

WHEN BASIC RESEARCH DOESN'T TRANSLATE TO THE BEDSIDE—LESSONS FROM THE MAGNESIUM BRAIN TRAUMA STUDY

Magnesium Sulfate for Neuroprotection After Traumatic Brain Injury: A Randomised Controlled Trial. Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J, Lucas T, Newell DW, Mansfield PN, Machamer JE, Barber J, Dikmen SS. *Lancet Neurol* 2007;6(1):29–38. **BACKGROUND:** Traumatic brain injuries represent an important and costly health problem. Supplemental magnesium positively affects many of the processes involved in secondary injury after traumatic brain injury and consistently improves outcome in animal models. We aimed to test whether treatment with magnesium favourably affects outcome in head-injured patients. **METHODS:** In a double-blind trial, 499 patients aged 14 years or older admitted to a level 1 regional trauma centre between August, 1998, and October, 2004, with moderate or severe traumatic brain injury were randomly assigned one of two doses of magnesium or placebo within 8 h of injury and continuing for 5 days. Magnesium doses were targeted to achieve serum magnesium ranges of 1.0–1.85 mmol/L or 1.25–2.5 mmol/L. The primary outcome was a composite of mortality, seizures, functional measures, and neuropsychological tests assessed up to 6 months after injury. Analyses were done according to the intention-to-treat principle. This trial is registered with Clinicaltrials.gov, number NCT00004730. **FINDINGS:** Magnesium showed no significant positive effect on the composite primary outcome measure at the higher dose (mean = 55 average percentile ranking on magnesium vs. 52 on placebo, 95% CI for difference –7 to 14; $p = 0.70$). Those randomly assigned magnesium at the lower dose did significantly worse than those assigned placebo (48 vs. 54, 95% CI –10.5 to –2; $p = 0.007$). Furthermore, there was higher mortality with the higher magnesium dose than with placebo. Other major medical complications were similar between groups, except for a slight excess of pulmonary oedema and respiratory failure in the lower magnesium target group. No subgroups were identified in which magnesium had a significantly positive effect. **INTERPRETATION:** Continuous infusions of magnesium for 5 days given to patients within 8 h of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury.

COMMENTARY

One of the most important areas of epilepsy research is the search for antiepileptogenic therapies. Treatments that reduce development of chronic epilepsy after a brain injury or forestall progression to medication resistant epilepsy could minimize or eliminate seizure-related disability in many individuals. In this search, posttraumatic epilepsy is one of the most studied conditions, not only because it is common, often severe, and resistant to medications, but also because it is temporally well defined—a time window exists before the development of chronic seizures in which intervention could be attempted. Clinical trials of potential antiepileptogenic therapies are inevitably linked to the search for neuroprotective treatments because head injury often results in severe neurological and cognitive impairment, although it should not be assumed that neuroprotective agents would necessarily prevent epilepsy.

Prior clinical trials, whether using various antiepileptic agents (including phenytoin and valproate) or any other treatment, have failed to show neuroprotection or antiepileptogenesis (1). Therefore, the choice of magnesium sulfate for a new clinical trial of neuroprotection was based on the hypothesis that an agent with multiple proven beneficial actions at the cellular level may have neuroprotective or antiepileptogenic effects. These cellular-level effects of magnesium sulfate include hyperpolarization, action as an ATP cofactor, inhibition of presynaptic excitatory neurotransmitters, blockade of NMDA and voltage-gated calcium channels, potentiation of presynaptic adenosine, vasodilatation by relaxation of smooth muscle, and others. Multiple experimental rodent studies have demonstrated decreased brain magnesium after injury (2), with worse outcome associated with magnesium deficiency (3). Indeed, magnesium supplementation before or after injury has been shown to improve outcome in rodents (3–6). A pilot human head injury study also suggested that magnesium supplementation improves outcome after head injury (7). Most of these preclinical studies were based on models of focal cortical injury (2–4) or impact acceleration diffuse brain injury (5,6).

The clinical trial by Temkin and colleagues was a single-site, parallel-group, randomized, double-blind study. Approximately half the patients were victims of motor vehicle accidents, and 5% had penetrating brain injuries. In the great majority, there was radiological evidence of cortical and/or diffuse axonal injury as well as subdural and epidural hematomas and skull fractures. It should be noted that the current standard of care is to correct magnesium deficiency, and this intervention therefore was allowed in both the magnesium and placebo groups. At the suggestion of the grant review study section, a target serum magnesium range of 1.25 to 2.5 mmol/L was initially used for randomization of 118 patients. At this dosage range, mortality

in the magnesium group was twice that of placebo, while blood pressure and cerebral perfusion pressure were lower than in the placebo group. After an interim analysis, the study was restarted with randomization of 381 patients, using a serum magnesium target range of 1.0 to 1.85 mmol/L, which did not produce significant differences from placebo in mortality, blood pressure, or cerebral perfusion pressure, but did show a significantly worse outcome than placebo in an analysis of a composite of 39 outcome markers. Early seizures were rare, although there was no screening for subclinical electrographic seizures, and late seizures were slightly lower in the placebo group, though not significantly. The negative results of this study are convincing and echo the findings of another large clinical trial assessing whether magnesium is neuroprotective for stroke (8). The head injury study of Temkin et al. had adequate statistical power, 93% follow-up at 6 months, and demonstrated no benefit in any of the 39 individual outcome measures with either magnesium concentration ranges.

In spite of its known beneficial properties, magnesium may have deleterious effects for patients with brain injury that offset any favorable effects. There could be a narrow concentration or time window to produce neuroprotective benefits, although these circumstances were not demonstrated by animal studies. All experimental work was done in the rat, but there could be species differences, for example, in magnesium's effect on vascular tone. One study has indicated that peripheral elevation of serum magnesium levels in humans results in only very modest increases in CSF concentration (9), which means that peripheral effects of magnesium infusion in humans (consisting of vasodilatation, with decreased blood pressure and cerebral perfusion) might predominate and potentially have negative effects on injured tissue. Finally, animal studies used fluid percussion and impact-acceleration models of injury, which are very good models of brain contusion and blood–brain barrier opening but do not reproduce the heterogeneous injuries of different severities that occur in the human. Indeed, human head injury often entails a large, diffuse axonal injury component in the absence of blood–brain barrier opening, which is not easily modeled in rodents (10). In the absence of sufficient blood–brain barrier opening in brain areas with diffuse axonal injury, magnesium may not have readily penetrated as it did in the preclinical models.

The fact that this carefully conceived and well-designed clinical study did not discover effective neuroprotective or antiepileptogenic treatments with magnesium infusion must be considered an indication of the extent to which the success of clinical trials is rooted in the completeness and soundness of the prior preclinical studies performed with experimental animals. Accordingly, it would be of great benefit if the laboratory studies identifying and investigating candidate agents became more comprehensive and more closely modeled the etiology of

human disease. Multiple models and different species need to be analyzed to probe the various aspects of the human pathology, and a close match must exist between the type of injuries being presented by patients entering a trial and the injuries reproduced by the preclinical models—of both neuroprotection and antiepileptogenesis—that are used for drug development.

by John W. Miller, MD, PhD, and Raimondo D'Ambrosio, PhD

References

1. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia* 2001;42(4):515–524.
2. McIntosh TK, Faden AI, Yamakami I, Vink R. Magnesium deficiency exacerbates and pretreatment improves outcome following traumatic brain injury in rats: ³¹P magnetic resonance spectroscopy and behavioral studies. *J Neurotrauma* 1988;5:17–31.
3. Saatman KE, Bareyre FM, Grady S, McIntosh TK. Acute cytoskeletal alterations and cell death induced by experimental brain injury are attenuated by magnesium treatment and exacerbated by magnesium deficiency. *J Neuropathol Exp Neurol* 2001;60(2):183–194.
4. Bareyre FM, Saatman KE, Raghupathi R, McIntosh TK. Postinjury treatment with magnesium chloride attenuates cortical damage after traumatic brain injury in rats. *J Neurotrauma* 2000;17:1029–1039.
5. Vink R, O'Connor CA, Nimmo AJ, Heath DL. Magnesium attenuates persistent functional deficits following diffuse traumatic brain injury in rats. *Neurosci Lett* 2003;336:41–44.
6. Heath DL, Vink R. Improved motor outcome in response to magnesium therapy received up to 24 hours after traumatic diffuse axonal brain injury in rats. *J Neurosurg* 1999;90:504–509.
7. Gennarelli T, Cruz J, McGinnis G, Jaggi J. *Development of Methods to Evaluate New Treatments for Acute Head Injury*. Atlanta: Centers for Disease Control and Prevention, 1997; R49/CCR303687.
8. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomized controlled trial. *Lancet* 2004;363:439–445.
9. McKee JA, Brewer RP, Macy GE, Borel CO, Reynolds JD, Warner DS. Magnesium neuroprotection is limited in humans with acute brain injury. *Neurocrit Care* 2000;2(3):342–351.
10. Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. *J Head Trauma Rehabil* 2003;18(4):307–316.