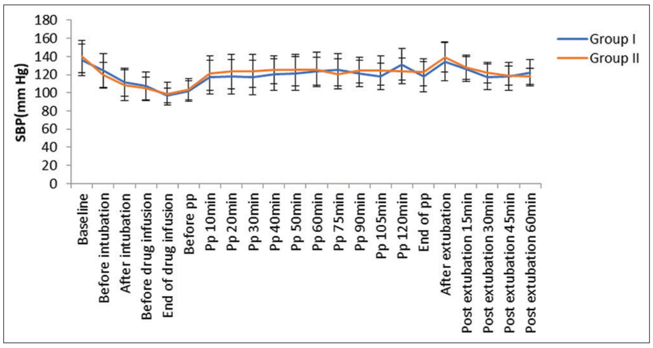


Figure 2: Comparison of SBP in both the groups

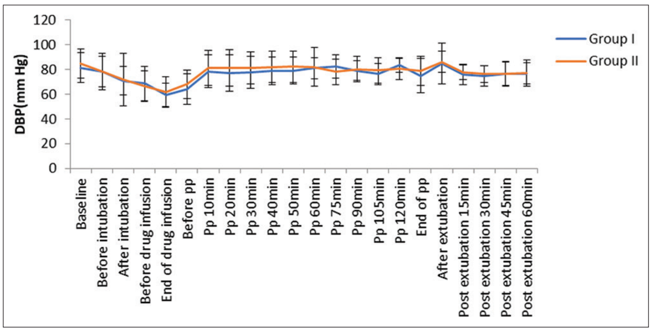


Figure 3: Comparison of DBP in both the groups

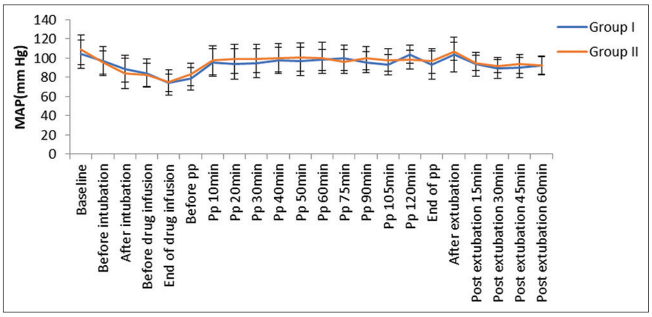


Figure 4: Comparison of MAP in both the groups

t-test. Numerical data were expressed as mean±standard deviation, and categorical data were expressed as ratio (%). The normality of the data was tested using the Kolmogrov-Smirnov test. Significance is assessed at a 5% level of significance. $P<0.05$ was considered significant, and highly significant if $P<0.001$.

Table 2: Comparison of TOF ratio at reversal and extubation in two groups

TOF Ratio (%)	Group I	Group II	P-value
Reversal	66.93±3.43	58.47±5.40	<0.001**
Extubation	97.47±1.59	93.70±2.39	<0.001**

Table 3: Comparison of recovery time in two groups

Recovery	Group I	Group II	P-value
Time in minutes	13.87±0.67	17.80±1.19	<0.001**

RESULTS

In total, 70 subjects were scheduled. Ten patients did not meet our inclusion criteria. Sixty patients were enrolled and randomly allocated into two groups (30 each). The distribution of patients in the two study groups is shown in Table 1.

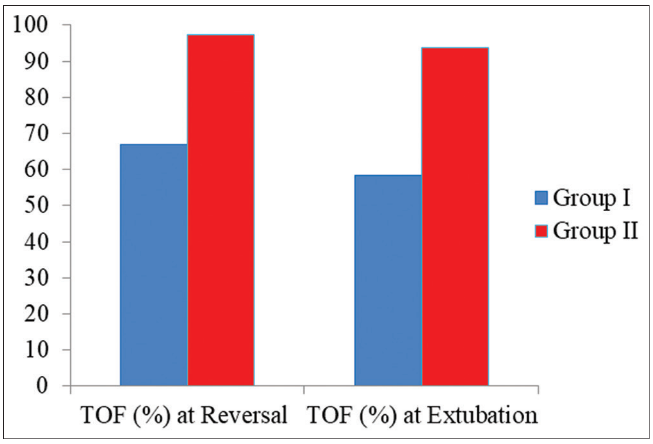
The two groups had comparable demographic profiles with respect to age, height, body weight, ASA status, duration of PP, and duration of surgery.

The mean age distribution is 44.17±13.14 years in group I and 43.73±11.41 years in group II. The mean weight in group I was 53.37±12.47 kg and 50.37±8.75 kg in group II. The difference was found to be statistically not significant. In group I, there were 18 patients in ASA Grade I and 12 patients in ASA Grade II, and in group II, there were 21 patients in ASA Grade I and 9 patients in ASA Grade II. There was no statistically significant difference between both groups with respect to ASA grade ($P=0.417$), showing that patients are independent of ASA grade. The mean duration of PP in group I was 72.57±32.66 min and 79.90±39.00 min in group II. The mean duration of surgery was 79.67±33.37 min in group I and 87.70±40.59 min in group II. There was no statistically significant difference between both groups (Table 1).

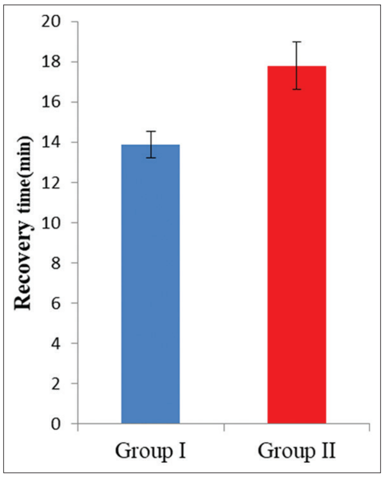
Figures 1-4 Comparison of HR (bpm), SBP (mmHg), DBP (mmHg), and MAP (mmHg) in the two groups studied.

The mean HR (bpm), SBP, DBP, and MAP (mmHg) were comparable with no clinical or statistical (P-value) significance between the two groups throughout the study period. There were no episodes of bradycardia or hypotension noted.

The mean TOF ratios (%) at reversal were 66.93±3.43% in group I and 58.47±5.40% in group II. The mean TOF ratios at reversal in group I was higher when compared to group II, which were significant clinically. Statistical evaluation revealed a P-value of $P<0.001$ (Table 2 and Graph 1).



Graph 1: Comparison of TOF ratio at reversal and extubation in two groups



Graph 2: Comparison of recovery time in both the groups

The mean TOF ratios (%) at extubation were 97.47±1.59% in group I and 93.70±2.39% in group II. The mean TOF ratio at extubation was higher in group I when compared to group II, which was clinically and statistically significant with $P<0.001$ (Table 2 and Graph 1).

The mean recovery time in minutes was 13.87±0.67 in group I and 17.80±1.19 min in group II. The recovery time in group II was longer when compared to group I, which was clinically significant (Table 3 and Graph 2).

Sedation was assessed using Ramsay Sedation Score was 3 in both studies. In both study groups, participants were responsive to verbal commands and were not drowsy in the post-operative period. There were no side effects such as bradycardia, nausea, or desaturation.

DISCUSSION

Carbon dioxide PP increases systemic vascular resistance, mediated mainly by the release of vasopressin and catecholamines.[4,5] Magnesium is well known to block the release of catecholamines from both adrenergic nerve terminals and the adrenal gland.[5] It has a direct effect on blood vessels, producing vasodilatation with a subsequent reduction in blood pressure. Apart from that, it also has the ability to attenuate vasopressin-mediated vasoconstriction.[14] Cardiovascular changes in PP an include increase in MAP with no significant change in HR.[1,2] It is also used to attenuate the pressor response associated with tracheal intubation.[15] Studies to investigate the role of Magnesium in laparoscopic surgeries have been conducted earlier.[6] Magnesium decreases the amount of acetylcholine released from the motor nerve terminal, leading to diminished excitability of the muscle fiber and a reduction in the amplitude of the end plate potential. It therefore potentiates the neuromuscular blockade produced by non-depolarizing neuromuscular blocking agents.[12]

Our study is the first randomized, double-blinded study to compare the effect of Magnesium Sulfate ($MgSo_4$) in doses of 30 mg/kg and 50 mg/kg intravenous infusion on attenuating hemodynamic response to CO_2 PP and its effect on recovery time by evaluating the TOF ratio at reversal and extubation.

Jee et al.,[16] investigated magnesium 50 mg/kg IV prior to PP in laparoscopic cholecystectomy and concluded that it effectively blunted the increase in blood pressure due to PP without any episode of severe hypotension or bradycardia. This attenuation is apparently related to reductions in the release of catecholamine, vasopressin, or both. Kalra et al.,[17] evaluated Magnesium (50 mg/kg) and clonidine (1 ug/kg and 1.5 ug/kg) in laparoscopic cholecystectomy prior to PP. Both Magnesium and Clonidine attenuated the hemodynamic response to PP. Magnesium at 50 mg/kg produced hemodynamic stability comparable to 1 μg/kg of clonidine. Clonidine 1.5 μg/kg blunted the hemodynamic response to PP more effectively. Dar et al.,[18] reported that $MgSO_4$ at 50 mg/kg attenuated the hemodynamic stress responses to PP and had lower HR compared to the control group in laparoscopic abdominal surgeries. Sengupta et al.,[19] found that MAP and HR were significantly lower throughout the PP, after the release of the PP, and after extubation in the magnesium group (30 mg/kg) in patients undergoing laparoscopic cholecystectomy. Bevinaguddaiah et al.,[20] studied hemodynamic response to Clonidine 1 μg/kg and magnesium 50 mg/kg in laparoscopic cholecystectomy. Systolic and diastolic blood pressures were significantly lower in the magnesium group during the entire period of PP as compared clonidine group. HR was significantly lower in magnesium group as compared to the clonidine group at all-time points. Magnesium 50 mg/kg attenuated hemodynamic response better than clonidine 1 μg/kg and prolonged time to extubation, along with prolonged time to verbal response. Wei et al.,[21] studied magnesium sulfate (30 mg/kg loading dose) and 15 mg/kg/h continuous maintenance infusion for 1 h versus magnesium sulfate (50 mg/kg followed by 30 mg/kg/h for 1 h) in gastrointestinal laparoscopy. Magnesium 50 mg/kg effectively attenuated the PP-related hemodynamics and improved postoperative pain. A systematic review and meta-analysis were done by Greenwood et al.,[22] to determine the effectiveness of intravenous Magnesium to attenuate hemodynamic fluctuations associated with the creation of PP in adults undergoing laparoscopic surgery. They observed that the administration of Magnesium consistently demonstrated improved hemodynamic measurements during laparoscopic surgery. All doses administered in the included studies proved beneficial compared to placebo. It was concluded that magnesium sulfate should be considered as an adjunct agent in laparoscopic surgery to blunt the sympathetic nervous system response to surgical stimulation. Zhang et al.,[23] conducted a systematic review and meta-analysis to explore the influence of magnesium sulfate on hemodynamic responses for laparoscopic cholecystectomy. Magnesium sulfate can reduce blood pressure, but with the increase in extubation time for laparoscopic cholecystectomy was concluded.

In all the previous studies where magnesium sulfate (30 mg/kg or 50 mg/kg) was compared with the control group (normal saline), there was a clinical and statistical difference in the hemodynamic parameters with respect to carbon dioxide PP with respect to HR, SBP, DBP, and MAP, which is attributable to the effect of Magnesium on the release of catecholamines and vasopressin during carbon dioxide PP. Serum magnesium concentrations of 2–4 mmol/l are needed to exert these effects. Its direct effect on the vascular smooth muscles of blood vessels, causing vasodilation, decreases the arterial pressure. Magnesium also supresses the increased systemic vascular resistance induced by PP.

However, in our study, we did not find any such significant differences in the HR, SBP, DBP, or MAP between the study groups when magnesium in doses of 30 mg/kg and 50mg/kg was administered. Probably both doses of Magnesium might have fairly attenuated hemodynamic responses, as we did not have a control group to compare these hemodynamic parameters.

In our study, we observed that the mean TOF ratios at reversal administration and at recovery time were lower in group II when compared to group I. The mean TOF ratio at reversal was 66.93±3.43% in group I and 58.47±5.40% in group II, respectively. The mean TOF ratio at recovery was 97.47±1.59% in group II and 93.70±2.39% in group I, respectively, which was clinically and statistically significant with $P<0.001$.

The Recovery time was longer in group II when compared to group I, which was clinically and statistically significant. The mean recovery time in minutes was 13.87±0.67 in group I and 17.80±1.19 in group II, with a $P\leq 0.001$.

Jee et al.,[16] found that the mean extubation time was 5.7 min in the control group and 7.2 min in the magnesium group when 50 mg/kg of Magnesium was administered in laparoscopic cholecystectomy. Dar et al.,[18] observed that extubation time was slightly prolonged in Magnesium 50 mg/kg (5.77±1.12 min verses 5.48±1.23 in the normal saline group), when Rocuronium was used. Kalra et al.,[17] used Clonidine at 1 μg/kg and 1.5 μg/kg and Magnesium at 50 mg/kg in laparoscopic cholecystectomy. Extubation time and time to respond to verbal commands like eye opening were significantly longer in the magnesium group. $MgSO_4$ potentiates the neuromuscular blockade induced by non-depolarizing muscle relaxants. Kamble et al.,[20] studied the response to Clonidine 1 μg/kg and Magnesium 50 mg/kg. The mean extubation time was 5.87±0.95 min in the Clonidine group when compared to 8.12±1.59 min in the magnesium group. Similar to the above studies, even in our study, group II patients took longer to recover from the neuromuscular blockade when compared to group I, which is attributable to the potentiation of non-depolarizing muscle relaxants by Magnesium at a dose of 50 mg/kg. Ryu et al.,[24] studied the effect of magnesium sulfate at 50 mg/kg over 10 min and then at 15 mg/kg/h by continuous infusion to maintain moderate neuromuscular blockade using rocuronium. Magnesium sulfate improved the quality of surgical space conditions and decreased neuromuscular blocking agent requirements and postoperative pain in patients undergoing laparoscopic gastrectomy. Altan et al.,[25] assessed the effects of magnesium sulfate and clonidine on peroperative hemodynamics, propofol consumption, and postoperative recovery. Clonidine caused bradycardia and hypotension, and magnesium caused delayed recovery but can be used as adjuvant agents with careful management.

In our study too, we found that $MgSo_4$ in a dose of 50 mg/kg will prolong the extubation time, delaying the recovery from the non-depolarizing muscle relaxants, which were similar to the above previous studies.

Competition by magnesium for calcium channels in the pre-synaptic nerve terminal inhibiting acetylcholine release at the motor endplate is dose-dependent at the neuromuscular junction; this is responsible for potentiation of non-depolarizing neuromuscular blockade, resulting in prolonged duration of action of non-depolarizing muscle relaxants.[26] Magnesium concentrations of more than 5 mmol/L at the neuromuscular junction produce significant presynaptic neuromuscular blockade.

There was no episode of respiratory depression or desaturation in the present study at any point of observation in both the groups.

Limitations of the study

In the present study, we did not have a control group to compare the hemodynamic parameters and recovery time. We have included both abdominal and pelvic cases together, as the positioning of patients is different during surgery, which may have affected the study parameters. A study was conducted among the female population; the male population was not studied. We did not measure the effect of serum magnesium on the effect of muscle relaxants or the degree of sedation.

In the future, research can be planned on evaluating the pressor response with the bispectral index, anesthetic consumption, and post-operative pain score.

CONCLUSION

From our study, we concluded that a single-dose intravenous infusion of Magnesium Sulfate in doses of 30 mg/kg and 50 mg/kg prior to PP showed comparable hemodynamics between the study groups during laparoscopic gynecological surgeries. Moreover, Magnesium sulfate at 50 mg/kg resulted in a prolonged recovery time from the non-depolarizingmuscle relaxants when compared to 30 mg/kg of magnesium, which necessitates close and careful neuromuscular monitoring.

Hence, 30 mg/kg of Magnesium Sulfate has a low risk of delayed recovery from non-depolarizing neuromuscular blockade and is safe.

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