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Preoperative effects of magnesium sulfate on hemodynamics and muscle relaxation

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Ethics Committee Approval
This study has been approved as a graduation thesis in Taksim Training and Research Hospital Department of Anesthesiology And Reanimation Clinic in 2012.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Although there are many studies on the effects of magnesium sulfate in the literature, there is no publication on the effects of low doses of magnesium sulfate, as we administered in our study. This prospective randomized study aimed to reveal that the use of low-dose magnesium sulfate ($MgSO_4$) shortens the onset time and prolongs the block duration of neuromuscular blockers (NMBs) without changing the hemodynamics in patients monitored using the train-of-four (TOF) ratio.
Methods: This is a prospective randomized study. A total of 60 cases aged between 18–65 years with American Society of Anesthesiologists classifications I–II who were scheduled for elective open cholecystectomy were randomly divided into 3 groups. Notably, 15 minutes before the anesthesia induction, 25 mg/kg $MgSO_4$ in intravenous 0.9% saline (total volume, 100 mL) was administered to the MgSO4 group (MS group), 0.03 mg/kg midazolam was administered to the midazolam group (MD group), and the same volume of 0.9% saline solution was administered to the control group (PSS group). Nerve-muscle conduction monitoring was performed using TOF-Watch® SX (Organon, Ireland) and anesthesia depth was monitored with a BIS® monitor (A-2000; Aspect Medical Systems, USA).
Results: NMB onset times were 83.95 (26.8), 111.15 (28.12), and 163.7 (34.16) seconds (P=0.001) in the MS, MD, and PSS groups, respectively. The times until additional rocuronium requirement after the intubation dose were 60.1 (4.19), 50.8 (4.99), and 38.25 (7.27) minutes in the MS, MD, and PSS groups, respectively, which was significantly longer in the MS group compared to the other groups (P<0.001). The recovery time to TOF of 0.9 and time to T1 height of >95% was longer in the MS group than in the other groups. No difference was found between the groups in terms of hemodynamic data.
Conclusion: Low-dose $MgSO_4$ administration before rocuronium injection significantly reduces neuromuscular agent consumption without altering hemodynamics and causing a residual neuromuscular block.

Keywords: Magnesium sulfate, Muscle relaxant, Bispectral index

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Introduction

Magnesium sulfate ($MgSO_4$) is prominently used as an adjuvant drug in multimodal anesthesia. It inhibits norepinephrine release by blocking N-type and partially L-type calcium channels, increases prostacyclin synthesis, and acts as a vasodilator by inhibiting angiotensin-converting enzyme activity, which make its use a promising strategy to induce controlled hypotension [1, 2]. $MgSO_4$ reduces the amount of acetylcholine released at the motor nerve terminals by inhibition of voltage-dependent P-/Q-type calcium channels, suppresses the endplate depolarizing effect of acetylcholine, and finally inhibits muscle fiber membrane excitability [2, 3]. Although MgSO4 only causes significant neuromuscular block at high plasma concentrations (6–10 mM) [4], its use along with nondepolarizing neuromuscular blockers (NMBs) causes the faster onset of nerve block [5, 6], longer duration [3, 7], and strengthening of the block effect [8-10]. In addition, $MgSO_4$ is a central nervous system depressant that antagonizes the N-methyl-D-aspartate receptor and inhibits the release of catecholamines [2, 11, 12].

This study aimed to reveal that the use of $MgSO_4$ before administering NMBs in patients monitored with the train-of-four (TOF) ratio shortens the onset time of the block and prolongs its duration. As a secondary outcome, we aimed to evaluate the hemodynamic changes in patients who received $MgSO_4$ infusion.

Materials and methods

The American Society of Anesthesiologists classifications I–II (age of 18–65 years; body mass index [BMI], 18.5–24.9 kg/m^2) and Mallampati I–II patients scheduled for elective open cholecystectomy were included in the study. All patients were informed verbally and in writing about the study, and written informed consent was obtained. Comprehensive preoperative clinical evaluation was performed immediately after hospitalization. Patients with rocuronium allergy, history of drug use affecting the neuromuscular function (e.g., aminoglycosides or phenytoin), neuromuscular diseases, hepatic, or renal failure, or expected difficult airway and pregnant patients were excluded from the study. All patients fasted for at least 6 hours before anesthesia induction, and no premedication was administered.

Before starting anesthesia induction, standard monitoring was performed with electrocardiography, noninvasive blood pressure (BP), end-tidal carbon dioxide pressure, and peripheral oxygen saturation (SpO_2). In addition, the TOF-Watch® SX monitor (Organon, Ireland) was used for nerve-muscle conduction monitoring, and the BIS® monitor (A-2000; Aspect Medical Systems, USA) was used for anesthesia depth monitoring. Before bispectral index [13] monitoring, after wiping the forehead area with an alcohol swab, BIS electrodes were placed and measured every 10 minutes during the operation.

The patients were randomly divided into the following 3 groups: PSS group (saline group, n = 20), MD group (midazolam group, n = 20), and MS group ($MgSO_4$ group, n = 20). Patients who met the inclusion criteria were included in the groups determined by simple randomization methods (coin toss). While determining the number of patients in this study, we used the number of patients in similar studies. Fifteen minutes before the anesthesia induction, 25 mg/kg MgSO4 in intravenous (IV) 0.9% saline (total volume, 100 mL) was administered to the MS group, 0.03 mg/kg midazolam was administered to the MD group, and the same volume of 0.9% saline solution was administered to the PSS group. At the end of the infusions, the IV line was cleared and anesthesia induction was initiated.

Neuromuscular monitoring

Neuromuscular monitoring was performed using TOF-Watch® SX (Organon, Oss, the Netherlands), provided that the blood pressure muff (BP) or intravenous (IV) cannula was on the other side. Neuromuscular functions were monitored using the transcutaneous electrodes (Red Dots 3M Health Care®; Neuss, Germany) placed on the cleansed skin over the ulnar nerve on the volar side of the wrist. The position of the transducer is fixed by placing the thumb in a hand adapter (Hand Adapters®; Organon). To minimize motion-induced changes in the twitch response during electromyography and prevent electrode displacement, the arm was fixed with a special board (cardboard TOF-Guards®; Organon) and kept in the same position throughout the study procedure. A temperature sensor was placed at the distal end of the forearm. Heating blankets covering the body and arm were positioned to keep the arm temperature at >32°C (Bair Huggers®; Arizant Healthcare Inc., Eden Prairie, MN). Propofol 2 mg/kg and fentanyl 1 μg/kg were used for anesthesia induction. After induction, TOF-Watch SX acceleromyography was calibrated and stimulation was initiated (supramaximal square wave, 4 stimuli of 2 Hz of 200 ms duration with 15-second intervals). After stable baseline measurements were obtained, a bolus dose of rocuronium 0.6 mg/kg was administered intravenously for 5 seconds. The time elapsed after rocuronium injection, depression of up to 95% of a single twitch (onset time), and TOF rate during neuromuscular block were measured. Continuous TOF stimulation began at a frequency of 2 Hz and 12 seconds. Intervals with a predetermined supramaximal stimulation and orotracheal intubation of the patient were performed when TOF was 0. Neuromuscular block was measured every 20 seconds from anesthesia induction until the end of skin closure.

In all groups, anesthesia was maintained with 50% (2 L/min) oxygen-air mixture and 60% (2 L/min) N_2O to keep the end-tidal carbon dioxide pressure between 4.6-6.0 kPa and 2% sevoflurane ventilation to keep the BIS values between 40 and 60. The time from the start of rocuronium injection until the TOF count reached 0 (onset of rocuronium), and the time from 95% depression of the first twitch of TOF (T1) (rocuronium time) were measured. Hemodynamic parameters, SpO_2, $EtCO_2$, BIS, and TOF values of the patients were monitored and measured regularly. Values were recorded every 10 minutes and finally when TOF was 1. When the T4-to-T1 ratio was 90% and BIS was ≥70 during skin closure, neuromuscular block was antagonized with 10 mg/kg atropine and 20 mg/kg neostigmine, and tracheal extubation was performed.

Statistical analysis

The Number Cruncher Statistical Systems 2007 software package program (Utah, USA) was used for all statistical analyses in this study. In addition to descriptive statistical methods (mean and standard deviation), one-way paired variance analysis was used in repeated measurements of

multiple groups, Newman-Keuls multiple comparison tests were utilized for subgroup comparisons, paired *t-test*, for paired comparisons of repetitive variables, one-way analysis of variance for intergroup comparisons, Tukey multiple comparison test for comparisons of subgroups, and chi-square and Fisher reality tests for comparisons of qualitative data. *P*-value <0.05 was considered statistically significant.

Results

The mean age of 60 patients (30 females and 30 males) enrolled in the study was 47.7 (11.5) years. The patients were divided into three groups of 20 each. Saline was administered to the first group (PSS group), midazolam to the second group (MD group), and MgSO4 to the last group (MS group). Patient demographics, such as age, gender, weight, height, BMI, and ASA distributions did not differ between the groups (*P*>0.05) (Table 1). Basal and postinduction BIS, $ETCO_2$, and SpO_2 values measured during anesthesia maintenance were also similar in all 3 groups.

Table 1: Patients' demographic features and BIS values at different time-points

	PSS Group (n=20)	MD Group (n=20)	MS Group (n=20)	*P*-value
Age (years)	44.15(11.95)	47.7(16.65)	44.65(11.54)	0.672
Sex (M/F)	11/9	10/10	9/11	0.819
Weight (kg)	73(21.16)	75.5(12.22)	73.95(9.94)	0.872
Height (cm)	165.6(10.05)	164.8(10.61)	166.8(10.09)	0.825
BMI ($kg.m^2$)	27.21(9.79)	28.2(6.09)	26.66(3.67)	0.780
ASA (I/II)	12 (60%) / 8 (40%)	14 (70%) / 6 (30%)	13 (65%) / 7 (35%)	0.803
BIS at baseline	98.05(0.95)	94.75(8.85)	97.15(0.88)	0.122
BIS at injection of rocuronium	37.8(6.63)	36.2(7.63)	37.5(7.52)	0.762

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate, BMI: Body Mass Index, BIS: Bispectral Index, ASA: American Society of Anesthesiologists, M/F: Male/Female

Intra- or postoperative hemodynamic instability was not observed in any patient, and the mean baseline values of hemodynamic parameters were similar between the groups. After anesthesia induction in all groups, systolic, diastolic, and mean arterial BPs and heart rate were lower than the baseline values (p > 0.05 for each group). These values increased after laryngoscopy and tracheal intubation. The comparison of hemodynamic parameters between the groups is summarized in Tables 2 and 3. The onset time of neuromuscular block was longest in the PSS group, followed by the MD group, and the shortest time was observed in the MS group (163.7 (34.16), 111.15 (28.12), and 83.95 (26.8) seconds, respectively) (*P*=0.001) (Table 4). After the intubation dose, the time until additional rocuronium requirement for maintenance was shortest in the PSS group, followed by the MD and MS groups (38.25 (7.27), 50.8 (4.99), and 60.1 (4.19) minutes, respectively) (*P*<0.001) (Table 5).

Table 2: Heart Rate (HR) Values of Groups

	HR (bpm)			
	PSS Group	MD Group	MS Group	*P*-value
Basal	80.75(11.36)	77.55(15.24)	78.45(16.95)	0.778
Post- infusion	80.55(12.68)	80.1(25.26)	78.55(15.96)	0.939
Post- induction	79.8(14.31)	73.2(15.42)	74.1(10.53)	0.258
Post-intubation	82.7(14.5)	79.8(17.93)	80.5(15.3)	0.836
5th min	75.9(12.09)	68.1(14.9)	74.1(11.56)	0.145
10th min	78.8(14.6)	77.25(11.85)	73.8(8.89)	0.409
20th min	73.5(10.38)	74.65(11.21)	71.45(12.28)	0.665
30th min	75.35(14.25)	71.35(11.63)	72.1(11.43)	0.564
40th min	77.05(12.34)	69.8(14.18)	71.35(8.92)	0.142

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate

Table 3: Mean Arterial Pressure (MAP) Values by Groups

	MAP (mmHg)			
	PSS Group	MD Group	MS Group	*P*-value
Basal	97(12.65)	93.15(20.16)	91.6(13.06)	0.537
Post- infusion	93.75(9.85)	94.55(14.6)	98.05(18.67)	0.623
Post- induction	88.9(16.08)	82.6(12.65)	83.75(14.41)	0.347
Post- intubation	89.15(13.35)	94.05(16.01)	93.5(23.58)	0.648
5th min	99.25(13.1)	91.5(15.96)	94.9(19.07)	0.325
10th min	90.4(16.21)	88.5(17.68)	87.15(12.77)	0.806
20th min	95.2(14.49)	90.2(20.23)	93.65(20.89)	0.691
30th min	97.95(17.09)	96.7(18.33)	94.15(16.62)	0.780
40th min	99.4(14.26)	96.15(17.92)	96(18.18)	0.773

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate

Table 4: Time until onset and duration of neuromuscular blockade after administration of rocuronium (total dose 0.6 $mg.kg^{-1}$) in patients randomly allocated to rocuronium alone (Control), midazolam pretreatment with rocuronium and magnesium pretreatment with rocuronium.

	PSS Group (n=23)	MD Group (n=23)	MS Group (n=23)	*P*-value
Onset; s	163.7(34.16)	111.15(28.12)	83.95(26.8)	<0.001
Duration; min	38.25(7.27)	50.8(4.99)	60.1(4.19)	<0.001

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate

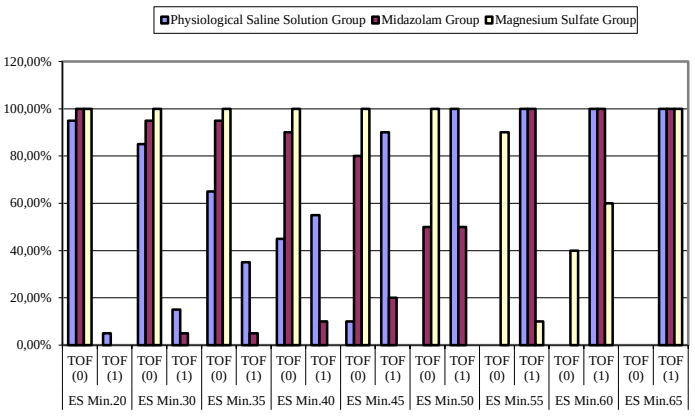
Table 5: Post-induction TOF values of groups

TOF	PSS Group	MD Group	MS Group	*P*-value
Post- induction	119.3(13.21)	121.05(22.42)	107.9(12.49)	0.038

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate, TOF: Train-of-Four

After the first 25 minutes of stabilization of the TOF ratio and T1 height (*P*=0.362 and *P*=0.153, respectively), T1 height started to increase in the SF and MD groups. In the MS group, T1 increase was seen 15 minutes after the MD group and 25 minutes after the PSS group. The TOF ratio first reached 0.9 at the 45^{th} minute in the SF group, 55^{th} minute in the MD group, and at the 65^{th} minute in the MS group (Figure 1).

Figure 1: TOF distribution of groups



PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate, TOF: Train-of-Four

Discussion

In this study in which we investigated the effects of IV $MgSO_4$ infusion administered before rocuronium injection, the NMB onset time was shorter in the MS group than the PSS group. We used acceleromyography for neuromuscular monitoring and determined the time until the start of T1 to be longer in the MS group compared to the PSS group. The TOF ratio reached 0.9 in a much shorter time in the PSS group than in the MS group. Thus, the duration of the clinical effect of rocuronium 0.6 mg/kg intubation dose was significantly prolonged after premedication with $MgSO_4$. BIS scores, mean arterial pressure, and heart rate were similar in all groups. In our study, we used the lowest dose of $MgSO_4$ according to the studies performed using $MgSO_4$ so far. Thus, while increasing the duration and effect of neuromuscular block by creating a safer dose interval, the hemodynamics were not affected. As a secondary gain, we did not observe residual neuromuscular block or negative respiratory distress among the groups.

In this study, we observed that the group treated with $MgSO_4$ had an earlier onset time of rocuronium-induced neuromuscular block and a longer clinical block duration than the PSS group. We determined the NMB onset time to be approximately 2 times longer in the PSS group than in the MS group. We attribute this to the fact that $MgSO_4$ is similar to "muscle relaxants." The primary mechanism of action of $MgSO_4$ is inhibiting the calcium-mediated acetylcholine release from the presynaptic terminal of the neuromuscular junction [2, 3]; its secondary mechanism is reducing synaptic sensitivity to acetylcholine and myocyte excitability [2]. These effects concretize the effect of nondepolarizing NMBs[12]. Accordingly, many clinical studies are reporting that MgSO4 shortens the onset time, prolongs the clinical duration, and increases the potency of nondepolarizing NMBAs [3, 5, 7, 12, 14-21]. In all these studies, the infusion time of $MgSO_4$, the rocuronium dose, and the time between $MgSO_4$ administration and NMB injection are similar to our study. However, although Kussman et al. [22] used a higher dose of $MgSO_4$ than our study, they administered it as an IV bolus injection within 1 minute just before rocuronium administration and suggested that MgSO4 did not affect the onset time; however, it prolonged the duration of rocuronium-induced neuromuscular block. The effect of $MgSO_4$ on the neuromuscular junction depends on concentration and time. Therefore, there may not be enough time left for magnesium ions to pass to the neuromuscular endplate at a measurable level. In our study, we administered $MgSO_4$ 15 minutes before anesthesia induction and as an IV infusion. However, owing to the different MgSO4 regimens, anesthesia techniques (propofol and inhaled anesthetics), high pharmacodynamic variability of rocuronium, and the lack of standards for neuromuscular measurement methods, it is difficult to compare our findings with similar previous studies.

Acceleromyography is an approved method for use in neuromuscular research studies [23]. Although some studies have observed that patients treated with $MgSO_4$ do not have a significant increase in recovery parameters when monitored through TOF [24, 25], we used TOF-Watch® for neuromuscular monitoring in this study. Therefore, we closely monitored the onset time and duration of action of NMBs. Neuromuscular monitoring is mandatory to assess a TOF rate of >0.9 at which extubation is considered safe [26]. In this study, we used the TOF-Watch that has a special algorithm to calculate the TOF ratio and found that the neuromuscular block time was significantly longer in the MS group. Therefore, in line with previous studies, we also observed a significantly lesser need for NMBs in the MS group [16, 21, 23, 24]. However, the fact that $MgSO_4$ decreases the height of all twitches of the TOF response may reduce its effect on TOF fading. Therefore, in addition to the fading of the TOF ratio, we also analyzed the time course of changes in the height of the initial twitch of the TOF complex (T1) and studied the T1 value and the TOF ratio in the intraoperative neuromuscular block monitoring. When the T2 value is higher than the T1 value, the TOF value is calculated by the T4-to-T2 ratio, and if this ratio is >1.0, a 100% value can be assigned [27]. Even though the importance of this is questioned, we evaluated the period until when T1 first started to form to eliminate this risk in this study [28]. The time that T1 first started to form was determined as 35 minutes in the PSS group and 55 minutes in the MS group. Thus, it was observed that T1 height in the MS group occurred 20 minutes after the PSS group. Similar results were reported by Czarnetzki et al. [3] and by Germano Filho et al. [29]. The duration of clinical effect of 0.6 mg/kg rocuronium (intubation dose) was significantly prolonged after premedication with $MgSO_4$. Our results indicate that IV $MgSO_4$ infusion significantly reduces the consumption of neuromuscular agents.

BIS monitoring is considered a valuable method in demonstrating adequate general anesthesia formation and intraoperative awareness [13, 30-34]. To objectively evaluate the effects of magnesium sulfate on the need for anesthesia, we kept the BIS scores in the 40-60 range and did not find any difference between the groups in terms of BIS scores. Ryu et al. also suggested that magnesium has no effect on propofol requirements in parallel with our study [24]. In the literature, investigators [25] compared different $MgSO_4$ doses in study groups with a control group and found that the BIS values of the study groups were significantly lower when $MgSO_4$ was administered by infusion. Manaa and Alhabib also found similar results in their studies and advocated that $MgSO_4$ was a safe and cost-effective additional agent in the general anesthesia regimen because it reduced total anesthesia requirements, including propofol, fentanyl, and rocuronium [34]. We believe that different inhaled anesthetic agents given and inhaled at different end-tidal concentration levels may have caused different BIS values, which is the reason for the differences between the studies [35]. In addition, when stable and reasonable MAC values and hemodynamic parameters increased by 20% from baseline, fentanyl administration may have prevented any possible awareness experience in our study.

In our study, no significant difference was found in the mean arterial pressures and heart rates of the two groups. In the literature, publications are reporting that the calcium inhibitory effect of $MgSO_4$ causes central arteriolar vasodilation and reduces the need for anesthetic agents (fentanyl, vecuronium, and sevoflurane), which decreases the BP and cardiac index [11, 34, 36, 37]. However, in parallel with our study, there are also publications reporting that there is no change in heart rate [22]. We believe that this difference is caused by the differences in analgesic drug dosage and technique, $MgSO_4$ dosage and route of administration, patient category, and surgical operations. Our results indicate that low-dose $MgSO_4$ administration significantly reduced neuromuscular agent consumption without significantly affecting mean arterial pressure and heart rate.

$MgSO_4$ concentrations of 1.8–3.1 mM were used to treat eclamptic convulsions. Higher concentrations can cause residual neuromuscular block and consequent fatal complications such as respiratory and cardiac arrest [38, 39]. However, $MgSO_4$ doses were considered safe in our study, as magnesium toxicity started at a serum concentration of 2.5–5 mmol/L [16], which was much higher than the highest level in the MS group. No events that would require discontinuation or treatment in any patient were reported. In addition, no residual neuromuscular block or negative respiratory distress was observed between the groups at the time of admission to the post-anesthesia care unit and until 1 hour postoperatively.

Limitations

Our study has some limitations. Although $MgSO_4$ was infused for only 15 minutes in the current study design, it increased peripheral blood flow, and consequently, transport of rocuronium molecules to the motor nerve terminals may have been accelerated compared with control patients. Ephedrine pretreatment accelerates the neuromuscular block of rocuronium [40].

We did not measure serum and cerebrospinal fluid $MgSO_4$ concentrations for 2 main reasons. The intracellular and extracellular $MgSO_4$ concentration has no clinical significance because they do not accurately predict $MgSO_4$ levels in other body tissues. Furthermore, because renal excretion depends on plasma $MgSO_4$ concentration, it is difficult to assume that doubling the infusion rate doubles the plasma $MgSO_4$ concentration. Therefore, we cannot determine how much higher the plasma $MgSO_4$ levels were.

Although the neuromuscular block was antagonized before, initiating the evaluation of healing indices in all cases and projecting the ongoing effects of the inversion may lead to longer recovery times. We assumed that the overlap potential is true for the entire population and leads to proportional increases in recovery. However, it is difficult to predict whether such a delay in reversing the accuracy of the $MgSO_4$ recovery assessment in the group using MgSO4 infusion was indeed intense. If we had shown complete restoration of neuromuscular conduction before recovery, the reliability of the available data would be increased.

Conclusion

Our study showed that IV $MgSO_4$ infusion administered before rocuronium injection increases the standard intubation initiation rate of rocuronium and decreases the duration. We also observed that it increased the block duration of NMBs in the MS group. In addition, we found no difference between the groups in terms of mean arterial pressure and heart rate. Therefore, our results indicate that low-dose $MgSO_4$ administration significantly reduces neuromuscular agent consumption without altering the hemodynamics and causing a residual neuromuscular block. However, the optimal timing and duration of $MgSO_4$ remain uncertain. In this context, further research is required.

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