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# Magnesium sulphate only slightly reduces the shivering threshold in humans†

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**Background.** Hypothermia may be an effective treatment for stroke or acute myocardial infarction; however, it provokes vigorous shivering, which causes potentially dangerous haemodynamic responses and prevents further hypothermia. Magnesium is an attractive anti-shivering agent because it is used for treatment of postoperative shivering and provides protection against ischaemic 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 h to decrease tympanic membrane temperature by ~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 a verbal rating score (VRS) from 0 to 10 and bispectral index (BIS) of the EEG. Peripheral muscle strength was evaluated using dynamometry and spirometry. Data were analysed using repeated measures ANOVA; $P<0.05$ was statistically significant.

**Results.** Magnesium reduced the shivering threshold (36.3 [SD 0.4] °C *vs* 36.6 [0.3] °C, $P = 0.040$). It did not affect the gain of shivering (control, 437 [289] ml $min^{-1}$ $°C^{-1}$; magnesium, 573 [370] 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, in view of the modest absolute reduction, this finding is considered to be clinically unimportant for induction of therapeutic hypothermia.

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Mild hypothermia provides substantial protection against ischaemic brain[1] and myocardial injury[2 3] in animal models. In humans, mild hypothermia improves neurological 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 ischaemic heart injury is currently under evaluation.[7]

Effective thermoregulatory defences prevent the induction of mild to moderate hypothermia[7 8] in unanaesthetized patients.[9] Drugs known to markedly impair thermoregulation are either anaesthetics[10] or major sedatives,[11] and they produce unacceptable amounts of respiratory depression. Thus the search continues for drugs which sufficiently improve thermoregulatory tolerance without simultaneously producing excessive sedation or respiratory depression. In practice, this constitutes a search for drugs which 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 this agent reduces the

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shivering threshold. Recently, the addition of intravenous magnesium sulphate to a pharmacological anti-shivering regimen increased the cooling rate in unanaesthetized volunteers.[13] The drug not only exerts a central effect,[15] but is also a mild muscle relaxant[16] and thus may simultaneously reduce the gain of shivering (incremental shivering intensity with progressing hypothermia). Magnesium also confers substantial neurological and cardiac protection in several animal models.[17–19]

Thus magnesium is an especially attractive candidate for inducing thermoregulatory tolerance since it may simultaneously protect against tissue ischaemia. Therefore we 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 the 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, and they fasted for at least 8 h before each study day. A minimum of 24 h 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 i.v. bolus of magnesium sulphate 80 mg $kg^{-1}$ administered by a syringe pump over a 30-min period. This was followed by an infusion of 2 g $h^{-1}$. 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; thus the study was 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 blanket (Cincinnati Sub-Zero, Cincinnati, OH) and a forced-air blanket (Augustine Medical Inc., Eden Prairie, MN) were placed under and on top of the volunteers, 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 i.v. bolus, drug infusion was initiated in order to maintain stable magnesium plasma levels (Fig. 1). Sedation, thermal comfort, and muscle strength were evaluated in the peribolus period. Ten minutes after the beginning of drug infusion, lactated Ringer's solution, cooled to ~4°C, was infused at rates sufficient to decrease the tympanic membrane temperature by ~1.5°C $h^{-1}$ (cooling phase). Fluid was infused until further reduction in core temperature no longer increased oxygen consumption (see section on data analysis) or a total of 70 ml $kg^{-1}$ had been given. This is a standard and effective way of reducing core temperature as demonstrated in previous studies. Blood samples were obtained at the end of the drug bolus (post-bolus), 10 min after the initiation of the drug infusion (precooling) and at the shivering threshold (Fig. 1). The volunteers were asked again about their thermal comfort level when the shivering threshold was detected.

### *Measurements*

Heart rate (HR) was measured continuously using an ECG; arterial pressure (MAP) was determined oscillometrically at 5-min intervals at the left ankle. A pulse oximeter continuously determined arterial oxygen saturation ($Sa_{O_2}$). End-tidal

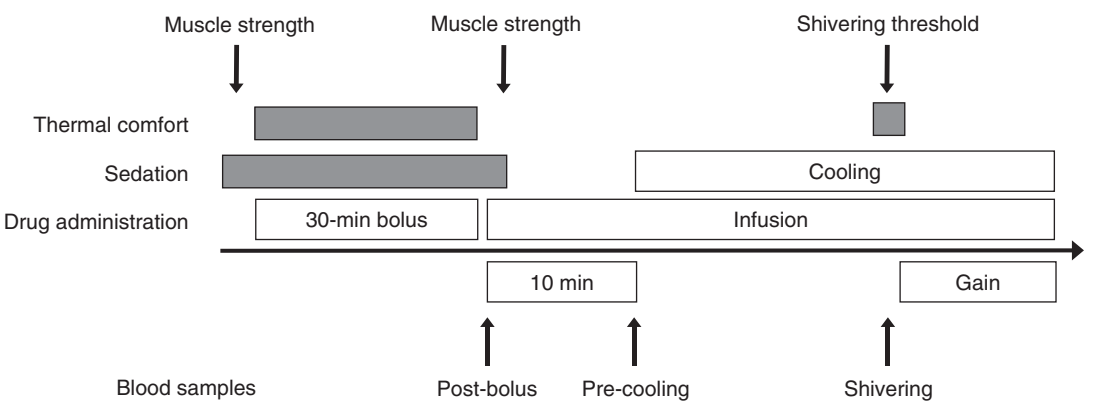


**Fig 1** Flow diagram of the trial. The various protocol interventions are indicated by arrows (evaluation of muscle strength, drawing of blood samples) and bars (evaluation of thermal comfort and sedation, cooling phase), in relation to the drug administration. The occurrence of the shivering threshold is also indicated by an arrow; the data collected beyond that point were used for the gain of shivering calculation.

carbon dioxide ($E'_{CO_2}$) and respiratory rate (RR) were measured using a nasal catheter connected to a capnometer device (Datex AS3 monitor, Datex-Engstrom, Ohmeda, Helsinki, Finland). Ambient temperature (°C) and relative humidity (%) were also recorded throughout the experiment on each study day.

All body temperatures were measured 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 was securely taped in place and a gauze bandage was positioned over the external ear. Mean skin surface temperature was determined from 15 area-weighted sites.[20] Temperatures were recorded from thermocouples connected to calibrated Iso-Thermex 16-channel electronic thermometers which had an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments International Corporation, Columbus, OH). Individual and mean skin temperatures were computed by a data acquisition system, displayed at 1-s intervals and recorded at 1-min intervals.

Arteriovenous shunt vasomotor tone was evaluated from forearm–fingertip and calf–toe skin temperature gradients. There is an excellent correlation between skin temperature gradients and volume plethysmography.[21] Vasoconstriction was defined by a forearm skin temperature gradient >0°C.

As in previous studies,[12 22–27] we used oxygen consumption, as measured by a DeltaTrac™ (SensorMedics Corporation, Yorba Linda, CA) metabolic monitor, to quantify shivering; the system was used in canopy mode. Measurements were averaged over 1-min intervals and recorded every minute. Oxygen consumption ($V_{O_2}$) measurement started immediately after the end of the bolus infusion and lasted throughout the trial. A substantial and sustained increase in $V_{O_2}$, ⩾25% above the baseline, identified the shivering threshold. Exhaust gases from the $E'_{CO_2}$ 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 10 min after the bolus (magnesium or saline) administration, just before the start of active cooling and at the shivering threshold.

Sedation was evaluated using a verbal rating score (VRS) for sleepiness (0=wide awake to 10=asleep) and the bispectral index (BIS) of the electroencephalogram. BIS data were collected using four sensors arranged in a frontotemporal montage after mild abrasion of the skin. Impedance of the sensors was evaluated at 15-min intervals and kept <5 kΩ. BIS values were transmitted to a data acquisition system every 5 s, and the smoothing window was set at 30 s. Volunteers were advised to keep their eyes closed, especially during the recording period.

Thermal comfort was also evaluated using a VRS (0=worst imaginable cold, 5=adequate thermal comfort, 10=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 3-min intervals during bolus administration and at the shivering threshold.

During bolus administration, cardiorespiratory physiology values (HR, MAP, $E'_{CO_2}$, RR, $Sa_{O_2}$), mean skin temperatures and core temperature were also evaluated every 3 min. At the same times, laser Doppler flowmetry[28] was used to detect changes in the skin blood flow associated with vasodilation. A laser detector was placed on the chest and an increase in values from the 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 and the subject generates force in an attempt to move the hand-held dynamometer that is held firmly in place by the test administrator.[29] The peak force generated after each test is recorded and digitally displayed in pounds (lb). 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 s ($FEV_1$) were measured using a hand-held spirometer (MicroPlus, Micro Medical Ltd, Rochester, UK).

### *Data analysis*

Threshold differences <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. Thus nine volunteers were required to provide a 90% power to detect a difference of 0.5°C in the shivering threshold with a cross-over design using a paired *t*-test with an α 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 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 until the maximum intensity of shivering were used for gain calculation. The paired *t*-test was used to compare values between the two treatments.

On each study day haemodynamic 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-min 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 mean (SD); $P<0.05$ was considered statistically significant.

## Results

The study subjects were aged 27 (18–40) yr, weighed 88 (14) kg and were 176 (8) cm tall. The data from all nine volunteers were 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 until 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. FVC also decreased slightly, but significantly, over time; 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 until the shivering threshold (bolus–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 (0.4) °C (paired $t$-test; $P=0.040$) (Fig. 2). The gain of the shivering response was 437 (289) ml $min^{-1}$ $°C^{-1}$ for the control and 573 (370) ml $min^{-1}$ $°C^{-1}$ for the magnesium treatment ($P=0.344$) (Table 4).

## Discussion

Magnesium is a naturally occurring calcium antagonist and a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors.[30] The exact protective mechanism

**Table 1** Serum magnesium concentrations during the trial. Data are presented as mean (SD). Interaction of time (post-bolus, precooling, shivering) with treatment (control, magnesium) was evaluated using two-factor ANOVA. This analysis confirms that magnesium levels were stable

| | Serum [magnesium] (mmol $litre^{-1}$) | | | *P*-value | |
|---|---|---|---|---|---|
| | Post-bolus | Precooling | Shivering | Time | 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) | | |

**Table 2** Sedation and muscle strength before and after bolus administration. Values before and after the 30-min bolus infusion are presented as mean (SD). Interaction of time (baseline, post-bolus) with treatment (control, magnesium) was evaluated using two-factor ANOVA. Muscle strength was measured using a hand-held dynamometer. Forced respiratory volumes were measured using a hand-held spirometer. VRS, verbal rating score for sleepiness; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 s

| | Control | | Magnesium | | *P*-value | |
|---|---|---|---|---|---|---|
| | Baseline | Post-bolus | Baseline | Post-bolus | Time | Treatment |
| Sedation level (VRS) | 1 (1) | 1 (1) | 1 (1) | 5 (2) | 0.010 | 0.366 |
| Muscle strength in right arm (lb) | 39 (7) | 43 (14) | 40 (10) | 36 (16) | 0.963 | 0.447 |
| Muscle strength in left leg (lb) | 41 (11) | 42 (9) | 46 (8) | 44 (12) | 0.888 | 0.386 |
| FVC (litre) | 4.0 (1.0) | 3.5 (0.7) | 3.8 (0.7) | 3.5 (0.8) | 0.011 | 0.515 |
| $FEV_1$ (litre) | 3.5 (0.7) | 3.4 (1.1) | 3.7 (0.7) | 3.3 (0.8) | 0.298 | 0.224 |

**Table 3** Results obtained during the bolus magnesium administration. Results obtained at 3-min intervals were first averaged within each volunteer across the 30-min 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

| | Control | Magnesium | *P*-value |
|---|---|---|---|
| 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 (mm Hg) | 98 (6) | 99 (10) | 0.973 |
| Heart rate (beats $min^{-1}$) | 69 (9) | 76 (10) | 0.030 |
| $Sa_{O_2}$ (%) | 99 (1) | 98 (3) | 0.318 |
| Ventilatory frequency (bpm) | 19 (4) | 17 (2) | 0.130 |
| End-tidal $CO_2$ (mm Hg) | 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 |

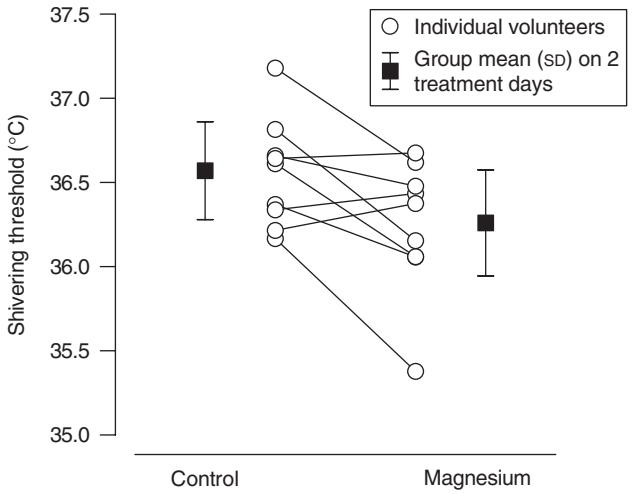


**Fig 2** The shivering threshold for the control and magnesium treatments. The shivering threshold was reduced by 0.31°C on the magnesium treatment day. ($P$=0.04.)

**Table 4** Major outcomes and confounding factors during the cooling period. Values above the line space were first averaged over the cooling period and then averaged among the volunteers; values below the line space are at the shivering threshold. *Time elapsed between the initiation of the drug bolus infusion and the shivering threshold. Data are presented as mean (SD). VRS, verbal rating score

| | Control | Magnesium | *P*-value |
|---|---|---|---|
| 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–shivering interval* (min) | 136 (40) | 115 (26) | 0.266 |
| Mean arterial pressure (mm Hg) | 106 (10) | 113 (11) | <0.001 |
| Heart rate (beats $min^{-1}$) | 70 (11) | 71 (9) | 0.44 |
| $Sa_{O_2}$ (%) | 98 (2) | 96 (3) | 0.003 |
| Ventilatory frequency (bpm) | 17 (5) | 17 (4) | 0.653 |
| End-tidal $CO_2$ (mm Hg) | 39 (5) | 41 (3) | 0.010 |
| Serum [Mg] (mmol $litre^{-1}$) | 0.83 (0.06) | 2.22 (0.35) | <0.0001 |
| Total lactated Ringer's solution (litre) | 3.2 (2.4) | 2.9 (1.1) | 0.715 |
| Cooling rate (°C $h^{-1}$) | 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 |

of magnesium remains uncertain, but it probably acts on multiple levels of the ischaemic cascade such as cerebral blood flow,[31] excitotoxicity,[32] energy conservation[33 34] and vascular homeostasis.[35] The cardioprotective effect of magnesium after experimental myocardial infarction is most likely caused by its ability to enhance adenosine production[19] or its antithrombotic effect[18] 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 stroke[36] or acute myocardial infarction.[37–39] Magnesium provides excellent neuro- and cardioprotection in various experimental models of ischaemia and has been shown to be an effective treatment for postoperative shivering. Thus it was an attractive potential agent for facilitating induction of therapeutic hypothermia. However, magnesium at a dose sufficient to raise plasma concentration more than 2-fold 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.

Currently, there is 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 it is an effective treatment for postoperative shivering.[14] That raises the question of how magnesium can be an effective treatment for postoperative shivering, and yet reduce the shivering threshold by only a few tenths of a degree Celsius. 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 few tenths of a degree Celsius may be sufficient to attenuate postoperative shivering.[40] However, such treatments will be inadequate for induction of therapeutic hypothermia.

Recently, the addition of magnesium sulphate to a meperidine-based pharmacological anti-shivering regimen increased the cooling rate in unaesthetized volunteers.[13] 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 contributory role in the induction of therapeutic hypothermia.

Magnesium sulphate, as used clinically, increases cerebrospinal fluid (CSF) magnesium concentrations by only about 20–25%, with a peak concentration reached after 2–4 h depending on the concentration gradient between plasma and CSF.[41] We used an intravenous infusion of magnesium as proposed by Sibai and colleagues[42] for seizure prophylaxis in pre-eclamptic women. Relatively high plasma concentrations were achieved immediately after the bolus administration; these were maintained until the shivering threshold was reached about 2 h 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 central[15] or peripheral origin.[16]

Despite the known central[15] and peripheral muscle relaxation[16] 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 sulphate 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. Thus it 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 2-fold reduced the shivering threshold marginally and did not significantly alter the gain of shivering in healthy volunteers. Thus magnesium 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 ischaemia.

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