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Magnesium Sulfate Only Slightly Reduces the Shivering Threshold in Humans

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Abstract

Background: Hypothermia may be an effective treatment for stroke or acute myocardial infarction; however, it provokes vigorous shivering, which causes potentially dangerous hemodynamic responses and prevents further hypothermia. Magnesium is an attractive antishivering agent because it is used for treatment of postoperative shivering and provides protection against ischemic injury in animal models. We tested the hypothesis that magnesium reduces the threshold (triggering core temperature) and gain of shivering without substantial sedation or muscle weakness.

Methods: We studied nine healthy male volunteers (18–40 yr) on two randomly assigned treatment days: 1) Control and 2) Magnesium (80 mg·kg⁻¹ followed by infusion at 2 g·h⁻¹). Lactated Ringer's solution (4°C) was infused *via* a central venous catheter over a period of approximately 2 hours to decrease tympanic membrane temperature ≈1.5°C·h⁻¹. A significant and persistent increase in oxygen consumption identified the threshold. The gain of shivering was determined by the slope of oxygen consumption *vs.* core temperature regression. Sedation was evaluated using verbal rating score (VRS, 0–10) and bispectral index of the EEG (BIS). Peripheral muscle strength was evaluated using dynamometry and spirometry. Data were analyzed using repeated-measures ANOVA; *P*<0.05 was statistically significant.

Results: Magnesium reduced the shivering threshold (36.3±0.4 [mean±SD] *vs.* 36.6±0.3°C, *P*=0.040). It did not affect the gain of shivering (Control: 437±289, Magnesium: 573±370

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ml·min⁻¹·°C⁻¹, $P=0.344$). The magnesium bolus did not produce significant sedation or appreciably reduce muscle strength.

Conclusions: Magnesium significantly reduced the shivering threshold; however, due to the modest absolute reduction, this finding is considered to be clinically unimportant for induction of therapeutic hypothermia.

Keywords

Magnesium; Temperature; Thermoregulation; Therapeutic hypothermia; Brain protection; Cardiac protection; Shivering

Introduction

Mild hypothermia provides substantial protection against ischemic brain¹ and myocardial injury^{2,3} in animal models. In humans, mild hypothermia improves neurologic outcome in survivors of cardiac arrest^{4,5}, and its application in that setting is now advised by the International Liaison Committee on Resuscitation (ILCOR)⁶. Similarly, the use of hypothermia in patients with ischemic heart injury is currently under evaluation⁷.

Effective thermoregulatory defences prevent the induction of mild-to-moderate hypothermia^{7,8} in unanesthetized patients⁹. Drugs known to markedly impair thermoregulation are either anaesthetics¹⁰ or major sedatives¹¹ and produce unacceptable amounts of respiratory depression. The search thus continues for drugs that sufficiently improve thermoregulatory tolerance without simultaneously producing excessive sedation or respiratory depression. In practice, this constitutes a search for drugs that reduce the shivering threshold (triggering core temperature) to a value approximating the target therapeutic core temperature^{12,13}.

Intravenous magnesium has been shown to suppress postoperative shivering,¹⁴ suggesting that the agent reduces the shivering threshold. Recently, the addition of intravenous magnesium sulfate to a pharmacological antishivering regimen increased the cooling rate in unanaesthetized volunteers¹³. The drug not only exerts a central effect¹⁵, but is also a mild muscle relaxant¹⁶ and may thus simultaneously reduce the gain of shivering (incremental shivering intensity with progressing hypothermia). Magnesium also confers substantial neurologic and cardiac protection in several animal models¹⁷⁻¹⁹.

Magnesium is thus an especially attractive candidate for inducing thermoregulatory tolerance since it may simultaneously protect against tissue ischemia. We therefore tested the hypothesis that magnesium sulphate administration reduces the threshold and gain of shivering sufficiently to permit the induction of hypothermia without causing clinically significant sedation or muscle weakness.

Methods

With approval of the Human Studies Committee at the University of Louisville and written informed consent, we studied nine healthy male volunteers. None was obese; taking medications; or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome.

Protocol

Volunteers participated on two study days; they fasted at least 8 hours before each study day. A minimum of 24 hours elapsed between the study days. On both days, the volunteers were minimally clothed and rested supine on a standard operating room table. Ambient temperature

was maintained near 21°C. On the first study day, each volunteer was randomly assigned in a double-blind manner to receive either normal saline (Control) or magnesium. The volunteers were given the alternative treatment on the subsequent study day. On the magnesium day, volunteers were given an intravenous bolus of 80 mg·kg⁻¹ magnesium sulphate that was administered by a syringe pump in a 30-min period. This was followed by an infusion of 2 g·hr⁻¹. On the control day, the volunteers received an equal volume of saline. An investigator who was not otherwise involved in the study prepared syringes containing saline or magnesium; the study was thus fully double-blinded.

A catheter was introduced into the superior vena cava *via* an antecubital vein. This catheter was used for cold-fluid infusion and blood sampling. A venous catheter was inserted in the other arm for drug administration. A circulating-water (Cincinnati Sub-Zero, Cincinnati, OH) and a forced-air (Augustine Medical, Inc., Eden Prairie, MN) blankets were placed under and on top of the volunteers body, respectively, to maintain mean-skin temperature at 31°C throughout the study. Furthermore, the back, upper body, and lower body were individually maintained at the designated value.

After a 30-min-long i.v. bolus, a drug infusion was initiated in order to maintain stable magnesium plasma levels (see Fig. 1). Sedation, thermal comfort and muscle strength were evaluated in the peri-bolus period. Ten minutes after the beginning of drug infusion, lactated Ringer's solution, cooled to ≈4°C, was infused at rates sufficient to decrease tympanic membrane temperature by ≈1.5°C·h⁻¹ (cooling phase consumption (see Data Analysis) or a total of 70 ml·kg⁻¹ was given. This is a standard and effective way of reducing core temperature as demonstrated in previous studies. Blood samples were obtained: a) at the end of the drug bolus (post-bolus), b) 10 min after the initiation of the drug infusion (pre-cooling), and c) at the shivering threshold (Fig. 1). The volunteers were asked again for their thermal comfort level when shivering threshold was detected.

Measurements

Heart rate (HR) was measured continuously using electrocardiogram; arterial pressure (BP) was determined oscillometrically at 5-minute intervals at the left ankle. A pulse oximeter continuously determined arterial oxygen saturation (SaO₂). End-tidal carbon dioxide (ETCO₂) and respiratory rate (RR) were measured using a nasal catheter connected with a capnometer device (Datex AS3 monitor, Datex-Engstrom, Ohmeda, Helsinki, Finland). Ambient temperature (°C) and relative humidity (%) were also recorded on each study day throughout the experiment. All body temperatures were obtained using Mon-a-therm thermocouples (Tyco-Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO). Core temperature was recorded from the tympanic membrane. Volunteers inserted the aural probe until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected gentle rubbing of the attached wire. The aural canal was occluded with cotton, the probe securely taped in place, and a gauze bandage positioned over the external ear. Mean skin-surface temperature was determined from 15 area-weighted sites²⁰. Temperatures were recorded from thermocouples connected to calibrated Iso-Thermex 16-channel electronic thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments International, Corp., Columbus, OH). Individual and mean-skin temperatures were computed by a data-acquisition system, displayed at 1-second intervals, and recorded at 1-minute intervals.

Arterio-venous shunt vasomotor tone was evaluated with forearm-minus-fingertip and calf-minus-toe skin-temperature gradients. There is an excellent correlation between skin temperature gradients and volume plethysmography²¹. Vasoconstriction was defined by a forearm skin-temperature gradient exceeding 0°C.

As in previous studies,^{12,22-27} we used oxygen consumption, as measured by a DeltaTrac™ (SensorMedics Corp., Yorba Linda, CA) metabolic monitor, to quantify shivering; the system was used in canopy-mode. Measurements were averaged over 1-minute intervals and recorded every minute. Oxygen consumption (VO_2) measurement started immediately after the end of the bolus infusion and lasted throughout the trial. A substantial and sustained increase in (VO_2), at least more than 25% above the baseline, identified the shivering threshold. Exhaust gases from the ETCO_2 monitor were returned to the oxygen consumption monitor.

To ascertain that the stability of the magnesium concentrations was within an acceptable clinical level throughout the trial, we obtained blood samples at: a) 10 minutes after the bolus (magnesium or saline) administration, b) just before the start of active cooling, and c) at the shivering threshold.

Sedation was evaluated using a verbal rating score for sleepiness (VRS, 0 = wide awake to 10 = asleep) and the bispectral index of the electroencephalogram (BIS). BIS data were gathered with four sensors arranged in a fronto-temporal montage after mild abrasion of the skin. Impedance of the sensors was evaluated at 15-minute intervals and kept lower than 5 k Ω . BIS values were transmitted to a data-acquisition system every 5 sec, while the smoothing window was set at 30 sec. Volunteers were advised to keep their eyes closed, especially during each recording period. Thermal comfort was also evaluated using a VRS (0 defined the worst imaginable cold, 5 as adequate thermal comfort, and 10 as the worst imaginable heat). On each study day, sedation level was evaluated before (by VRS), during (VRS and BIS) and after (VRS) bolus administration of magnesium or saline. Thermal comfort (VRS) was evaluated at three-minute intervals during bolus administration and at the shivering threshold.

During bolus administration, cardiorespiratory physiology values (HR, BP, ETCO_2 , RR, SaO_2), mean skin temperatures, and core temperature were also evaluated every 3 minutes. At the same times, laser Doppler flowmetry²⁸ was used to detect changes in the skin blood flow associated with vasodilation. A laser detector was placed on the chest. Increase in values from baseline of laser Doppler flowmetry indicated increasing blood flow.

Muscle strength was evaluated in the right upper and left lower extremities using a hand-held dynamometer (*MICROFET2*, Hoggan Health Industries, Inc, Drapper, UT). This is a simple hand-held device with a small internal load cell capable of measuring muscular force. It is applied to the subject's limb; the subject generates force in an attempt to move the hand-held dynamometer that is held firmly in place by the test administrator²⁹. The peak force generated after each test is recorded and digitally displayed in pounds (lbs). The average of three measurements taken before and after bolus administration was used for further analysis. At the same time as an additional index of peripheral muscle strength, forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1) were measured using a hand-held spirometer (MicroPlus, Micro Medical Limited, Inc., Rochester, England).

Data Analysis

Threshold differences of less than 0.5°C are of questionable clinical importance. Previous similar studies in volunteers indicate that the standard deviation of shivering threshold measurements is 0.4°C. Nine volunteers were thus required to provide a 90% power to detect a difference of 0.5°C in the shivering threshold with a crossover design using a paired *t*-test with an alpha level of 0.05. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test shivering threshold data for normality.

A substantial and sustained increase in oxygen consumption identified the shivering threshold. The baseline for this analysis was the steady-state value after the bolus administration but before core cooling had started. Maximum intensity of shivering was identified by an oxygen

consumption, which failed to increase further despite continued reduction in core temperature. The gain of shivering was determined by the slope of oxygen consumption vs. core temperature regression. Data from the threshold till the maximum intensity of shivering were used for gain calculation. Paired *t*-test was used to compare values between the two treatments.

On each study day hemodynamic and respiratory responses, as well as ambient temperature and relative humidity, were averaged within each volunteer; these values were then averaged across volunteers. The 30-minute bolus administration and cooling periods were treated separately.

Interaction between the time (baseline, post-bolus) and the drug (magnesium, saline) administered was evaluated using two-factor analysis of variance (ANOVA). Results of repeated measures during the bolus administration on the two study days were compared using repeated measures ANOVA. To confirm magnesium concentrations were stable, plasma concentrations at the different time-points were compared between the two treatments (magnesium, saline) using two-factor ANOVA (interaction of time with treatment). Results are expressed as means \pm SDs; $P < 0.05$ was considered statistically significant.

Results

The study subjects were 27 ± 4 years old, weighted 88 ± 14 kg, and were 176 ± 8 cm tall. The data from all nine volunteers was used for the threshold calculation. Technical difficulties with data acquisition prevented the collection of oxygen consumption values in one volunteer after the shivering threshold. Consequently, the gain analysis was based on results from the remaining eight volunteers.

Two-factor ANOVA showed that magnesium serum concentration on both study days was maintained essentially stable over time, from the post-bolus time-point till the shivering threshold ($P = 0.619$, Table 1).

Sedation increased slightly, but significantly, over time from baseline to post-bolus; however, the increase was similar on the control and magnesium treatments. Functional vital capacity (FVC) also decreased slightly, but significantly, over time; but again, the reduction was similar on the control and magnesium treatments (Table 2). During the bolus infusion, magnesium increased thermal comfort score and heart rate (Table 3). These changes were not associated with any objective signs of vasodilation and dissipated by the end of the bolus infusion.

Mean skin temperature was maintained near 31°C on each study day throughout the cooling period. All the volunteers were vasoconstricted before the cold fluid infusion started. Vasoconstriction was determined with the forearm to finger temperature gradient. A negative gradient implied vasoconstriction. Serum concentrations of magnesium remained constant throughout the cooling period for both the control and magnesium treatments, but were more than doubled on the magnesium day. Cardiovascular and respiratory physiology was similar with each treatment. The elapsed time from the initiation of the bolus infusion till the shivering threshold (bolus-to-shivering interval) was the same between the two treatments (Table 4).

Kolmogorov-Smirnov ($P = 0.150$) and Shapiro-Wilk ($P = 0.684$) tests showed a normal distribution for the shivering threshold data. Magnesium reduced the shivering threshold by $0.3\pm 0.4^{\circ}\text{C}$ (paired *t*-test, $P = 0.040$) (Fig. 2). The gain of shivering response was 437 ± 289 $\text{ml}\cdot\text{min}^{-1}\cdot^{\circ}\text{C}^{-1}$ for the control and 573 ± 370 $\text{ml}\cdot\text{min}^{-1}\cdot^{\circ}\text{C}^{-1}$ for the magnesium treatment, ($P = 0.344$, Table 4).

Discussion

Magnesium is a naturally occurring calcium antagonist and a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors³⁰. The exact protective mechanism of magnesium remains uncertain, but it probably acts on multiple levels of the ischemic cascade such as cerebral blood flow³¹, excitotoxicity³², energy conservation^{33,34}, and vascular homeostasis³⁵. The cardio-protective effect of magnesium after experimental myocardial infarction is most likely caused by its ability to enhance adenosine production¹⁹, its anti-thrombotic effect¹⁸, or both. Because magnesium is safe, inexpensive, and readily available, many clinicians favour its use for various ischaemic insults – despite the lack of any clear benefit of magnesium on the mortality and morbidity outcomes after stroke³⁶ or acute myocardial infarction³⁷⁻³⁹. Magnesium provides excellent neuro- and cardio-protection in various experimental models of ischaemia and has been shown to be an effective treatment for postoperative shivering. It was thus an attractive potential agent for facilitating induction of therapeutic hypothermia. However, magnesium at a dose sufficient to raise plasma concentration more than twofold only slightly restrained thermoregulatory defences to hypothermia. Compared with those treated with placebo, the shivering threshold in volunteers given magnesium decreased by only 0.3 °C, to a core temperature of 36.3°C.

There is currently little evidence that hypothermia protects against ischaemia in humans, although the evidence is overwhelming in animals. There is certainly little basis for recommending a specific target temperature for therapeutic hypothermia. Nonetheless, target temperatures from 33 to 34°C are being used clinically by some physicians and in ongoing clinical trials. Because magnesium reduces the shivering threshold only about a tenth of the amount necessary, it seems unlikely that magnesium has the potential to facilitate induction of therapeutic hypothermia, at least as a lone agent.

Magnesium seemed likely to induce thermoregulation tolerance because is an effective treatment for postoperative shivering¹⁴. That then raises the question of how magnesium can be an effective treatment for postoperative shivering, yet reduce the shivering threshold by only a few tenths of a °C. The answer is that many postoperative patients have core temperatures only slightly below the normal shivering threshold. This may be the case even when core temperature is relatively low because residual anaesthetics impair thermoregulatory control. Consequently, treatments that reduce the shivering threshold by a couple of tenths of a degree centigrade may be sufficient to attenuate postoperative shivering⁴⁰. Such treatments will nonetheless be inadequate for induction of therapeutic hypothermia.

Recently, the addition of magnesium sulfate in a meperidine-based pharmacological antishivering regimen increased the cooling rate in unaesthetized volunteers¹³. This effect was attributed to the observed vasodilation in the majority of the volunteers and associated with increased thermal comfort. In our study, increased thermal comfort during magnesium bolus was not related to peripheral vasodilation in our subjects, as determined by extremity temperature gradients. It seems that, despite the modest effect of magnesium on the shivering threshold, this agent could potentially play a contributing role for induction of therapeutic hypothermia.

Magnesium sulfate, as used clinically, increases cerebrospinal fluid (CSF) magnesium concentrations by only about 20-25%, with a peak concentration reached after two-to-four hours depending on the concentration gradient between plasma and CSF⁴¹. We used an intravenous infusion of magnesium as proposed by Sibai, *et al.*⁴² for seizure prophylaxis in preeclamptic women. Relatively high plasma concentrations were achieved immediately after the bolus administration; these were maintained until the shivering threshold was reached about two hours after magnesium bolus initiation, thus ensuring adequate CSF levels. Because of

this, we were unable to determine whether the observed thermoregulatory action of magnesium was of central¹⁵ or peripheral origin¹⁶.

Despite the known central¹⁵ and peripheral muscle relaxation¹⁶ effects of magnesium, we were unable to demonstrate any significant changes in the sedation level or muscle strength during the bolus administration. It is likely that larger doses of magnesium sulfate would produce both greater thermoregulatory effects and a greater risk of complications. Nonetheless, previous studies indicate that the thermoregulatory response to most intravenous drugs is a linear function of plasma concentration^{43,44}. Thus, an even larger, potentially hazardous dose of magnesium seems unlikely to produce a useful reduction in the shivering threshold.

A limitation of our study is that it was conducted in healthy volunteers. Most results from volunteer studies can be extrapolated to patients; however, patients with underlying disease and those who are critically ill may respond differently. It thus remains possible that magnesium will prove more effective at inducing thermoregulatory tolerance in patients with stroke or other serious neurological problems.

In summary, magnesium in doses sufficient to increase plasma concentrations more than twofold reduced the shivering threshold marginally and did not significantly alter the gain of shivering in healthy volunteers. Magnesium thus exerts a clinically unimportant effect, as a sole agent; however, it remains to be studied as a potentially useful adjunct for induction of therapeutic hypothermia in patients with stroke or myocardial ischemia.

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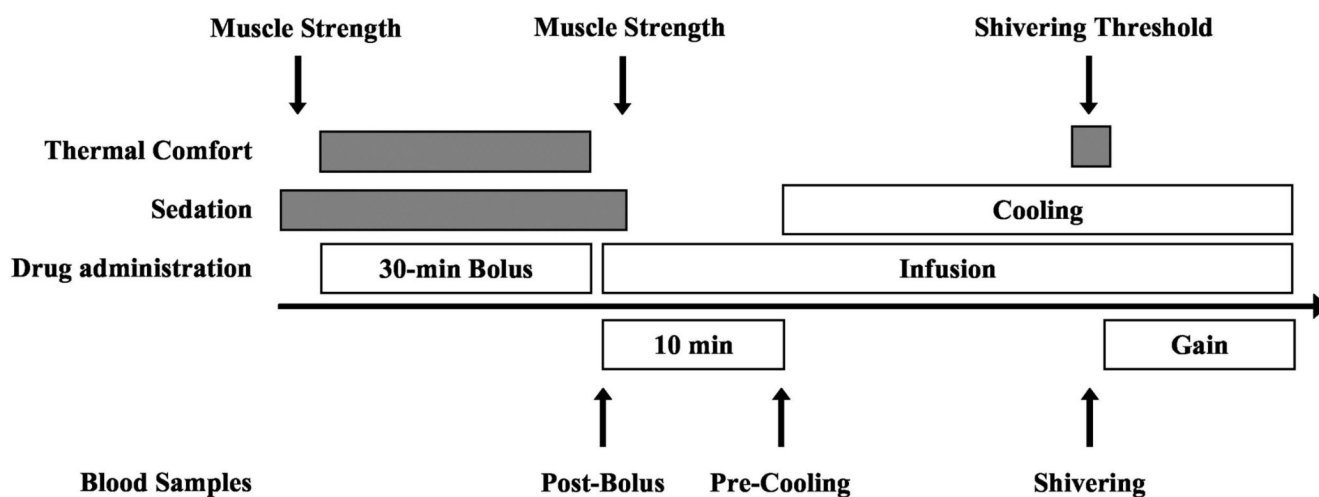


Fig. 1.

Flow diagram of the trial. The various protocol interventions are indicated by arrows (evaluation of muscle strength, drawing of blood samples) and bars (evaluation of thermal comfort and sedation, cooling phase), in relation to the drug administration. The occurrence of shivering threshold is also indicated by an arrow, while the data collected beyond that point were used for the gain of shivering calculation.

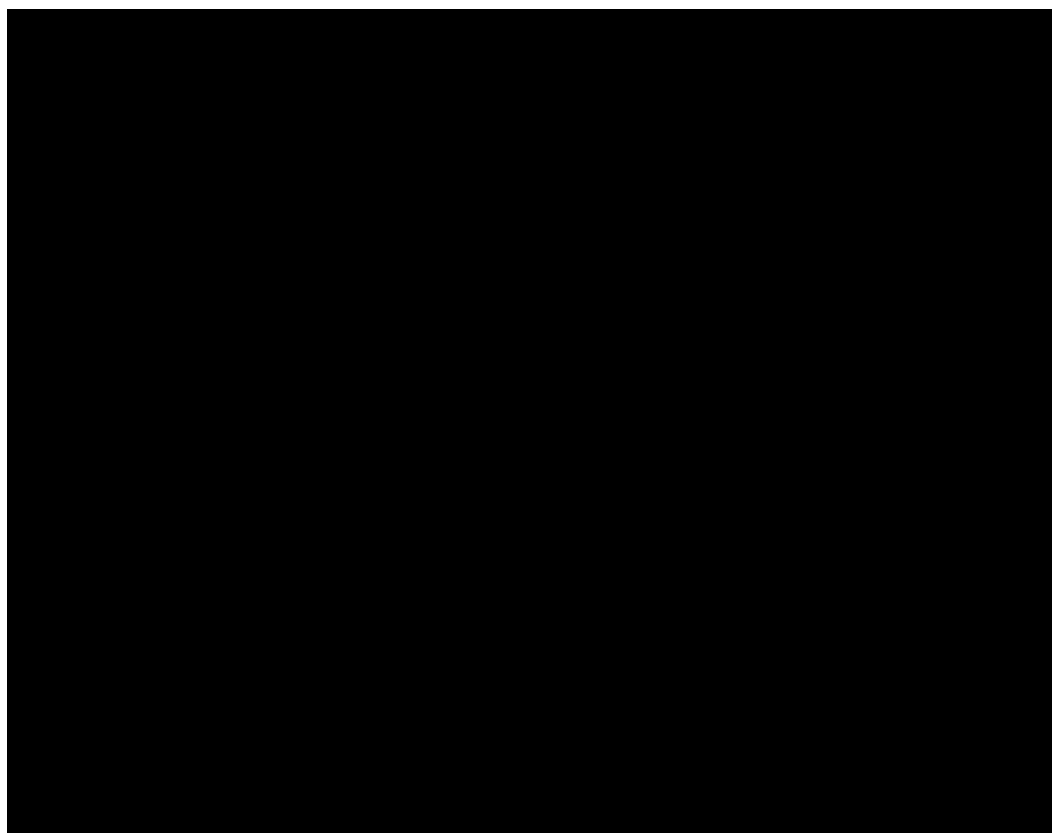


Fig. 2. The shivering threshold for the Control and Magnesium treatments. Open circles represent individual volunteers. Filled squares show the group means (\pm SDs) on the two treatment days. The shivering threshold was reduced by 0.31°C on the magnesium-treatment day (* $P = 0.04$).

Table 1.
Serum Magnesium Concentrations during the Trial

	Post-Bolus	Serum [Magnesium] (mmol·L ⁻¹) Pre-Cooling	Shivering	Time	P Treatment
Control	0.86 ± 0.08	0.86 ± 0.04	0.86 ± 0.04	0.619	0.0001
Magnesium	1.89 ± 0.25	2.01 ± 0.21	2.21 ± 0.33		

Values are presented as means ± SDs. Interaction of time (post-bolus, pre-cooling, shivering) with treatment (control, magnesium) was evaluated using two-factor ANOVA. This analysis confirms that magnesium levels were stable.

Table 2.
Sedation and Muscle Strength before and after Bolus Administration.

	Control		Magnesium		Time	P Treatment
	Baseline	Post-Bolus	Baseline	Post-Bolus		
Sedation Level (VRS)	1 ± 1	1 ± 1	1 ± 1	5 ± 2	0.010	0.366
Muscle Strength in right arm (lbs)	39 ± 7	43 ± 14	40 ± 10	36 ± 16	0.963	0.447
Muscle Strength in left leg (lbs)	41 ± 11	42 ± 9	46 ± 8	44 ± 12	0.888	0.386
FVC (L)	4.0 ± 1.0	3.5 ± 0.7	3.8 ± 0.7	3.5 ± 0.8	0.011	0.515
FEV ₁ (L)	3.5 ± 0.7	3.4 ± 1.1	3.7 ± 0.7	3.3 ± 0.8	0.298	0.224

Values before and after the 30-minute bolus infusion presented as means ± SDs. Interaction of time (baseline, post-bolus) with treatment (control, magnesium) was evaluated using two-factor ANOVA. Muscle strength was measured with a handheld dynamometer. Forced respiratory volumes were measured using a handheld spirometer. VRS = verbal rating score for sleepiness; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second.

Table 3.
Results during the Bolus Magnesium Administration.

	Control	Magnesium	P
Core temperature (°C)	36.8 ± 0.3	36.6 ± 0.2	0.379
Mean Skin temperature (°C)	33.6 ± 1.3	33.2 ± 0.7	0.618
Arm Gradient (°C)	1.4 ± 2.9	0.7 ± 2.9	0.603
Mean Arterial Pressure (mmHg)	98 ± 6	99 ± 10	0.973
Heart Rate (bpm)	69 ± 9	76 ± 10	0.030
SaO ₂ (%)	99 ± 1	98 ± 3	0.318
Respiratory Rate (breaths per min)	19 ± 4	17 ± 2	0.130
End-Tidal CO ₂ (mmHg)	40 ± 5	42 ± 3	0.615
Thermal Comfort (VRS)	5 ± 1	7 ± 1	0.019
Sedation (VRS)	5 ± 3	5 ± 2	0.528
Bispectral Index	90 ± 9	93 ± 9	0.347
Laser Flowmetry	21 ± 16	11 ± 8	0.136

Results obtained at 3-minute intervals were first averaged within each volunteer across the 30-minute-long bolus administration period and then averaged among the volunteers for each drug treatment. Repeated-measures ANOVA over time was used to compare the two treatments for the presented outcomes. VRS = verbal rating score.

Table 4.
Major Outcomes and Confounding Factors during the Cooling Period.

	Control	Magnesium	P
Ambient Temperature (°C)	23.5 ± 1.4	23.0 ± 1.6	0.444
Relative Humidity (%)	27 ± 6	30 ± 5	0.462
Arm Gradient at Cooling (°C)	4.5 ± 3.1	4.1 ± 1.6	0.295
Bolus - to - Shivering Interval (min)	136 ± 40	115 ± 26	0.266
Mean Arterial Pressure (mmHg)	106 ± 10	113 ± 11	0.001
Heart Rate (bpm)	70 ± 11	71 ± 9	0.44
SaO ₂ (%)	98 ± 2	96 ± 3	0.003
Respiratory Rate (breaths per min)	17 ± 5	17 ± 4	0.653
End-Tidal CO ₂ (mmHg)	39 ± 5	41 ± 3	0.010
Serum [magnesium] (mmol·L ⁻¹)	0.83 ± 0.06	2.22 ± 0.35	0.0001
Total Lactated Ringer's (L)	3.2 ± 2.4	2.9 ± 1.1	0.715
Cooling rate (°C·hr ⁻¹)	1.2 ± 0.3	1.1 ± 0.4	0.501
Thermal Comfort (VRS)	2 ± 2	1 ± 1	0.545
Mean Skin Temperature (°C)	31.0 ± 0.3	31.0 ± 0.2	0.983
Core Temperature (°C)	36.6 ± 0.3	36.3 ± 0.4	0.040
Gain of Shivering (ml·min ⁻¹ ·°C ⁻¹)	437 ± 289	573 ± 370	0.344

Values above the line were first averaged over the cooling period and then averaged among the volunteers; values below the line are at the shivering threshold. "Bolus-to-shivering interval" indicates the time elapsed between the initiation of the drug bolus infusion and the shivering threshold. Data are presented as means ± SDs. VRS = verbal rating score.