Original Article

Multicenter Randomized Controlled Trial of Therapeutic Hypothermia Plus Magnesium Sulfate Versus Therapeutic Hypothermia Plus Placebo in the Management of Term and Near-term Infants with Hypoxic Ischemic Encephalopathy (The Mag Cool Study): A Pilot Study

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ABSTRACT

Background: Therapeutic hypothermia provides up to 30% neuroprotection in moderate to severe hypoxic ischemic encephalopathy (HIE). Additional neuroprotection may be achieved by using concomitant pharmacologic neuroprotective agents. Aim: The aim was to evaluate the safety of concomitant neuroprotective therapy of therapeutic hypothermia and magnesium sulfate (MgSO₄) in the management of moderate and severe HIE in term and near-term infants. Study Design: Multicenter double-blind randomized controlled trial. Methodology: Term and near-term newborn infants (≥35 weeks) with a clinical diagnosis of moderate or severe HIE were randomized to either Arm A (therapeutic hypothermia plus MgSO₄) or Arm B (therapeutic hypothermia plus placebo) using a net-based randomization system. Both groups received, within 6 h of birth, standard hypothermia therapy (72 h of cooling to 33.5°C followed by slow rewarming over a period of 8 h) plus either MgSO₄ (250 mg/kg/dose ×3 doses) or placebo (normal saline). The groups were compared for short-term predischarge adverse outcomes. Results: A total of 60 patients were randomized (29 in Arm A and 31 in Arm B). Both groups had similar baseline characteristics (P > 0.05) including severity of HIE. There were no differences in the short-term adverse outcomes (death, seizures, thrombocytopenia, coagulopathy, renal failure, elevated liver function test's, hypotension, intracranial hemorrhage, necrotizing enterocolitis, pulmonary hemorrhage, persistent pulmonary hypertension, and pulmonary air leak syndromes) between the two groups (P > 0.05). Conclusions: The combined use of therapeutic hypothermia and MgSO₄ appears to be safe particularly with respect to maintaining normal blood pressure and coagulopathy. Long-term survival and neurodevelopmental outcomes remain to be evaluated.

Key words:
Hypoxic ischemic encephalopathy, magnesium sulfate, neuroprotection, newborn, therapeutic hypothermia

INTRODUCTION

There is convincing evidence that moderate therapeutic hypothermia (33–34°C for 72 h), when initiated within 6 h after birth among term and near-term infants (≥35 weeks) with moderate to severe hypoxic-ischemic encephalopathy (HIE) reduces the risk of death or major disability¹–⁴ and increases the rate of disability-free survival at 6–7 years of age.⁵–⁶ The National Institute of Clinical Excellence endorsed therapeutic hypothermia for routine clinical practice in United Kingdom in 2010.⁷ Similar national guidelines have been issued in many other countries with the result that therapeutic hypothermia has now become a standard of care for moderate to severe HIE in term and near-term infants in Neonatal Intensive Care Units (NICU’s) worldwide.⁸ Despite the remarkable beneficial effects of hypothermia therapy, the result of meta-analyses has shown that therapeutic hypothermia...
provides on the average up to 25% neuroprotection.[4] However, it is possible that pharmacologic neuroprotective therapies may add incrementally to the proven benefit of hypothermia.[5] This approach of adding a pharmacologic neuroprotective agent to supplement the neuroprotective role of therapeutic hypothermia has brought a new global era of neuroprotective research in neonatal practice called “the hypothermia plus therapy.” The potential neuroprotective pharmacologic agents include erythropoietin, melatonin, magnesium sulfate (MgSO4), topiramate, xenon, and allopurinol.[6]

Magnesium sulfate is a low cost readily available drug worldwide. The cochrane meta-analysis 2009[7] concluded that MgSO4 has a proven neuroprotective benefit in preterm newborn babies when given to their pregnant mothers antenatally. This conclusion is supported by the most recent review by Tataranno et al.[1] Although the postnatal neuroprotective use of MgSO4 in human infants with HIE, without concomitant hypothermia therapy, has confirmed safety as well as efficacy,[12–15] a recent preclinical study on animal models of term HIE[16] has failed to find a consistent neuroprotective role of MgSO4. Since a combination of therapeutic hypothermia and MgSO4 has never been tested for its therapeutic safety and neuroprotective efficacy in term human infants with HIE; we conducted this pilot study to compare and analyze the in-hospital mortality and short-term predischarge morbidity outcomes of this combined therapy as compared to hypothermia therapy alone.

**METHODOLOGY**

**Study design**

The study was set up as a prospective, double-blind (for MgSO4), placebo (0.9% saline) controlled multi-center randomized controlled trial (MRCT) and multinational randomized controlled trial, which was conducted in the tertiary care NICU’s in Qatar, Turkey, Saudi Arabia, Egypt, Malaysia, and Abu Dhabi between September 2012 and August 2013. The study population included all term and near-term newborns (≥35 completed weeks) with moderate to severe HIE. The severity of HIE was determined using the Sarnat and Sarnat criteria.[17] Therapeutic hypothermia was started as a standard of care in all babies within 6 h after birth using either total body cooling method (Teicotherm Neo Insp Inc., UK) or head cooling (Olympic Cool-Cal system) depending upon the individual unit policy. The babies were cooled to a core body temperature (rectal) of 33.5°C (range: 33.0–34.0°C) for a period of 72 h followed by slow re-warming over a period of 8 h at a rate not exceeding 0.5°C/h. Each newborn infant was provided standard intensive care as per individual unit protocol. Informed parental consent was obtained from the parents of eligible babies who met the inclusion and exclusion criteria given in Panel 1.

**Randomization to magnesium sulfate or placebo and study drug administration**

After parental consent, the babies were randomized using a net-based randomization system provided by a London-based independent clinical trials randomization company (sealed envelope).[18] Each recruitment center had its own unique password and PIN code for using the system. Each randomization was immediately notified by E-mail directly from the randomization website to the data coordinating center in Doha, Qatar. Each

**Panel 1**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. <strong>Condition at birth:</strong> Infants ≥35 completed weeks gestation admitted to the NICU with at least one of the following</td>
</tr>
<tr>
<td>1. Apgar score of &lt;5 at 10 min after birth due to birth asphyxia/perinatal depression</td>
</tr>
<tr>
<td>2. Continued need for resuscitation, including endotracheal or mask ventilation, at 10 min after birth</td>
</tr>
<tr>
<td>3. Acidosis within 60 min of birth (defined as any occurrence of umbilical cord, arterial or capillary pH &lt;7.00)</td>
</tr>
<tr>
<td>B. <strong>Evidence of moderate to severe encephalopathy,</strong> consisting of altered state of consciousness (lethargy, stupor or coma) and at least one of the following</td>
</tr>
<tr>
<td>1. Hypotonia</td>
</tr>
<tr>
<td>2. Abnormal reflexes including oculomotor or pupillary reflexes</td>
</tr>
<tr>
<td>3. Absent or weak suck</td>
</tr>
<tr>
<td>4. Clinical seizures</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>A. <strong>Infants expected to be &gt;6 h of age at the time of randomization</strong></td>
</tr>
<tr>
<td>B. <strong>Major congenital abnormalities,</strong> such as diaphragmatic hernia requiring ventilation or congenital abnormalities suggestive of chromosomal anomaly or other syndromes that include brain dysgenesis</td>
</tr>
<tr>
<td>C. <strong>Very severe HIE where the elective withdrawal is justified by the attending clinician</strong></td>
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</tbody>
</table>
randomized baby received a unique randomization code with two letters and one number. The code was prescribed by the physician at a dose of 2.5 ml/kg/day q 24 h for three doses which would be equivalent to 250 mg/kg/dose of 10% MgSO_4 or 2.5 ml/kg/dose of normal saline. Once the coded prescription was received by the pharmacist, he/she un-coded the prescription and dispensed the study medication in a sealed syringe labeled with the code and study number. The study medicine was administered as slow intravenous (IV) infusion over a period of 30 min within 6 h of birth.

Data collection
Data were collected on standard printed daily log books approved by the Institutional Review Board. The baseline characteristics and short-term outcome variables were ascertained as per approved study protocol [Tables 1 and 2].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total patients analyzed: 60</th>
<th>P</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stages of HIE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (48.3)</td>
<td>19 (61.3)</td>
<td>0.311</td>
</tr>
<tr>
<td>Severe</td>
<td>15 (51.7)</td>
<td>12 (38.7)</td>
<td>0.570</td>
</tr>
<tr>
<td>Seizures</td>
<td>18 (62.1)</td>
<td>17 (54.8)</td>
<td>0.708</td>
</tr>
<tr>
<td>Meconium aspiration</td>
<td>3 (10.3)</td>
<td>5 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Culture-proven sepsis</td>
<td>3 (10.3)</td>
<td>1 (3.2)</td>
<td>0.475</td>
</tr>
</tbody>
</table>

HIE = Hypoxic ischemic encephalopathy

Definitions
Moderate hypotension was defined as the need for volume therapy and/or one inotrope. Severe hypotension was defined as the need for two or more inotropes or antihypotensive medication, e.g. hydrocortisone.

Statistical analysis
The decoding of individual patients was done by the study statistician keeping the investigators blinded. For statistical analysis, the patients were grouped into Arm A (therapeutic hypothermia plus MgSO_4) or Arm B (therapeutic hypothermia plus placebo). The Chi-square test of significance or Fisher exact test (for expected count <5 in at least one cell) were used to compare short-term predischarge adverse outcomes between the two groups. The level of significance was set at P < 0.05.

RESULTS
A total of 60 infants were randomized (29 in Arm A and 31 in Arm B). Both groups had similar baseline characteristics (P > 0.05) including severity of HIE, incidence of fetal sepsis and seizures as well as evidence of fetal distress (meconium aspiration) as shown in Table 1. All babies were treated with standard therapeutic hypothermia for 72 h followed by 8 h of re-warming. Therapeutic hypothermia had to be terminated in one baby due to severe sinus bradycardia. Overall 55% (n = 33) had moderate HIE and 45% (n = 27)
severe HIE. Totally, 55 babies (91.7%) were cooled by total body cooling (Teicotherm Neo Insp Inc., UK) and five babies (8.3%) by head cooling (Olympic Cool-Cal System).

There were no differences in the short-term adverse outcomes (death, seizures, thrombocytopenia, coagulopathy, renal failure, raised liver function test, hypotension, intracranial hemorrhage, necrotizing enterocolitis, pulmonary hemorrhage, pulmonary hypertension, and pulmonary air leak syndromes) between the two groups (P > 0.05) as shown in Table 2.

**DISCUSSION**

Perinatal asphyxia remains a major cause of neonatal mortality as well as long-term sensorineural impairments and disabilities. The incidence has been almost static: 1–2/1000 births in developed countries and up to 5/1000 birth and even higher in some developing countries. There was no specific neuroprotective treatment available for affected infants till the recent discovery of therapeutic hypothermia which has been proven to reduce death and major disabilities; both at 18–24 months and in middle childhood. However, the neuroprotective achievement remains far from perfect. Despite effective therapeutic hypothermia delivered according to the standard research protocols, 50% of newborns with moderate-to-severe HIE will still continue to die or survive with major disabilities including cerebral palsy (CP) and major neurodevelopmental delay; hence, the search to discover additional neuroprotective therapies continues.

The term “hypothermia plus therapy” has been used for adding a pharmacologic agent with potential neuroprotective action to the standard hypothermia therapy. The pharmacologic agents with potential additive neuroprotective role in neonatal HIE include MgSO4, xenon, topiramate, allopurinol, and erythropoietin. Antenatal MgSO4 administered to pregnant women with preterm labor has an established role in preterm neonatal neuroprotection. MgSO4 given to women at risk of premature birth significantly reduced the risk of CP without increasing the risk of perinatal or infant death. According to the cochrane meta-analysis 2009, the neuroprotective role for antenatal MgSO4 therapy given to women at risk of preterm birth for the preterm fetus is now established. Another recent meta-analysis also found persuasive evidence that MgSO4 administered to women at high risk of delivery before 34 weeks of gestation reduces the risk of CP in their children. The National Institute of Child Health and Human Development meta-analysis of 2009 also concluded that fetal exposure to MgSO4 in women at risk of preterm delivery significantly reduces the risk of CP without increasing the risk of death. The most recent review article by Tataranno et al states that “recent evidences demonstrate that fetal exposure to MgSO4 in women at risk for preterm delivery significantly reduces the risk of CP without increasing the risk of death.” However, there are views contrary to this as well. The preclinical study by Galinsky et al using term HIE animal models suggests that magnesium is not consistently neuroprotective for perinatal hypoxia-ischemia in term-equivalent animal HIE models.

The postnatal neuroprotective use of MgSO4 in human infants, without concomitant hypothermia therapy, has confirmed safety as well as efficacy. The results from the recent systematic review and meta-analysis by Tagin et al on the use of MgSO4 in newborns with HIE indicates an improvement in the short-term composite outcome of survival without abnormalities in any of the following: Neurodevelopmental examination, neuroimaging or neurophysiologic studies. It is plausible that a concomitant use of MgSO4 may add to the established neuroprotective efficacy of therapeutic hypothermia therapy. However, the neuroprotective efficacy of a combination of hypothermia and MgSO4 has been tested only in animals. Campbell et al, in their study on rat models, have shown that combined MgSO4 and hypothermia treatment reduced infarct volumes by 54% at 2 h (P = 0.048) and by 39% at 4 h (P = 0.012), but there was no treatment effect detected at 6 h or in the hypothermia alone or MgSO4 alone groups. Similarly Zhu et al from their study of global cerebral ischemia in rats, have shown that posts ischemic modest hypothermia (35°C) combined with IV magnesium is more effective at reducing neuronal death than either treatment used alone. Since MgSO4 is a low-cost medicine and is readily available in resource restricted countries which bear the highest share of the global burden of perinatal asphyxia, we decided to test MgSO4 for hypothermia plus therapy. To our knowledge, Mag Cool study is the first MRCT of combined hypothermia plus MgSO4 therapy in human infants with moderate to severe HIE. Hence, the current pilot study was essential to establish the safety of combined use of MgSO4 and therapeutic hypothermia in human infants with HIE before proceeding any further with the full trial which would test the neuroprotective efficacy at 18–24 months.

Tagin et al, in their meta-analysis, have reported a statistically insignificant higher trend in mortality in the MgSO4 group. On the other hand, in our study, the trend of mortality was higher in the placebo group which was also statistically nonsignificant. The use of MgSO4 also carries the potential transient risk of systemic hypotension and respiratory depression. The likelihood of hypotension is high in the clinical scenario of a baby with moderate to severe HIE and concomitant use of hypothermia therapy.
Inadvertent overcooling and inappropriate rapid rewarming during hypothermia therapy can produce hypotension. The study by Levene et al. has shown that MgSO4 given to term babies with HIE, as slow IV infusion in a dose of 250 mg/kg/dose once a day for 3 days (low dose) is less likely to produce hypotension as compared to a dose of 400 mg/kg/dose once a day for 3 days (high dose). The studies of Bhat et al. and Khashaba et al. have also shown no difference in the incidence of hypotension between the MgSO4 and the control groups. Both studies used low dose MgSO4 (250 mg/kg/dose once a day). None of these studies used a concomitant hypothermia therapy. We also used low dose MgSO4 (250 mg/kg/dose once a day) as IV infusion and despite the concomitant use of standard therapeutic hypothermia therapy, there was no difference in the incidence of moderate to severe hypotension between the MgSO4 group and placebo group. The sedative effect of MgSO4 was neither estimated nor considered a problem because all babies were on respiratory support during the first 72 h of life. The difference between other short-term, in the hospital, predischARGE adverse outcomes was also nonsignificant between the MgSO4 and placebo groups in our study.

The results of our pilot data show that combined use of therapeutic hypothermia and MgSO4 in the management of moderate to severe HIE in term and near-term infants is safe; both in terms of mortality as well as predischARGE in-hospital morbidity. Hence, it is reasonable to conduct a well-designed, large MRCT to evaluate the long-term safety, as well as neuroprotective efficacy of hypothermia plus MgSO4, as compared to hypothermia therapy alone.

**SUMMARY**

The on-going research on “hypothermia plus therapies” carries a potential promise of additional neuroprotection in term and near-term babies with moderate to severe HIE. The combined use of therapeutic hypothermia and MgSO4 is one such therapy which appears to be safe particularly with respect to the risk of mortality and short-term adverse outcomes. Long-term survival and neurodevelopmental outcomes remain to be evaluated.

**ACKNOWLEDGMENTS**

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**REFERENCES**


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36. Campbell K, Meloni BP, Knuckey MW. Combined magnesium and mild hypothermia (35 degrees C) treatment reduces infarct volumes after permanent middle cerebral artery occlusion in the rat at 2 and 4, but not 6 h. Brain Res 2008;130:258-64.


Erratum: Multicenter Randomized Controlled Trial of Therapeutic Hypothermia Plus Magnesium Sulfate Versus Therapeutic Hypothermia Plus Placebo in the Management of Term and Near-term Infants with Hypoxic Ischemic Encephalopathy (The Mag Cool Study): A Pilot Study

In the article, "Multicenter Randomized Controlled Trial of Therapeutic Hypothermia Plus Magnesium Sulfate Versus Therapeutic Hypothermia Plus Placebo in the Management of Term and Near-term Infants with Hypoxic Ischemic Encephalopathy (The Mag Cool Study): A Pilot Study", which appeared in the pages 158-163, Issue 3, Vol 4 of Journal of Clinical Neonatology, the last author “on behalf of the Mag Cool Study Group*” marked with an “*” had the following list of contributors of the group which was missing:

“*Mag cool Study Group: Participating Hospitals (number of patients recruited) and investigators:

Hamad Medical Corporation Qatar (11) - Sajjad Ur Rahman; Samawal Lutfi; Lina Haboub; Hussain Parappil, Mohammad Rigims. Zekai Tahir Burak Hospital Turkey (25) - Fuat Emre Canpolat; Mehmet Yekta Oncel, Abdurrahman Evli, Ugur Dilmen. Sulaiman Al Habib Medical Group, Riyadh Saudi Arabia (08) - Jasim Anabrees, Khalid Hassan, Rochelle Loja, Muhammad Shams Khan. Mansoura University Children’s Hospital Egypt (05) - Mohamed Khashaba; Islam Ayman Noor. Universiti Malaya Medical Center Kuala Lumpur Malaysia (05) - Lucy Chai See Lum; Anis Siham Zainal Abidin, Hasimah Zainol, Norina Abdul Muin, Chin Seng Gan. Diyarbakir Children Hospital Turkey (03) - Melek Akar; Heybet Tuzun. Tawam Hospital UAE (2) - Aiman Rahmani, Moghis Rehman; Fares Chedid, Universiti Kebangsaan Kuala Lumpur Malaysia (01) - Rohana Jaafar; Lai Yin Key.”

This has now been corrected and reposted online.

Saleh Al-Alaiyan
Editor in Chief - Journal of Clinical Neonatology

REFERENCE


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