J Anesth (2007) 21:86–89
DOI 10.1007/s00540-006-0452-3

Journal of
Anesthesia

Effects of magnesium sulfate on neuromuscular function and spontaneous breathing during sevoflurane and spinal anesthesia

Ryohei Serita, Hiroshi Morisaki, Chikako Tanaka, Shizuko Kosugi, Shigeki Sakuraba, and Junzo Takeda

Department of Anesthesiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Abstract
The purpose of the present study was to determine the effects of magnesium sulfate ($MgSO_4$) on the neuromuscular function and spontaneous breathing of patients under sevoflurane and spinal anesthesia. Twenty-two patients with a history of arrhythmia undergoing elective knee surgery were randomly assigned to two groups: group M ($n = 11$), administered with $MgSO_4$ 40 mg·kg^{-1}, and group S ($n = 11$), administered with saline. A combination of spinal anesthesia with 2% sevoflurane inhalation was applied to all patients under spontaneous breathing. Tidal volume (Vt), respiratory rate (RR) and end-tidal carbon dioxide (ET_{CO_2}) were measured before the $MgSO_4$ or saline injection and measurements were repeated at 5, 15, 30, and 45 min after the injection. Neuromuscular function was continuously monitored with an acceleromyograph to record the acceleration of the adductor pollicis by stimulating the ulnar nerve at a frequency of 0.1 Hz. The Vt, RR, and ET_{CO_2} showed little change in either group, and there was no significant difference between, the groups. The single-twitch response showed significant differences between the two groups ($P = 0.0006$). The present study indicated that the $MgSO_4$ had a minimal effect on spontaneous breathing in patients undergoing sevoflurane and spinal anaesthesia, but that it attenuated the safety margin of neuromuscular function.

Key words Magnesium sulfate · Neuromuscular function · Respiratory function · Sevoflurane

Magnesium sulfate ($MgSO_4$) has been used as an antiarrhythmic agent during non-cardiac anesthesia as well as cardiac anesthesia [1,2]. Although the prophylactic use of $MgSO_4$ for arrhythmia has been controversial [3], Terzi et al. [2] showed that the prophylactic use of $MgSO_4$ reduced the incidence of atrial arrhythmias in thoracic surgery.

Address correspondence to: R. Serita
Received: December 22, 2005 / Accepted: September 14, 2006

On the other hand, $MgSO_4$ has been shown to potentiate the action of muscle relaxants and is reported to cause muscle weakness associated with respiratory insufficiency when administered at a comparatively high dose [4,5]. The mechanism of the muscle relaxant effect of $MgSO_4$ is shown as a result of competition with calcium ion (Ca^{2+}) for membrane channels and the inhibition of acetylcholine (ACh) release from the neuromuscular junction [6]. During inhalational and spinal anesthesia, these effects of $MgSO_4$ in patients with arrhythmia may be enhanced by interaction with volatile anaesthetics, and calcium channel blockers, and by advanced age [7–9]. However, it is still unknown how $MgSO_4$ per se affects neuromuscular function and spontaneous breathing under anesthesia. The purposes of the present study were to determine the effect of $MgSO_4$ in attenuating neuromuscular function and spontaneous breathing during sevoflurane and spinal anesthesia.

After obtaining institutional ethics committee approval from the Keio University School of Medicine, and obtaining informed consent from the patients, 22 patients undergoing elective knee surgery were enrolled in this double-blinded, randomized, placebo-controlled, prospective study. The patients fulfilled the following criteria: (1) American society of Anesthiologists (ASA) physical status II or III and (2) a history of arrhythmias. Patients who had any neurological abnormalities were excluded from the study.

All patients were premedicated with hydroxyzine 25–50 mg and atropine sulfate 0.5 mg intramuscularly 1 h before induction. The patients received spinal anesthesia with 0.5% isobaric bupivacaine through the L3/4 interspace. Fifteen minutes after spinal anesthesia was induced, and at the end of the operation, the blocking height was confirmed by the pin-prick method below Th10. Anesthesia was induced with propofol 2–2.5 mg·kg^{-1} intravenously, for the placement of a laryngeal mask airway, and maintained with the inhalation of oxygen-air (fraction of inspired oxygen) ([$F_{I_{O_2}}$], 0.4) and

2% sevoflurane under spontaneous breathing. A standard optimal circle system was used with high fresh gas flow (6 l·min^{-1}) during anesthesia.

Thirty minutes after induction, baseline respiratory variables, including tidal volume (VT), respiratory rate (RR), and end-tidal carbon dioxide (ET_{CO_2}), were measured by using an expiration gas analyzer (Datex; Capnomac Ultima-SVi, Helsinki, Finland). Mean indirect arterial pressure (MAP) and heart rate (HR) were also measured. The eligible patients were randomly assigned to two groups: group M received 40 mg·kg^{-1} $MgSO_4$ injection, considered as the initial dose for the treatment of arrhythmias [10], and group S received an equal volume of saline. An independent investigator, who was not involved in the data collection, prepared the solution in advance. The measurements were repeated at 5, 15, 30, and 45 min after injection.

Neuromuscular function was evaluated by an acceleromyograph (TOF-Guard; Organon Teknika, Turnhout, Belgium) to record the acceleration of the adductor pollicis by stimulating the ulnar nerve. After induction, the stimulating mode was initially set as the autonomic stimulating mode (TOF I mode) to stimulate supramaximally, and reset as single-twitch mode with a frequency of 0.1 Hz. The control single-twitch height was recorded before sevoflurane anesthesia, and the single-twitch height was monitored continuously during the study. We measured TOF values at the end of study if the single-twitch height was reduced by more than 30%. Data were recorded and analyzed using Card Reader Ver.1.1 software (Organon Teknika). Palmar skin and body temperature were monitored and kept above 34°C and 36.5°C, respectively. Supplemental oxygen (6 l·min^{-1}) was administered via a face mask during 6 h after the operation.

All data values are expressed as means (SD) [ranges] unless otherwise described. Before we started the present study, in 8 other patients administered with $MgSO_4$, we determined the number of subjects needed to achieve 90% power to detect a difference of 20% in single-twitch height, with $\alpha = 0.05$. Based on a power calculation, it was shown 22 subjects were needed. The patients' characteristics were analyzed by using Student's *t*-test and the χ^2 test for differences between the groups. The measurement variables were analyzed by two-way repeated-measures analysis of variance between the groups, followed by Student's *t*-test with Bonferroni correction at each time point. The Mann-Whitney *U*-test was used to compare differences in the minimum single-twitch height. A P value of <0.05 was considered as statistically significant.

Patient characteristics were not significantly different between the two groups (Table 1). Three of the 11 $MgSO_4$ patients had been medicated with nifedipine to treat hypertension. No patient was receiving steroid therapy or aminoglycoside antibiotics.

Hemodynamic and respiratory variables in the two groups showed similar changes and did not change significantly throughout the study period (Table 2). The single-twitch responses in group M were significantly depressed throughout the study period ($P = 0.0006$) (Fig. 1). The minimum twitch-height responses were significantly lower in group M than in group S (76.2% (18.3%) [40%–90]% versus 95.8% (3.7%) [90%–100]%, respectively; $P = 0.002$), and the duration from $MgSO_4$ or saline injection to that point was 246.3 (65.2) [200–360] s in group M. Three patients in group M (aged 71, 76, and 76 years) showed over 30% reductions in twitch responses (51%, 70%, and 67% of control, respectively). The TOF ratio (T4/T1) of these three patients was not decreased at the end of the study (110%, 102%, and 108%, respectively).

While three patients in group S showed arrhythmias (one, premature ventricular contractions and the others, supraventricular premature contractions) during anesthesia, no patient in group M had any arrhythmias ($P = 0.06$; χ^2 test). In group M, no patient was observed to have hypoventilation, desaturation (defined as

Table 1. Patients' characteristics

	Group S ($n = 11$)	Group M ($n = 11$)
Age (years)	66 (9.3) [55–75]	73 (4.6) [66–81]
Height (cm)	151.5 (9.4) [139–171]	149.2 (7.8) [141–162]
Weight (kg)	57.8 (9.0) [45–73]	53.8 (7.0) [44–62]
Sex (M/F)	3/8	3/8
ASA physical status (II/III)	8/3	8/3
Type of arrhythmia		
Supraventricular	9	7
Ventricular	2	4
Treatment with calcium channel blocker	2	3

Values are means (SD) [ranges] or numbers of patients. There were no significant differences between the groups

Table 2. Respiratory and hemodynamic changes after injection

	Group	Baseline	Time after injection (min) 5	15	30	45
Heart rate (min^{-1})	S	75.8 (9.8) [57–90]	75.3 (9.9) [56–92]	73.6 (10.2) [55–90]	73.6 (9.9) [54–85]	73.9 (9.1) [54–84]
	M	67.2 (10.1) [54–84]	67.5 (13.2) [49–94]	65.6 (10.0) [53–80]	66.3 (11.1) [50–78]	67.3 (13.3) [50–81]
Mean arterial pressure (mmHg)	S	66.5 (8.0) [54.3–78]	65.4 (7.3) [53–78]	63.6 (7.0) [55.3–77.3]	63.8 (8.1) [54.7–77]	67.3 (11.1) [53.7–93]
	M	70.8 (7.7) [62–83]	64.5 (6.8) [56.3–79]	68.2 (5.1) [64–79]	66.4 (7.4) [63–81]	71.8 (4.0) [65.3–78.3]
Tidal volume ($ml \cdot kg^{-1}$)	S	4.8 (0.8) [3.7–6.3]	4.8 (0.8) [3.7–6.4]	4.8 (0.9) [3.7–6.2]	4.7 (0.7) [3.8–6.0]	4.7 (0.8) [3.6–6.0]
	M	4.9 (0.8) [4.0–6.1]	4.9 (0.8) [4.0–6.3]	4.9 (0.9) [3.7–6.7]	4.8 (0.8) [3.8–6.4]	4.8 (0.7) [4.0–6.2]
End-tidal CO_2 (mmHg)	S	43.1 (3.6) [37–48]	42.6 (3.2) [37–46]	43.0 (3.6) [37–48]	42.6 (3.3) [37–46]	42.0 (3.8) [38–48]
	M	40.6 (3.8) [36–47]	40.4 (3.7) [36–47]	40.4 (3.9) [35–47]	39.7 (3.9) [33–47]	39.1 (4.0) [31–45]
Respiratory rate (min^{-1})	S	17.9 (4.2) [10–26]	18.1 (4.1) [11–26]	18.2 (3.9) [11–26]	18.1 (4.1) [10–25]	18.6 (4.0) [11–26]
	M	17.6 (5.7) [11–31]	18.0 (5.4) [11–29]	18.0 (5.8) [11–32]	18.6 (6.3) [11–35]	19.8 (6.3) [11–36]

Values are means (SD) [ranges]. There were no significant differences between the groups

Fig. 1. The single-twitch responses in *group M* (treated with $MgSO_4$ 40 $mg \cdot kg^{-1}$) were significantly depressed compared with those *group S* (treated with saline) until 45 min after the injection ($P = 0.0006$ two-way repeated measures analysis of variance). $^*P < 0.002$ vs group S (Student's *t*-test with Bonferroni correction)

peripheral oxygen saturation [$S_{P_{O_2}}$] < 95% under supplemental oxygen therapy), or delayed awakening.

Although $MgSO_4$ use has been controversial as a prophylactic anti-arrhythmic agent, it has been used as such an agent during non-cardiac anesthesia. We therefore studied patients with a history of arrhythmia who were likely to be administered with $MgSO_4$ during non-cardiac anesthesia and who may have been more sensitive to the neuromuscular inhibition of $MgSO_4$ as a result of aging and administration of a calcium channel blocker. The present study indicated that the administration of $MgSO_4$ at a moderate dose (40 $mg \cdot kg^{-1}$) in patients with a history of arrhythmia seemed to have little effect on spontaneous breathing and did not cause hypoventilation during sevoflurane and spinal anesthesia. However, the single-twitch responses had diminished by about 20% at the end of the study. These findings suggest that $MgSO_4$ should be used cautiously in patients with a history of arrhythmia during sevoflurane and spinal anesthesia.

The major factors that enhanced the effect of $MgSO_4$ on the neuromuscular system in present study might be considered as an interaction with sevoflurane, the spinal anesthesia, the age of the patients, and the use of calcium channel blockers [7–9]. First, although sevoflurane brought about little change of the twitch responses in the control group, sevoflurane has been shown to potentiate the effect of neuromuscular blocking agents [7]. Sevoflurane may act synergistically with $MgSO_4$ on the neuromuscular junction, but the present study did not confirm this effect. On the other hand, $MgSO_4$ administration had little effect on spontaneous breathing. Inhalational anesthetics depress the function of the parasternal intercostal muscles and cause diaphragmatic

function to be dominant under spontaneous respiration [11,12]. Furthermore, the diaphragma is more resistant to neuromuscular blocking agents than peripheral muscle [13]. Therefore, there was some possibility that such a sparing effect of respiratory muscles could have occurred in our patients treated with $MgSO_4$.

Secondly, spinal blockade may modify the functional state of the neuromuscular junctions through the depression of afferent impulses. The blockade of afferent impulses into the central nervous system is reported to have lessened the dose of sedatives required [14]. Central neural influences on neuromuscular transmission may explain the frequent failure of evoked electromyographic responses, but no investigation has been performed to clarify the alterations of neuromuscular function during spinal anesthesia. The possibility of an effect of spinal blockade, however, could not be excluded in our study.

Thirdly, with aging, there may be overactivity in response to magnesium at the neuromuscular junction, because the acetylcholine (ACh) content at the neuromuscular junction is reduced with aging [9]. In the present study, three patients aged over 70 years showed a marked reduction of single-twitch height. Because the TOF ratio in these three patients did not decrease, it seems that $MgSO_4$ did not inhibit the release of ACh from the neuromuscular junction with the moderate dose administered. However, high-dose administration of $MgSO_4$ during anesthesia should be used cautiously in older patients.

Finally, patients with arrhythmias may have other cardiovascular complications, e.g., hypertension and ischemic heart disease, and these patients may have been medicated with a calcium channel blocker, such as nifedipine, which has been shown to enhance neuromuscular blockade [8]. In our patients, 3 of the 11 treated with $MgSO_4$ had been medicated with nifedipine to treat hypertension. The reduction of single-twitch height in these patients was similar to that in the other patients, but further study is needed to evaluate the possible interaction of calcium channel blockers with $MgSO_4$.

In regard to the limitations of our study, we observed the responses of single-twitch height for only 45 min after $MgSO_4$ injection, because $MgSO_4$ ($40\,mg \cdot kg^{-1}$) had been reported to prolong the duration of recovery to 75% of the twitch height of vecuronium ($0.1\,mg \cdot kg^{-1}$) for approximately 30 min [15]. However, it should be noted that the responses of single-twitch height were depressed about by 20% at 45 min after the $MgSO_4$ injection. Such prolonged effects of $MgSO_4$ on the neuromuscular system suggest that we should keep monitoring the single-twitch for a longer time period. We did not measure obvious indicators in our subjects, such as the plasma magnesium concentration.

In summary, the current preliminary study indicated that $MgSO_4$ injection at the initial dose used for the treatment of arrhythmias caused a substantial, but not clinically apparent, risk of limiting spontaneous breathing in patients with a history of arrhythmia under sevoflurane and spinal anaesthesia. However, we investigated only V_T, RR, and ET_{CO_2} and did not determine other optimal variables, such as maximum inspiratory pressure. A further study would be needed to evaluate in detail the effects of $MgSO_4$ on the respiratory system during anesthesia.

References

1. Dorman BH, Sade RM, Burnette JS, Wiles HB, Pinosky ML, Reeves ST, Bond BR, Spinale FG (2000) Magnesium supplementation in the prevention of arrhythmias in pediatric patients undergoing surgery for congenital heart defects. Am Heart J 139:522–528
2. Terzi A, Furlan G, Chiavacci P, Dal Corso B, Luzzani A, Dalla Volta S (1996) Prevention of atrial tachyarrhythmias after noncardiac thoracic surgery by infusion of magnesium sulfate. Thorac Cardiovasc Surg 44:300–303
3. Fuchs-Buder T, Tassonyi E (1996) Magnesium sulphate enhances residual neuromuscular block induced by vecuronium. Br J Anaesth 76:565–566
4. Morisaki H, Yamamoto S, Morita Y, Kotake Y, Ochiai R, Takeda J (2000) Hypermagnesemia-induced cardiopulmonary arrest before induction of anesthesia for emergency cesarean section. J Clin Anesth 12:224–226
5. Hubbard JI, Jones SF, Landau EM (1968) On the mechanism by which calcium and magnesium affect the release of transmitter by nerve impulses. J Physiol 196:75–86
6. Ross RM, Baker T (1996) An effect of magnesium on neuromuscular function in parturients. J Clin Anesth 8:202–204
7. Suzuki T, Munakata K, Watanabe N, Katsumata N, Saeki S, Ogawa S (1999) Augmentation of vecuronium-induced neuromuscular block during sevoflurane anaesthesia: comparison with balanced anaesthesia using propofol or midazolam. Br J Anaesth 83:485–487
8. Sekerci S, Tulunay M (1996) Interactions of calcium channel blockers with non-depolarising muscle relaxants in vitro. Anaesthesia 51:140–144
9. Smith DO (1984) Acetylcholine storage, release and leakage at the neuromuscular junction of mature adult and aged rats. J Physiol 347:161–176
10. Fawcett WJ, Haxby EJ, Male DA (1999) Magnesium: physiology and pharmacology. Br J Anaesth 83:302–320
11. Warner DO, Warner MA, Ritman EL (1995) Human chest wall function while awake and during halothane anesthesia. I. Quiet breathing. Anesthesiology 82:6–19
12. Ide T, Kochi T, Isono S, Mizuguchi T (1993) Diaphragmatic activity during isoflurane anaesthesia in dogs. Acta Anaesthesiol Scand 37:253–257
13. Laycock JR, Donati F, Smith CE, Bevan DR (1998) Potency of atracurium and vecuronium at the diaphragm and the adductor pollicis muscle. Br J Anaesth 61:286–291
14. Pollock JE, Neal JM, Liu SS, Burkhead D, Polissar N (2000) Sedation during spinal anesthesia. Anesthesiology 93:728–734
15. Fuchs-Buder T, Wilder-Smith OH, Borgeat A, Tassonyi E. Burkhead D, Polissar N (1995) Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. Br J Anaesth 74:405–409