Effects of Magnesium Sulphate on Sugammadex Reversal of Rocuronium-Induced Neuromuscular Blockade in Gynaecology Patients

Jinekolojik Hastalarda Roküronyum ile Oluşturulan Nöromusküler Bloğun Sugammadeks ile Geri Çevrilmesine Magnezyum Sülfatın Etkisi

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ABSTRACT Objective: Magnesium sulphate potentiates the effects of neuromuscular blockers and prolongs their duration. Sugammadex is a modified gamma-cyclodextrin, a highly selective encapsulating agent of rocuronium. The aim of the study was to evaluate the effect of magnesium sulphate on 4 mg/kg sugammadex reversal of rocuronium-induced neuromuscular block. **Material and Methods:** Eighty patients, aged 18 to 60 years, American Society of Anesthesiologists physical status I-II, undergoing elective gynecological surgery were enrolled. Anaesthesia was induced with propofol and fentanyl and was maintained with 60% nitrous oxide and oxygen in 2% sevoflurane. The magnesium sulphate group received 50 mg/kg intravenous magnesium sulphate as a bolus and 15 mg/kg/h by continuous infusion until the completion of surgery. The placebo group recieved the equivalent volume of isotonic saline. For intubation, 0.6 mg/kg rocuronium was administered and 0.1 mg/kg was added when train-of-four counts reached 1 during the procedure. At the end of the surgery at a train-of-four count of 1, 4 mg/kg sugammadex intravenous was administered. Patients were observed until a train-of-four ratio of 0.9 was achieved after then extubated. **Results:** The incidence of rocuronium-induced injection pain was significantly less and the onset time for rocuronium was shorter in the magnesium sulphate group (p=0.005, p=0.000; respectively). Mean total intraoperative rocuronium supplementation was similar between the two groups. The times to recovery for train-of-four ratio of 0.9 were longer in the magnesium sulphate group (2.1 (0.9) minutes) compared to the placebo group (1.6 (0.6) minutes, p=0.005). **Conclusion:** Magnesium sulphate had no clinically significant effect on reversal time after 4 mg/kg sugammadex administration. The observed difference of approximately 0.5 minutes for recovery of a train-of four ratio ≥0.9 between the two groups is clinically negligible.

Key Words: Magnesium sulfate; rocuronium; sugammadex; anesthesia, obstetrical

ÖZET Amaç: Magnezyum sülfat, nöromusküler blokörlerin etkilerini potansiyalize eder ve etki sürelerini uzatır. Sugammadeks, roküronyuma yüksek selektif olan enkapsüle edici modifiye bir gamma-siklodekstrindir. Bu çalışmanın amacı, magnezyum sülfatın roküronyum ile indüklenen nöromusküler bloğun 4 mg/kg sugammadeks ile geri çevrilmesine etkisini araştırmaktır. **Gereç ve Yöntemler:** Elektif jinekolojik cerrahi olacak Amerikan Anestezistler Derneği I-II fiziki duruma sahip, 18-60 yaş arası 80 hasta çalışmaya dahil edildi. Propofol ve fentanil ile anestezi indüksyonu, %60 azot protoksit ve oksijen içinde %2 sevofluran ile anestezi idamesi sağlandı. Magnezyum sülfat grubuna cerrahi bitimine kadar; 50 mg/kg magnezyum sülfat intravenöz bolus ve 15 mg/kg/sa sürekli infüzyon uygulandı. Kontrol grubu ise aynı hacimde izotonik salin aldı. Entübasyon için 0,6 mg/kg intravenöz roküronyum uygulandı ve cerrahi sırasında train-of-four 1 atım gösterdiğinde 0,1 mg/kg ek doz uygulandı. Cerrahi bitiminde train-of-four 1 atım gösterdiğinde ise 4 mg/kg sugammadeks uygulandı. Train-of-four oranı 0,9 olana kadar hastalar gözlendi ve sonra ekstübe edildi. **Bulgular:** Magnezyum sülfat grubunda roküronyumla indüklenen enjeksiyon ağrısı, belirgin olarak daha az ve roküronyum etki başlama süresi de daha kısadır (sırasıyla; p=0,005, p=0,000). Ortalama toplam intraoperatif roküronyum ek doz gereksinimi iki grupta da benzerdir. Train-of-four oranının 0,9 olması için geçen süre magnezyum sülfat grubunda (2,1 (0,9) dakika) ile kontrol grubuna kıyasla uzundu (1,6 (0,6) dakika, p=0,005). **Sonuç:** Magnezyum sülfatın roküronyum ile oluşturulan nöromusküler bloğun 4 mg/kg sugammadeks ile geri döndürülmesine klinik açıdan belirgin bir etkisi yoktur. İki grup arasında train-of-four oranının ≥0,9 olma süreleri arasında gözlenen 0,5 dakikalık fark klinik açıdan önemsizdir.

Anahtar Kelimeler: Magnezyum sülfat; rokuronyum; sugammadeks; anestezi, obstetrik

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The medical use of magnesium sulphate ($MgSO_4$) has increased considerably over the last two decades. A large number of studies have shown that administration of $MgSO_4$ significantly decreased maternal mortality for patients with severe pre-eclampsia or eclampsia. Increasingly, $MgSO_4$ is used in obstetrics because of its tocolytic, hypotensive and anticonvulsive effects.[1]

$MgSO_4$ potentiates the effects of neuromuscular blockers and prolongs their duration. $MgSO_4$ may diminish the minimum alveolar concentration of inhaled anaesthetics. It inhibits calcium-mediated acetylcholine release from the presynaptic nerve terminal and it decreases sensitivity to acetylcholine-induced end-plate depolarization.[2] $MgSO_4$ acts as an antagonist for the N-methyl-D-aspartate (NMDA) glutamate receptor, which is responsible for pain perception.[3] But its effects on postoperative pain has not been firmly established.

Sugammadex, a modified gamma-cyclodextrin, is a highly selective encapsulating agent of aminosteroidal neuromuscular blockers, particularly rocuronium. Sugammadex has been evaluated for different depths of neuromuscular blockade, for different patient weights and for dose-dependence in paediatric to elderly populations.[4-8]

To our knowledge, this is the first study to assess the efficacy of 4 mg/kg sugammadex for the reversal of rocuronium-induced neuromuscular blockade in $MgSO_4$-infused female patients. 4 mg/kg is the dose for the reversal of deep neuromuscular blockage. To eliminate the gender differences and because of real magnesium sulphate infused patients were women we decided to choose female patients in this trial.

The primary objective of this study was to explore the efficacy of 4 mg/kg sugammadex for the reversal of rocuronium-induced neuromuscular blockade following the administration of $MgSO_4$. Secondary objectives were to evaluate the effects of $MgSO_4$ on rocuronium-induced injection pain, rocuronium onset time and peroperative rocuronium supplementation.

MATERIAL AND METHODS

Approval was obtained from the Local Research Ethics Committee and written informed patient consent was obtained from all patients prior to enrollment in November 2012. Eighty female patients with American Society of Anesthesiologists (ASA) physical status I or II and between 18-60 years of age who were undergoing elective gynecological surgery requiring endotracheal intubation were randomly enrolled in this prospective study. Patients who had body mass index > 35; gastroeosophageal reflux; a history of allergy or used medication known to interact with the drugs being used in this trial; who experienced expected or unexpected difficulty during intubation or ventilation; had neuromuscular disease, hepatic or renal insufficiency; were pregnant; were ASA III or IV; or had a family history of malignant hypertermia or detection of low or high control plasma magnesium levels (lower than 1,6 mg/dL or higher than 4 mg/dL) were excluded from the study.

An intravenous (iv) cannula was inserted, patients were premedicated with 0.03 mg/kg midazolam iv and an infusion of a crystalloid solution was initiated at the preoperative care unit. After arrival at the operating theater, standard monitoring, including; ECG, noninvasive blood pressure (NIBP), heart rate (HR), pulse oximetry and capnography, was initiated. Patients were randomly assigned to one of two treatment groups: $MgSO_4$ or saline (placebo). The $MgSO_4$ group received 50 mg/kg $MgSO_4$ iv as a bolus over 2-5 minutes and 15 mg/kg/h $MgSO_4$ iv as a continuous infusion until the completion of surgery. The placebo group recieved an equivalent volume of isotonic saline. Anesthesia was induced with 3 mg/kg propofol iv and 1 μg/kg fentanyl. Just after anesthesia induction, a second iv cannula was inserted in the opposite arm and basal magnesium sample was taken. Anesthesia was maintained with sevoflurane in a mixture of 60% nitrous oxide and oxygen. While patients were ventilating via facemask, neuromuscular function of the adductor pollicis was monitored using an acceleromyograph

(Train-of-four (TOF) Watch SX; Organon Ltd., Dublin, Ireland) according to the guidelines for Good Clinical Research Practice in pharmacodynamic neuromuscular studies.[9] Neuromuscular monitoring continued until the recovery of a TOF ratio above 0.9. Skin temperature over the adductor pollicis was monitored and maintained >32°C using forced-air warming blankets (Warm Touch, Tyco Healthcare Ltd, London, UK) until the completion of surgery. Just after the iv bolus dose of $MgSO_4$ was administered, 0.6 mg/kg rocuronium was administered. When no response was received upon TOF stimulation, patients were intubated. A blinded observer recorded the effects of $MgSO_4$ on rocuronium-induced injection pain (as assessed by observing the patient's movements of the wrist and arm or generalized movements) and onset time of rocuronium (the mean time beginning just after administration of rocuronium until no response was received upon TOF stimulation). During surgery, 0.1 mg/kg rocuronium (esmeron; Merck Sharp & Dohme Ltd., Hertforshire, UK) was administered when 1 response was received upon TOF stimulation. The mean total intraoperative rocuronium supplementations (mg) were recorded. Additionally, the duration of anesthesia and surgery were recorded. Upon completion of the surgery, infusions were stopped and $MgSO_4$ samples were collected from the opposite side of the infused arm. When 1 response was received upon TOF stimulation, 4 mg/kg sugammadex (bridion; Merck Sharp & Dohme Ltd., Hertforshire, UK) iv was administered, and the mean times for TOFs of 0.7, 0.8 and 0.9 were recorded. For postoperative analgesia and vomiting, 1 mg/kg tramadol and 4 mg ondansetron iv were administered at the end of surgery. Postoperative residual block was measured at the postoperative care unit (PACU) using TOF stimulation by a blinded investigator with the same acceleromyograph that was used on that patient during anesthesia. Postoperative residual block was defined as TOF ratio < 0.9. Adverse reactions such as; urticeria, allergy, anaphlaxia, SpO_2 < 95, bronchospasm, nausea and vomiting, bradicardia, and arrhythmia were recorded.

Statistics; the sample size calculation was based previously generated data from Duvaldestin et al., with the mean time for achieving a TOF ratio of 0.9 as 1.7(0.7) minutes (min) with 4 mg/kg sugammadex.[10] We calculated our sample size of 31 patients per group to be sufficient to find a 30% difference between the groups according to TOF 0.9 achieving times. Anticipating the possibility that some patients would be excluded, we enrolled 40 patients per group. We used the chi-square test for categorical data. We used the Kolmogrov Smirnov test for calculating that the data contributes to normal distribution or not. For comparing the groups, we used Student-t and Mann Whitney-U test when apropriate. P<0.05 was calculated as statistically significant.

RESULTS

This study was conducted from December 2012 to May 2013. A total of 80 patients were enrolled in this study, but three patients in the $MgSO_4$ group and four patients in placebo group were excluded because of the detection of low basal plasma magnesium levels (lower than 1.6 mg/dl) or problems related the acceleromyograph. In all, 73 patients were analysed. Patients were comparable with respect to age, weight, height, ASA status, basal $MgSO_4$ levels and temperature measurement at the beginning of the study (Table 1). The duration of surgery and anesthesia were similar

TABLE 1: Demographics and baseline characteristics of patients and the procedure. Values were presented as number (n), or mean (Standard Deviation).

	MgSO4 group (n=37)	Placebo group (n=36)	p
Age, years	39.4 (10.6)	41.3 (10.3)	0.4
Weight, kg	69.8 (11.7)	69.5 (10.8)	0.9
Height, cm	162 (6)	161 (4)	0.9
ASA physical satus I:II	25 : 12	25 : 11	0.9
Control skin temperature (ºC)	34.0 (1.0)	34.6 (0.7)	0.06
Basal $MgSO_4$ level (mg.dl-1)	1.95 (0.2)	1.91 (0.2)	0.3
Basal TOF ratio	94.8 (7.3)	95.3 (7.3)	0.7
Duration of Anesthesia (min)	109 (42.7)	103 (29.2)	0.5
Duration of surgery (min)	86.5 (42.3)	85.3 (29.2)	0.9

C: Celsius; kg: kilogram; cm: centimeter; mg: milligram; dL: deciliter.

between the groups (Table 1). Surgery types were myomectomy, hysterectomy, laparoscopy and laparotomy. The overall incidence of rocuronium-induced injection pain was lower and rocuronium onset time was shorter in $MgSO_4$ group than the placebo group; however, mean total rocuronium supplementations were similar between groups (Table 2). There was no statistically significant difference with regard to TOF 0.7 achieving times between the groups, but TOF 0.8 and 0.9 achieving times were significantly longer in the $MgSO_4$ group than the placebo group (Table 2).

Postoperatively, nausea and vomiting occured in two patients in the $MgSO_4$ group and one in the placebo group. No shivering or bronchospasm were recorded. Bradicardia was detected in one patient in the $MgSO_4$ group and 2 patients in the placebo group, and this was corrected with 0.5 mg atropine iv. Pulse oximetry (SpO_2) decreased to 95% in one patient in the $MgSO_4$ group. Arrhythmia and urticaria occurred in one patient in the placebo group. When basal and final $MgSO_4$ levels were compared, the final $MgSO_4$ level was increased in the $MgSO_4$ group from 1.95(0.2) to 3.64 (0.6) mg/dl. Hemodynamic parameters (MAP and HR) before and 1, 5 and 10 min after reversal were similar in both groups. No evidence of residual block was observed in either group at the PACU.

TABLE 2: Effects of $MgSO_4$ on rocuronium-induced injection pain; onset time of rocuronium; mean total peroperative rocuronium supplementation; TOF 0.7, 0.8 and 0.9 achieving times. Values were presented as numbers (n), or mean (Standard Deviation).

	$MgSO_4$ group (n=37)	Placebo group (n= 36)	p
Rocuronium injection pain (Yes:No)	0 : 37	7 : 29	0.005*
Rocuronium onset time (min)	1.05 (0.4)	1.5 (0.5)	<0.001†
Mean total rocuronium supplementation (mg)	11.2 (5.9)	11.2 (6.6)	1
TOF 0.7 time (min)	1.2 (0.5)	1 (0.4)	0.08
TOF 0.8 time (min)	1.6 (0.5)	1.3 (0.3)	0.01*
TOF 0.9 time (min)	2.1 (0.9)	1.6 (0.6)	0.005*
Temperature at reversal (º)	33.7 (1.2)	33.8 (1.1)	0.7

*: p<0.05; †: p<0.001.

DISCUSSION

The major finding of this study was that $MgSO_4$ administration statistically decreased rocuronium-induced injection pain, shortened rocuronium onset time and prolonged its reversal by sugammadex without residual block. However, this prolongment is clinically negligible. We were not able to demonstrate a reductive effect of $MgSO_4$ on mean total rocuronium supplementation in female patients undergoing gynecological procedures < 2 hour duration.

Consistent with the previous studies, $MgSO_4$ has been found to be effective in reducing the rocuronium-induced injection pain in this study.[11,12] In this work, rocuronium onset time was shorter in the $MgSO_4$ group (1.05±0.4 min) when compared to placebo (1.5±0.5 min) under sevoflurane anesthesia also. It was shown that, the administration of a 50 mg/kg and higher iv boluses of $MgSO_4$ shortened the rocuronium onset time and prolonged the spontaneous recovery of rocuronium-induced neuromuscular blockade.[13-17]

In a recent study, $MgSO_4$ was administered as a 30 mg/kg bolus plus 10 mg/kg/h continuous administration during gynecologic surgery. This work reported lower rocuronium requirements, more elevated magnesium levels compared to preoperative levels (1.99 vs 2.17 $mg.dl^{-1}$), significantly delayed recovery (up to 10 minutes) after neostigmine administration and decreased fentanyl consumption in the postoperative period compared to placebo.[18] In our study, 50 mg/kg iv bolus plus 15.mg/kg/h infusion were administered. Postoperative magnesium levels were higher than preoperative values (1.95 vs 3.64 mg/dl) and rocuronium was provided as required during surgery. Despite this, TOF ratios reached satisfactory levels (TOF>O.9) two minutes after sugammadex administration in the $MgSO_4$ group.

Neostigmine's reduced efficacy was well documented in a paper by Fuchs-Buder et al. longer recovery times seen after neostigmine when magnesium levels were elevated.[19] Another study

showed that a 50 mg/kg iv bolus followed by 8 mg/kg/h continuous $MgSO_4$ administration reduced the requirement of rocuronium, prolonged the recovery period and decreased the analgesic consumption in patients undergoing cholesistectomy.[20]

Previously it was shown that pretreatment with a 50 mg/kg iv bolus of $MgSO_4$ may re-establish a clinically relevant degree of muscle relaxation in the postoperative care unit following spontaneous recovery from rocuronium-induced neuromuscular block.[21] In contrast, we observed no residual block in either the $MgSO_4$ or the placebo group following sugammadex administration.

In the present study, sevoflurane was used as the primary anesthetic agent. Median recovery times from a starting dose of 4 mg/kg sugammadex iv at a TOF count of 1 after continuous infusion of rocuronium was found to be rapid and effective at achieving a TOF ratio of 0.9, regardless of previously administered propofol or sevoflurane anesthesia.[22,23]

There are some limitations of our study; first we use a high dose (4 mg/kg) of sugammadex and larger differences could be seen if 2 mg/kg dose was administered. Second, our patients were not preeclamptic or eclamptic. Further studies that will work on real eclamptic settings were needed.

The results of the present study indicated that in female patients, the administration of $MgSO_4$ minimally prolonged the 4 mg/kg sugammadex reversal of rocuronium-induced neuromuscular blockade and did not lead to residual block. This prolongation was clinically negligible.

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