Cardiothoracic Anesthesia, Respiration and Airway

Magnesium potentiates neuromuscular blockade with cisatracurium during cardiac surgery

[Le magnésium potentialise le blocage neuromusculaire réalisé avec du cisatracurium en cardiochirurgie]

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Purpose: Magnesium potentiates the effect of nondepolarizing neuromuscular blocking agents. It is used in cardiac anesthesia to prevent hypertension and arrhythmias. This study was performed to measure the interaction between magnesium and cisatracurium in cardiac surgery.

Methods: Twenty patients scheduled for elective cardiac surgery were randomly assigned to receive magnesium sulfate (70 $mg \cdot kg^{-1}$ at induction followed by 30 $mg \cdot kg^{-1} \cdot hr^{-1}$) or placebo. The ulnar nerve was stimulated and the electromyographic response of the adductor pollicis was measured. Cisatracurium 0.1 $mg \cdot kg^{-1}$ was given at induction, followed by 0.05 $mg \cdot kg^{-1}$ when the first twitch in the train-of-four reached 25%.

Results: Ionized magnesium was 1.32 ± 0.24 $mmol \cdot L^{-1}$ in the treatment group *vs* 0.47 ± 0.4 $mmol \cdot L^{-1}$ in the control group. Duration of action of the intubating dose was longer in the magnesium group (74 ± 20 min) than in the placebo group (42 ± 6 min, $P = 0.0001$). Duration of the first maintenance dose was 69 ± 16 min in the magnesium group *vs* 35 ± 7 min in the placebo group ($P = 0.0001$). Total dose of cisatracurium administered throughout surgery was 0.19 ± 0.07 $mg \cdot kg^{-1}$ in the magnesium group compared with 0.29 ± 0.01 $mg \cdot kg^{-1}$ in the placebo group ($P = 0.017$). Hemodynamic variables and temperature were similar in both groups.

Conclusion: In patients undergoing cardiac surgery, administration of magnesium sulfate, resulting in ionized levels of 1.3 $mmol \cdot L^{-1}$, results in a 30–35 min prolongation of the neuromuscular blockade induced with intubating and maintenance doses of cisatracurium and does not alter hemodynamic stability.

Objectif : *Le magnésium est utilisé en clinique pour traiter les arythmies et prévenir l'hypertension. Le but de cette étude est de mesurer l'interaction entre le cisatracurium et le magnésium en chirurgie cardiaque.*

Méthode : *Vingt patients devant subir une intervention cardiaque programmée ont été randomisés pour recevoir du sulfate de magnésium (70 $mg \cdot kg^{-1}$ à l'induction puis 30 $mg \cdot kg^{-1} \cdot h^{-1}$) ou un placebo. Le nerf ulnaire était stimulé et la réponse électromyographique du muscle adducteur du pouce était enregistrée. Pour l'intubation, 0,1 $mg \cdot kg^{-1}$ de cisatracurium était utilisé et les doses suivantes de 0,05 $mg \cdot kg^{-1}$ ont été administrées lorsque T1 atteignait 25 %.*

Résultats : *Le magnésium ionisé était de 1,32 ± 0,24 $mmol \cdot L^{-1}$ dans le groupe traité vs 0,47 ± 0,4 $mmol \cdot L^{-1}$ dans le groupe placebo. La durée d'action des doses d'intubation et de maintien dans le groupe traité au magnésium (74 ± 20 min et 69 ± 16) était plus longue que dans le groupe placebo (42 ± 6 et 35 ± 7, $P = 0,0001$). Les variables hémodynamiques et la température sont restés similaires dans les deux groupes. La quantité de cisatracurium administrée durant l'opération était moins grande dans le groupe ayant reçu du magnésium comparé au placebo (0,19 ± 0,07 $mg \cdot kg^{-1}$ vs 0,29 ± 0,01 $mg \cdot kg^{-1}$, $P = 0,017$).*

Conclusion : *Chez des patients subissant une intervention cardiaque, une magnésémie de 1,3 $mmol \cdot L^{-1}$ produit peu de changements hémodynamiques mais augmente la durée du bloc neuromusculaire produit par le cisatracurium d'environ 30–35 min.*

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INTRAVENOUS magnesium sulfate has many uses in clinical practice. Initially reported as a sole anesthetic agent in 1916,[1] it has been used more recently for its antiarrhythmic, anticonvulsant, and antihypertensive properties, especially in the anesthetic, obstetrical, and cardiac fields.[2–7] During cardiac surgery, magnesium sulfate is frequently used to control ventricular arrhythmias or to lower systemic or coronary vascular resistance.[4,8,9]

An interaction between magnesium sulfate and nondepolarizing neuromuscular blocking agents (NMBAs) has been documented for many years. In 1968, a prolongation in duration of neuromuscular blockade was described in obstetrical patients when they were treated with magnesium for pre-eclampsia.[10] Several reports have since confirmed this interaction with vecuronium, rocuronium, pancuronium, and mivacurium, but it has not been determined for cisatracurium.[11–18] The doses of magnesium used in these studies were variable and serum concentrations of magnesium were not measured. Furthermore, none of these investigations were performed in cardiac surgery, where magnesium might be useful and widely used and none used cisatracurium, which has an elimination profile suitable for cardiac patients who are at risk of renal and hepatic failure.

The purpose of this study was to quantify the interaction between magnesium sulfate and cisatracurium by measuring the duration of neuromuscular blockade in a randomized, double-blind controlled study in cardiac surgery patients, using a standardized dosage of magnesium to obtain stable levels throughout the procedure.

Methods

The protocol was approved by the Institutional Review Board and patients gave written informed consent. Twenty American Society of Anesthesiology (ASA) physical status class II or III patients between 18 and 80-yr-old, undergoing elective cardiac surgery, were included in this study. Patients with any of the following criteria were excluded: morbid obesity (body mass index over 30 $kg \cdot m^{-2}$), history of neuromuscular disease, diabetic neuropathy, or abnormal renal function (serum creatinine > 176 $\mu mol \cdot L^{-1}$), and patients receiving magnesium supplementation or drugs known to have a significant interaction with NMBAs.

Premedication included morphine 0.15 $mg \cdot kg^{-1}$ *im*, scopolamine 0.2–0.4 mg *im* and the patient's usual cardiac medication. When the patient arrived in the operating room (OR), oxygen was administered by nasal cannula and standard monitors (electrocardiogram, pulse oximeter, noninvasive blood pressure) were applied. Sedation with midazolam 1–2 mg *iv* boluses and/or propofol 10–20 mg *iv* were administered as required to maintain sedation during insertion, under local anesthesia, of a radial artery cannula and the introduction of a pulmonary artery catheter via the internal jugular route.

TABLE I Demographic data (mean ± SD when applicable)

	Placebo *n = 10*	*Magnesium* *n = 10*	*P-value*
Gender (M/F)	7/3	9/1	0.3
Age (yr)	62 ± 12	65 ± 7	0.4
Weight (kg)	77 ± 14	71 ± 10	0.3
Height (cm)	165 ± 9	164 ± 9	0.8
Type of surgery (CABG/others)	7/3	7/3	1
Unstable angina	3 (30%)	3 (30%)	1
Hypertension	6 (60%)	6 (60%)	1
Heart failure	2 (20%)	4 (40%)	0.3
Diabetes	1 (10%)	1 (10%)	1
COPD	1 (10%)	1 (10%)	1
Beta-blockers	8 (80%)	5 (50%)	0.2
ACE inhibitors	3 (30%)	4 (40%)	0.6
Calcium channel blockers	5 (50%)	7 (70%)	0.4
Diuretics	1 (10%)	1 (10%)	1

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease.

Neuromuscular function was monitored with a relaxograph (Datex, Helsinki, Finland), which uses an electromyographic technique. The response of the adductor pollicis muscle was recorded over the thenar eminence after supramaximal train-of-four (2 Hz for 2 sec) stimulation of the ulnar nerve at the wrist every 20 sec. The neuromuscular monitor was calibrated before administration of the study drug (magnesium or placebo) and induction of anesthesia. Skin temperature was measured using a temperature monitor (Shiley, CA, USA) applied to the skin surface of the hypothenar site of the same hand.

Following calibration of the neuromuscular monitor, patients were randomly allocated to receive either magnesium 70 $mg \cdot kg^{-1}$ over ten minutes prior to induction of anesthesia, followed by an infusion of 30 $mg \cdot kg^{-1} \cdot hr^{-1}$ (Group A), or an equal volume of normal saline solution (Group B). The study drug infusion was maintained until the beginning of sternal closure towards the end of surgery. Randomization was made by the pharmacist, who was the only unblinded person in the study, from sealed envelopes. The investigator was blinded to the contents of the perfusion syringe and to the results of plasma magnesium levels. There were ten patients in each group.

TABLE II Core and cutaneous temperature

Time (min)	*Skin temperature (°C)*		*P-value*	*Core temperature (°C)*		*P-value*
	Placebo n = 10	*Magnesium n = 10*		*Placebo n = 10*	*Magnesium n = 10*	
0	33.4	34.9	NS	NA	NA	NA
15	33.9	33.6	NS	35.7	35.5	NS
30	34.0	33.4	NS	35.4	35.4	NS
45	34.1	33.2	NS	35.5	35.2	NS
60	33.9	33.0	NS	35.0	35.1	NS
75	33.8	33.0	NS	34.6	33.9	NS
90	33.7	32.9	NS	34.5	33.1	NS
105	33.8	33.2	NS	34.0	32.7	NS
120	33.8	33.7	NS	33.7	33.6	NS
135	34.0	34.0	NS	34.2	34.6	NS

NA = not applicable; NS = not significant.

TABLE III Pharmacodynamics of cisatracurium and plasma potassium levels (mean ± SD)

	Placebo n = 10	*Magnesium n = 10*	*P-value*
Duration to 25% (first dose) (min)	42.6 ± 6	74.2 ± 21	0.0002
Duration to 25% (second dose) (min)	35.3 ± 7	68.8 ± 16	0.0001
Total dose, cisatracurium ($mg \cdot kg^{-1}$)	0.29 ± 0.01	0.19 ± 0.07	0.017
Ionized Mg, arrival ICU ($mmol \cdot L^{-1}$)	0.53 ± 0.22	1.11 ± 0.17	0.0001
Ionized K, arrival ICU ($mmol \cdot L^{-1}$)	4.09 ± 0.6	4.77 ± 1.0	0.08
Duration of surgery (min)	271 ± 51	247 ± 42	0.5

ICU = intensive care unit.

After preoxygenation, anesthesia was induced and maintained with *iv* midazolam, propofol and sufentanil with the dosages being at the anesthesiologist's discretion. Cisatracurium 0.1 $mg \cdot kg^{-1}$ (2 × ED_{95}) *iv* was administered to facilitate tracheal intubation. Laryngoscopy was performed when first twitch height (T1) was < 15%. Mechanical ventilation with oxygen at a FIO_2 of 1.0 was set at a tidal volume of 9–12 $mL \cdot kg^{-1}$ at a rate of 8–10 $breaths \cdot min^{-1}$. No volatile anesthetic agents were allowed at any time throughout the surgery.

Muscle relaxation was maintained by administering repeated boluses of cisatracurium 0.05 $mg \cdot kg^{-1}$ (1 × ED_{95}) *iv* when neuromuscular function recovered to 25% of T1 until the beginning of sternal closure at which time neuromuscular function was allowed to recover spontaneously. At the end of surgery, reversal of blockade was achieved with neostigmine 0.05 $mg \cdot kg^{-1}$ and glycopyrrolate 10 $\mu g \cdot kg^{-1}$ *iv,* administered only when four twitches were present on the train-of-four stimulation. After surgery, patients were transferred to the intensive care unit (ICU), where mechanical ventilation was continued until normothermia, stable hemodynamics, spontaneous breathing, and consciousness were achieved.

Neuromuscular blockade was measured every 20 sec from induction of anesthesia until the end of the skin closure. The following variables were recorded after each dose of cisatracurium: time to 90% T1 depression, maximum block and time from injection to 25% T1 recovery. After the last dose, duration to 75% spontaneous T1 recovery was also recorded. Systolic blood pressure and heart rate were taken on arrival in the OR, prior to bolus of study medication, at the end of the bolus, and following tracheal intubation. Systolic blood pressure, heart rate, skin and core temperature were also recorded every 15 min after the administration of cisatracurium.

Blood samples for magnesium, electrolytes and arterial blood gases were drawn before and after the initial bolus of study drug, after induction of anesthesia and on arrival in the ICU. Ionized magnesium was measured (NOVA STAT Profile Ultra C Analyzer, [ion selective electrode technique], NOVA Biomedical, Waltham, MA, USA - normal range 0.45–0.75 $mmol \cdot L^{-1}$ of ionized magnesium in whole blood) and the results of the test were not disclosed to the investigator.

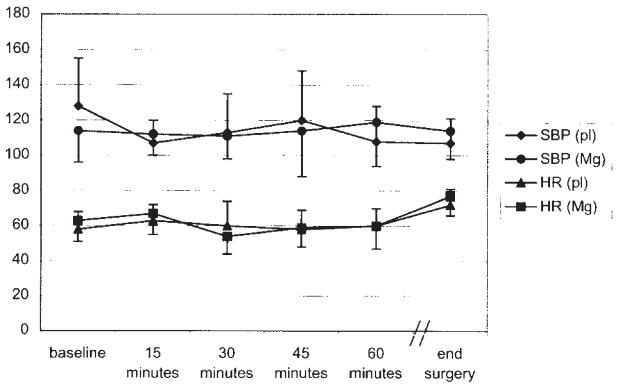

FIGURE 1 Systolic blood blood pressure (SBP) and heart rate (HR) in placebo (pl) and magnesium-treated (Mg) groups. Values are expressed as means ± standard deviations.

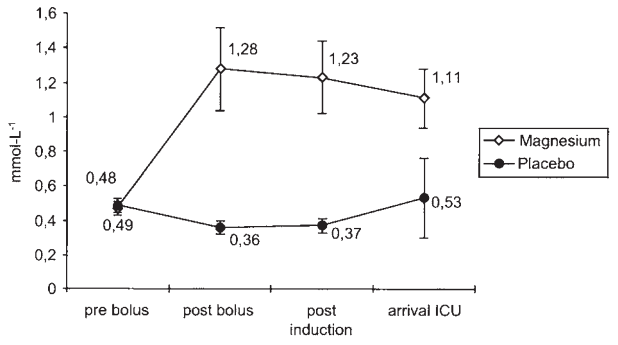

FIGURE 2 Whole blood ionized magnesium throughout surgery and on arrival in intensive care unit (ICU). Values are expressed as means ± standard deviations

Statistical analysis

Sample size was determined from a pilot study on five patients who received magnesium. The expected duration of neuromuscular block was estimated at 46 ± 10 min [mean ± standard deviation (SD)] from the study by Searle *et al.*[19] in the same hospital. Using Student's t test, we calculated a sample size of ten patients per group to detect a clinically significant difference, due to magnesium, of 30% with an alpha value of 0.05 and a power of 0.8. Results are presented as mean ± SD. Comparison of demographic data (age, weight, and height) was performed using two-sided Student's t test. Frequency of coexisting diseases and medication usage were analyzed using Chi-square and Fisher exact tests where appropriate. Blood pressure, heart rate, temperature, ionized plasma magnesium, and duration of neuromuscular blockade analysis were performed using comparison of the mean with one-way ANOVA and were adjusted for inequality of variance when needed. A *P*-value less than 0.05 was considered to indicate a statistically significant difference.

Results

There were no differences between the study groups with respect to demographic data, ASA physical status, coexisting disease, preoperative medication, type of surgery or duration of cardiopulmonary bypass (Table I). Total doses of midazolam, propofol, and sufentanil were 1–19 mg, 0–1570 mg, and 80–400 μg respectively.

Systolic blood pressure and heart rate are shown in Figure 1. There were no statistical differences in these variables between the two groups on arrival in the OR, at baseline, prior to bolus of study medication, at the end of the bolus of study medication or at the end of surgery, and prior to transfer to the ICU. Core and cutaneous temperatures were similar in both groups throughout the whole surgery (Table II).

Ionized magnesium levels were similar between the two groups at baseline (0.48 ± 0.04 $mmol \cdot L^{-1}$ in Group A *vs* 0.49 ± 0.04 $mmol \cdot L^{-1}$ in Group B, $P = 0.7$), but significantly higher in the magnesium-treated group (1.32 ± 0.2 $mmol \cdot L^{-1}$ *vs* 0.47 ± 0.3 $mmol \cdot L^{-1}$, $P = 0.0001$) following bolus administration and remained higher throughout surgery and on arrival in the ICU (Figure 2). There was no statistically significant difference in plasma potassium levels on arrival in the ICU between both groups (Table III).

Single twitch remained stable at the end of bolus administration (T1 = 98% of control in both groups). Maximum blockade was 100% in all patients. When compared with the control group, there was a significant prolongation in neuromuscular blockade in the group receiving magnesium. The duration to 25% recovery after the intubating dose (0.1 $mg \cdot kg^{-1}$) was 32 min longer in the magnesium-treated group compared with the placebo group ($P = 0.0001$, Table III). The effects of the first maintenance dose of cisatracurium (0.05 $mg \cdot kg^{-1}$) also lasted 34 min longer ($P = 0.0001$, Table III). Comparisons were made only for the first maintenance dose because some magnesium-treated patients received only one maintenance dose. Patients given magnesium received 2.5 ± 0.5 maintenance doses, whereas those in the control group were given 4.8 ± 1.9 maintenance doses. Total dose of cisatracurium was significantly less in the magnesium group (0.19 ± 0.07 $mg \cdot kg^{-1}$) compared with the place-

bo group (0.29 ± 0.01 mg·kg^{-1}, P = 0.017). Because several patients did not receive reversal of NMBA and single twitch did not recover to control values, evaluation of neuromuscular blockade to full recovery at the end of surgery was not possible.

Discussion

At dosages commonly used in cardiac patients, this study demonstrates that magnesium causes a significant prolongation of the effects of cisatracurium on the neuromuscular junction without cardiovascular effects. The dosage of magnesium selected is commonly used in cardiac surgery when treating shivering or pre- and postoperative arrhythmia,[8] and in obstetrical patients.

In this study, pharmacological agents such as volatile agents or aminoglycosides were avoided because of their significant potentiation of the effects of nondepolarizing NMBA.[19] Other drugs such as calcium channel blockers and beta-blockers may have an effect on muscle relaxation. However, this effect is not clinically important,[20] and patients already taking these medications were equally distributed between both groups.

The dosage of magnesium sulfate was chosen in an attempt to obtain plasma concentrations which preserve cardiovascular stability and prevent arrhythmia. In cardiology, the therapeutic level to prevent and treat arrhythmia is generally in the range of 3–6 mEq·L^{-1}, or 1.5–3 mmol·L^{-1} total plasma magnesium, of which two thirds are ionized. The mean ionized magnesium level was 1.2 mmol·L^{-1} in the treatment group, which suggests that the dose given was adequate to achieve a level close to the one required for treatment of arrhythmia. No significant effect was observed on heart rate and blood pressure. The number of patients was too small to determine whether magnesium was effective in preventing arrhythmia, and this was not the purpose of this investigation.

Body temperature can have an influence on neuromuscular function. Buzello *et al.* have found that hypothermic cardiopulmonary bypass induces reversible twitch depression,[21] but the central and peripheral temperature of the patients during bypass were not reported. Recently, Cammu *et al.* studied the effects of hypothermic cardiopulmonary bypass on dose requirements of cisatracurium and rocuronium.[22] They demonstrated that temperature had an important effect on the dose of cisatracurium needed to maintain adequate neuromuscular blockade. This is probably due to breakdown of cisatracurium, which is more dependent on pH and temperature compared with other NMBA.[23] In our study, central and cutaneous temperatures were recorded throughout the surgery, and were not different in the two groups. The duration of neuromuscular blockade associated with the initial bolus of cisatracurium was measured before the onset of cardiopulmonary bypass, that is before the lower body temperature could produce a significant confounding effect.

In 1954, Del Castillo *et al.* described three effects of magnesium on the neuromuscular junction: decreased release of acetylcholine at the motor nerve terminal,[9] diminished depolarizing action of acetylcholine, and depressed excitability of the muscle fibre membrane, with the first effect being the most important.[24] In 1968, Giesecke *et al.* confirmed these observations in cats and further found that magnesium sulfate potentiates the effects of succinylcholine or d-tubocurarine.[10] Others have also demonstrated an interaction between magnesium and NMBAs. Ghoneim and Long observed magnesium-treated toxemic patients and wrote that "when magnesium was combined with a subliminal blood level of d-tubocurarine, severe paralysis ensued".[15] In an attempt to speed up the onset of NMBA, magnesium has been given before pancuronium, but its effects were marginal in this setting.[16] Fuchs-Buder *et al.* showed that the onset time of vecuronium was faster in the presence of magnesium, and the duration of vecuronium induced neuromuscular blockade was almost doubled.[12,13] Administration of $MgSO_4$ after return of neuromuscular function leads to recurarization profound enough to compromise respiration. Rocuronium[17] and mivacurium[11] are also known to have longer lasting effects with concurrent administration of magnesium.

In our study, the duration of action of cisatracurium in patients not given magnesium was comparable to that reported in studies where the same dose (0.1 mg·kg^{-1}) was given. In magnesium-treated subjects, the duration of a bolus dose of cisatracurium 0.1 mg·kg^{-1} was increased by 76% (74 *vs* 42 min) and this is comparable to what would be expected with cisatracurium 0.2 mg·kg^{-1}.[24] Our finding suggests that an increased ionized-magnesium plasma concentration to 1.2 mmo·L^{-1} is associated with an increase in the sensitivity of the neuromuscular junction by a factor of approximately 2. Ionized magnesium corresponds to approximately 65–72% of total magnesium in blood.[25] Total magnesium is more often measured than ionized magnesium. An ionized whole blood magnesium of 1.2 mmol·L^{-1} corresponds to a plasma level of approximately 1.7 mmol·L^{-1} of total magnesium.

The NMBAs affect the neuromuscular function by binding to the postsynaptic receptors. An excess of acetylcholine enhances neuromuscular transmission,

and this is the mechanism involved when reversing neuromuscular blockade with neostigmine. On the other hand, magnesium, as mentioned, decreases the amount of acetylcholine released by the nerve terminals at the neuromuscular junction. Consequently, in the presence of magnesium, competition between acetylcholine and NMBA to bind postsynaptic receptors is tilted in favour of NMBA; thus, the duration of the neuromuscular blockade is enhanced.

Magnesium is known to lower systemic blood pressure by directly acting on blood vessels and by inhibiting many vasoconstrictor substances such as calcium, acetylcholine, angiotensin and epinephrine.[26–28] In our study, the magnesium sulfate bolus (70 $mg \cdot kg^{-1}$) was administered over ten minutes and we did not observe any significant decrease in systolic and diastolic blood pressure or any significant increase in heart rate compared with placebo. Therefore, we conclude that neuromuscular transmission is impaired significantly at blood magnesium levels which have virtually no hemodynamic effects.[26]

In conclusion, we observed a clinically significant increase in duration of cisatracurium induced neuromuscular blockade during cardiac surgery. We feel this finding is important because this interaction is clinically significant when magnesium is given to treat or prevent arrhythmia, systemic hypertension, low cardiac output with high systemic vascular resistance, or postoperative shivering. In these situations, recovery of neuromuscular function must be assessed more carefully when magnesium has been administered. On the other hand, giving magnesium with cisatracurium allows us to use approximately half the dose of cisatracurium to achieve and maintain the desired level of neuromuscular blockade.

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