Magnesium Sulfate Increases the Rate of Hypothermia Via Surface Cooling and Improves Comfort

Richard M. Zweifler, MD; Marc E. Voorhees, PhD; M. Asim Mahmood, MD; Mel Parnell, RN, BSN

Background and Purpose—Therapeutic hypothermia shows promise as a treatment for acute stroke. Surface cooling techniques are being developed but, although noninvasive, they typically achieve slower cooling rates than endovascular methods. We assessed the hypothesis that the addition of intravenous MgSO₄ to an antishivering pharmacological regimen increases the cooling rate when using a surface cooling technique.

Methods—Twenty-two healthy volunteers were studied. Hypothermia was induced using a surface technique with a target tympanic temperature (Tycling) of 34.5°C (target range 34 to 35°C). Subjects received 1 of the following pharmacological regimens: (1) meperidine monotherapy (n=5); (2) meperidine plus buspirone, 30 to 60 mg PO administered at the time of initiation of cooling (n=4); (3) meperidine and ondansetron, 8 to 16 mg IV administered as an 8 mg bolus at the time of initiation of cooling with an optional second dose after 4 hours as needed for nausea (n=5); or (4) meperidine, ondansetron, and MgSO₄, 4 to 6 g IV bolus followed by 1 to 3 g per hour infusion (n=8). Thermal comfort was evaluated with a 100-mm-long visual analog scale.

Results—More subjects who received MgSO₄ were vasodilated during hypothermia induction (7 of 8 [88%] versus 4 of 14 [29%]; P=0.0244). MgSO₄ (coefficient -17.265; P=0.039), weight (1.838, 0.001), and the initial 2-hour meperidine dose (0.726, 0.003) were found to significantly impact the time to achieve Ttym of 35°C. Subjects who received MgSO₄ had significantly higher mean comfort scores than those who did not (48.1 ± 15 versus 38.1 ± 12; P<0.001).

Conclusions—Administration of intravenous MgSO₄ increases the cooling rate and comfort when using a surface cooling technique. (Stroke. 2004;35:2331-2334.)

Key Words: hypothermia ■ magnesium sulfate ■ neuroprotection ■ stroke

Therapeutic hypothermia has been proven effective after cardiac arrest¹,² and shows promise as a treatment for acute stroke.³,⁴ Surface cooling techniques are being developed but, although noninvasive, they typically achieve slower cooling rates than endovascular methods.⁵-⁷ MgSO₄ has antishivering effects⁸,⁹ and may enhance the cooling rate because of its vasodilatory properties. Furthermore, MgSO₄ has potential neuroprotective effects,¹⁰,¹¹ and experimental data suggest the neuroprotective effect of hypothermia can be increased with combination therapy that includes MgSO₄.¹² We assessed the hypothesis that the addition of intravenous MgSO₄ to an antishivering pharmacological regimen will increase the cooling rate when using a surface cooling technique (Arctic Sun Temperature Management System).

Materials and Methods

After approval from the institutional review board at the University of South Alabama, healthy volunteers were recruited, and written informed consent was obtained. Exclusion criteria included any of the following: history of cryoglobulinemia, paramyotonia congenita, recent myocardial ischemia, pregnancy, or recent use of phenothiazines, monoamine oxidase inhibitors, alcohol, or narcotics. Females of childbearing potential were screened with a urine pregnancy test.

All subjects underwent cardiac and neurologic examinations and 12-lead electrocardiography before initiation of cooling.

Five Arctic Sun Energy Transfer Pads (Medivance, Inc) were applied to the thighs and chest and either connected to an Arctic Sun model 200 temperature control module with interfacing recirculating chiller (Kodiak RC011G02BG1; Lytron; n=9) or to an Arctic Sun model 2000 with integrated chiller (n=13). Both models used the same algorithm to control pad water temperature. Core temperatures were measured continuously at the tympanic membrane and rectum. After otoscopic confirmation that the ear canal was free of wax, the tympanic probe was inserted slowly until the subject felt the thermocouple touching the tympanic membrane; appropriate placement was confirmed when subjects easily detected gentle rubbing of the attached wire. The probe was then taped securely in place, the ear canal occluded with cotton, and the external ear covered with a gauze bandage. Rectal probes (YSI 400 compatible) were inserted 15 cm and taped securely to the buttocks. Thermoregulatory vasodilation was evaluated using forearm minus fingertip skin-temperature gradients.¹³ A positive gradient was defined as representing vasodilation.¹⁴,¹⁵ Nonrectal temperatures were measured using Mon-a-Therm thermocouple probes connected to Mallinckrodt model 6510 2-channel electronic thermometers having accuracy near 0.1°C (Mallinckrodt Anesthesia Products). Rectal temperatures were measured with probes connected to the Arctic Sun equipment. Temperatures were recorded before cooling was started (ie, baseline) and subsequently at 15-minute intervals. Up to 3 baseline measurements recorded at 5-minute intervals were obtained.

Received April 8, 2004; final revision received June 5, 2004; accepted July 7, 2004.

From the University of South Alabama Stroke Center (R.M.Z., M.A.M., M.P.), Mobile, Ala; and Medivance, Inc. (M.E.V.), Louisville, Colo.

Dr Zweifler serves as a consultant to Medivance, Inc., and Dr Voorhees is an employee of Medivance, Inc.

Correspondence to Dr Richard M. Zweifler, USA Stroke Center, 2451 Fillingim St, Mobile, AL 36617. E-mail rzweifle@usouthal.edu

© 2004 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000141161.63181.fl
A single oral dose of 1000 mg of acetaminophen was administered within 20 minutes before treatment, and a bolus of intravenous meperidine (50 to 100 mg) was given within 5 minutes of the start of cooling. Additional meperidine (25 to 50 mg IV bolus) was administered as needed for shivering. Subjects received 1 of the following pharmacological regimens: (1) meperidine monotherapy (n=5); (2) meperidine plus buspirone, 30 to 60 mg PO administered at the time of initiation of cooling (n=4); (3) meperidine and ondansetron, 8 to 16 mg IV administered as an 8-mg bolus at the time of initiation of cooling with an optional second dose after 4 hours as needed for nausea (n=5); or (4) meperidine, ondansetron, and MgSO4, 4 to 6 mg IV bolus followed by 1 to 3 g per hour infusion (n=8). The MgSO4 bolus was administered over 15 to 45 minutes during the initiation of cooling, and the infusion continued until rewarming (at ~300 minutes). The total dose of MgSO4 was 8.75 to 16.75 g.

Active cooling was initiated, and inlet water temperature was automatically controlled to achieve a target tympanic temperature (T tym) of 34.5°C (target range 34 to 35°C). Active cooling and maintenance of hypothermia continued for ≤5 hours; subjects were actively rewarmed over 1.5 to 3 hours to a tympanic temperature of 36°C.

The presence of shivering was noted by physical examination, electromyographic artifact during continuous electrocardiography, or by subject report. Overall thermal comfort was evaluated at 15-minute intervals (while subjects were awake) with a 100-mm-long visual analog scale on which 0 mm defined the worst imaginable cold, 50 mm identified thermal neutrality, and 100 mm indicated unbearable heat. A new, unmarked scale was used for each assessment. Heart rate and oxyhemoglobin saturation were monitored using electrocardiography and pulse oximetry; arterial blood pressure was recorded oscillometrically at 15-minute intervals.

Data Analysis
Multiple linear regression was used to evaluate variables affecting the time to achieve T tym of 35°C. Variables included in the model were gender, age (years), height (centimeters), weight (kilograms), body surface area (squared meters), baseline T tym (degrees Celsius), the initial meperidine bolus (milligrams), the total meperidine dosage within the first 1 and 2 hours of cooling (milligrams), and exposure to magnesium. ANOVA on ranks was performed to compare the total meperidine dosages within the first 2 hours of cooling for subjects receiving the pharmacological regimes of meperidine monotherapy, meperidine and buspirone, meperidine and ondansetron, or meperidine, ondansetron, and MgSO4. The Fisher exact test was used to compare proportions of subjects who were vasodilated in the group receiving magnesium; in the group not receiving magnesium. Repeated-measures ANOVA was performed to compare mean changes in physiological parameters. Because subjects were not awakened from sleep, comfort was only analyzed during the first 90 minutes of induction because of incomplete data.

Results
Baseline subject characteristics for those subjects receiving and not receiving MgSO4 are summarized in Table 1. All subjects reached the T tym range with a mean time to 35°C of 93 ± 40 minutes.

Multiple linear regression analysis indicated that weight, total meperidine dosage within the first 2 hours of cooling, and administration of magnesium significantly impacted the rate of cooling (Table 2). For example, for every 10 kg of additional body weight, the time to achieve T tym of 35°C was delayed by 18 minutes (P=0.001). For every additional 50 mg of meperidine administered within the first 2 hours of cooling, the time to achieve T tym of 35°C was delayed by 36 minutes (P=0.003). Administration of magnesium reduced the time to achieve T tym of 35°C by 17 minutes (P=0.039). However, the study was not powered adequately to analyze the influence of magnesium dosage on cooling rate. Total meperidine dosages within the first 2 hours of cooling did not differ in subjects receiving meperidine monotherapy (230 ± 27 mg), meperidine and buspirone (213 ± 25 mg), meperidine and ondansetron (200 ± 35 mg), or meperidine, ondansetron, and MgSO4 (200 ± 38 mg; P=0.416). Significantly more subjects who received magnesium were vasodilated during hypothermia induction (7 of 8 [88%] subjects receiving magnesium versus 4 of 14 [29%] subjects not receiving magnesium; P=0.024).

There was no statistically significant change in systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, or oxygen saturation during cooling in all subjects, except heart rate was significantly lower at the 150-minute time point only (P<0.05). When considering only subjects receiving magnesium, heart rate was lower at the 195-minute (P<0.05) and 225-minute (P<0.05) time points; otherwise, there were no statistically significant changes in physiological parameters. Because subjects were not awakened from sleep, comfort was only analyzed during the first 90 minutes of induction because of incomplete data.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Subject Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>No. of Subjects</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Female/male</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
</tr>
<tr>
<td>Mean BP</td>
</tr>
<tr>
<td>HR (bpm)</td>
</tr>
<tr>
<td>Baseline T tym (°C)</td>
</tr>
<tr>
<td>Baseline T rec (°C)</td>
</tr>
<tr>
<td>Baseline O₂ Saturation</td>
</tr>
<tr>
<td>Baseline Comfort</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD except for baseline comfort without MgSO₄, which is expressed as median and (interquartile range) and gender.

<table>
<thead>
<tr>
<th>TABLE 2. Multiple Linear Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dependent Variable</strong></td>
</tr>
<tr>
<td>Time to 35°C, minutes</td>
</tr>
<tr>
<td>Interception</td>
</tr>
<tr>
<td>MgSO₄</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>2-hour meperidine, mg</td>
</tr>
</tbody>
</table>

Multiple linear regression analysis was performed to evaluate the effects of MgSO₄, weight, and meperidine on the time to reach 35°C.
at later time points. Relative comfort for the subjects receiving MgSO\textsubscript{4} and for subjects not receiving MgSO\textsubscript{4} over time are shown in the figure. Subjects who received MgSO\textsubscript{4} had significantly higher mean comfort scores than those who did not (48\(\pm\)15 versus 38\(\pm\)12; \(P<0.001\)). There were no adverse events associated with the addition of MgSO\textsubscript{4} to the meperidine-based regimen.

**Discussion**

The ideal method to induce therapeutic hypothermia is safe, simple, well tolerated, and able to produce rapid cooling. To meet such goals in awake patients requires overcoming normal thermoregulatory mechanisms (ie, vasconstriction and shivering). Because of its special anti-shivering and analgesic effects, administration of intravenous meperidine permits surface cooling using the Arctic Sun. We have shown that the addition of intravenous MgSO\textsubscript{4} to a meperidine-based antishivering protocol increases the cooling rate and comfort during induction of hypothermia. The mechanism by which MgSO\textsubscript{4} increases cooling rate is likely, at least in part, because of peripheral vasodilation, and the lack of effect on systemic blood pressure is noteworthy.

Not unexpectedly, we found that increasing body weight decreases the cooling rate. This result is consistent with the findings of Toner et al\textsuperscript{16} for subjects immersed in cool water and at rest. Results of the multiple linear regression analysis revealed that body surface area was not a significant independent variable in predicting the time to 35\(^\circ\)C. The independent variable body surface area/(body volume) has been reported as a significant independent variable for the cooling rate of subjects immersed in cold water.\textsuperscript{17} Body surface area/(body volume) was not included as an independent variable in our analysis. We also found that increased meperidine dosage within the first 2 hours of cooling was associated with a decreased cooling rate. This is explained by the fact that we dosed meperidine on the basis of observed shivering. Therefore, higher meperidine dosage reflects increased shivering in the first 2 hours, which resulted in a slower cooling rate attributable to heat generation.

The total meperidine dosage at 2 hours was not significantly different in the subjects receiving the meperidine monotherapy, meperidine and buspirone, meperidine and ondansetron, or meperidine, ondansetron, and MgSO\textsubscript{4} pharmacological regimens. The fact that the subjects receiving meperidine and buspirone received similar dosages of meperidine within the first 2 hours compared with the subjects receiving meperidine monotherapy is in contrast with the findings of Mokhtarani et al.\textsuperscript{18} Their data suggest that meperidine dosage in the subjects receiving meperidine and buspirone should be less than for the subjects receiving meperidine monotherapy.

Our study is exploratory and suggests further study of MgSO\textsubscript{4} in the setting of therapeutic hypothermia is warranted. In addition to its impact on cooling rate and comfort, potential neuroprotective benefits make MgSO\textsubscript{4} an attractive agent to investigate in the setting of acute ischemic neuronal injury.\textsuperscript{11,19} Despite the recently reported Intravenous Magnesium Efficacy in Stroke Trial, which revealed no benefit of intravenous MgSO\textsubscript{4} when administered within 12 hours of stroke onset,\textsuperscript{20} the clinical investigation of MgSO\textsubscript{4} continues with a trial of ultra-early, prehospital administration (Field Administration of Stroke Therapy–Magnesium Trial).\textsuperscript{18} Because of the small sample size, we are unable to draw any conclusions regarding the optimal dosage of MgSO\textsubscript{4} and, in particular, whether there is any benefit of an infusion during the maintenance phase of hypothermia with respect to comfort or reducing total meperidine dosage.

In summary, the addition of intravenous MgSO\textsubscript{4} to a pharmacological antishivering regimen increases the cooling rate and comfort when using a surface cooling technique in unanesthetized, nonintubated subjects and may, in part, be attributable to peripheral vasodilation. Further study evaluating the role of MgSO\textsubscript{4} in therapeutic hypothermia is warranted.

**Acknowledgments**

This work was supported in part by Medivance, Inc.

**References**

Magnesium Sulfate Increases the Rate of Hypothermia Via Surface Cooling and Improves Comfort

Richard M. Zweifler, Marc E. Voorhees, M. Asim Mahmood and Mel Parnell

Stroke. 2004;35:2331-2334; originally published online August 19, 2004;
doi: 10.1161/01.STR.0000141161.63181.f1

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/10/2331

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/