

# Magnesium Sulfate Tocolysis

## Time to Quit

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Intravenous magnesium sulfate tocolysis remains a North American anomaly. This therapy rose to prominence based on poor science and the recommendations of authorities. However, a Cochrane systematic review concluded that magnesium sulfate is ineffective as a tocolytic. The review found no benefit in preventing preterm or very preterm birth. Moreover, the risk of total pediatric mortality was significantly higher for infants exposed to magnesium sulfate (relative risk 2.8; 95% confidence interval 1.2–6.6). Given its lack of benefit, possible harms, and expense, magnesium sulfate should not be used for tocolysis. Any further use of magnesium sulfate for tocolysis should be restricted to formal clinical trials with approval by an institutional review board and signed informed consent for participants. Should tocolysis be desired, calcium channel blockers, such as nifedipine, seem preferable.

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Intravenous magnesium sulfate is ineffective in stopping premature labor; that it remains the most common tocolytic in the United States today is unexplained but reflects inadequate progress toward rational

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therapeutics in obstetrics. This commentary will describe the scope and patterns of use, reveal its shaky scientific origins, review the evidence of benefit, describe harms of therapy, and discuss alternative agents.

### SCOPE OF USE

Although precise figures on magnesium sulfate tocolysis are elusive, the number of pregnant women and fetuses exposed is large. In 2003, 12.3% of all births in the United States were preterm. Of these approximately one half million preterm births, a substantial proportion, involved tocolysis (with any agent). The National Center for Health Statistics reported that 86,000 women had tocolysis associated with a live birth in that year. The total number exposed one or more times during pregnancy was larger.

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Others have estimated that about 150,000 U.S. women receive tocolytic therapy at 34 weeks of gestation or less each year.<sup>1</sup> If 80%<sup>1</sup> of these women receive magne-

sium as the tocolytic agent, then the annual number of women exposed would approximate 120,000. Magnesium sulfate has been used for tocolysis by family physicians, generalist obstetricians, and perinatologists alike.

### A SHAKY START: POOR SCIENCE AND WORSE ETHICS

As often happens in obstetrics, this treatment became firmly entrenched in practice long before proper evaluation.<sup>2</sup> Based on the potential ability of magnesium to suppress smooth-muscle nerve transmission and to quiet myometrial cells, clinicians began to use the agent in uncontrolled (and possibly unethical) human experiments. After an early report from Germany, American investigators launched a study. The first U.S. trial allocated patients to three intravenous treatment groups: magnesium sulfate, ethanol, or dextrose (the placebo). No mention was made of approval by an institutional review board or informed consent. The allocation was done by final digit of hospital number, which is not random and which prevents allocation concealment. How nine participants were chosen “at random” to receive dextrose, while 31 women received magnesium and another 31 got ethanol is unexplained. Imbalances in cervical dilation upon entry into the study suggest selection bias. The outcome was also inappropriate:



stopping contractions and having a period of at least one day before their recurrence. No infant outcomes were reported.

No significant difference emerged between magnesium and placebo. The relative risk (RR) of “success” was 1.7 (95% confidence interval [CI] 0.8–3.7) for magnesium compared with placebo. Despite these methodologic flaws, the authors claimed that, “We have found that delivery can be delayed with intravenous magnesium sulfate for the required 48 hours in the vast majority of instances.” This statement seems all the more peculiar, given that their observation period ended at 24 hours.

This cohort study was followed by studies of even less scientific rigor. A case-series report of 192 women without a comparison group concluded that, “The present study demonstrates the effectiveness of magnesium sulfate as a tocolytic agent to treat premature labor.” Another retrospective case-series report on 355 patients (without a control group) reached a similar untenable conclusion, “MgSO<sub>4</sub> was found to be a successful, inexpensive, and relatively nontoxic tocolytic agent that had few side effects.”<sup>3</sup> However, studies without a comparison group do not allow causal inferences to be made.

## RECOMMENDATIONS OF AUTHORITIES

Pronouncements, often in prestigious journals or from famous medical institutions, reinforced the efficacy of magnesium in clinicians’ minds. Like the early investigators, recent commentators have lauded magnesium. A review article in the *New England Journal of Medicine* claimed that, “Magnesium sulfate is safe and has become the first-line treatment for preterm labor in North America.”<sup>4</sup> (No evidence was provided as to why this should be so.) A recent Canadian medical newsletter

proclaimed that according to the Mayo Clinic and the Medical University of South Carolina, “Magnesium tocolysis stops preterm labor in its tracks” (Dent E. Magnesium tocolysis stops preterm labor in its tracks. *National Review of Medicine*. Available at: [http://www.nationalreviewofmedicine.com/issue/2005/02\\_28/2\\_clinical11\\_04.html](http://www.nationalreviewofmedicine.com/issue/2005/02_28/2_clinical11_04.html). Retrieved January 18, 2006). The study in question was an unpublished retrospective case series of 172 patients. The March of Dimes also suggests magnesium is an effective tocolytic agent.

## SYSTEMATIC REVIEWS OF THE EVIDENCE

A Cochrane review of the world’s randomized controlled trials, encompassing more than 2,000 women in 23 trials, concluded that magnesium sulfate tocolysis is not only ineffective but also harmful to infants.<sup>5</sup> Magnesium sulfate was compared with no tocolytic in three trials (saline, sedation plus hydration, or sedation), beta mimetics in ten, calcium channel blockers in four, prostaglandin synthetase inhibitors in two, nitroglycerin in one, ethanol in one, and other combinations of agents in two. Whether compared with no tocolytic drug or with an alternative tocolytic agent, magnesium sulfate had no clinical benefit. Methodologic problems with these trials included inadequate descriptions of allocation concealment and handling of losses to follow-up.<sup>5</sup>

No difference emerged in the risk of delivery within 48 hours when magnesium was compared with the controls. No reduction in risk of preterm (less than 37 weeks) or very preterm (less than 34 weeks) delivery occurred. Ironically, the risk of fetal and pediatric death was increased significantly for infants exposed to magnesium sulfate (RR 2.8, 95% CI 1.2–6.6), based on seven stud-

ies encompassing 727 infants. These trials all featured an intravenous loading dose of magnesium sulfate (4 to 6 g), followed by continuous infusion (1.5 to 5 g/h). A test of statistical heterogeneity in these seven trials was insignificant ( $P=.21$ ).<sup>5</sup> No infant benefit in respiratory distress syndrome, intraventricular hemorrhage, infection, or necrotizing enterocolitis was evident. Magnesium sulfate was less likely than betamimetics to cause maternal adverse effects requiring discontinuation, but was more likely than other treatments to cause unpleasant adverse effects.

An independent review from Canada found the North American preference for magnesium sulfate unexplained: “Despite the lack of clear tocolytic effects, magnesium sulfate is one of the most popular tocolytics in North America.”<sup>6</sup> A systematic review commissioned by the U.S. Agency for Healthcare Research and Quality evaluated randomized controlled trials published between 1966 and 1999. This review found two trials that compared magnesium sulfate with placebo. One found that women receiving magnesium were less likely to deliver in 48 hours, but infants of the placebo group had a higher estimated gestational age at birth. The other trial found similar birth outcomes with magnesium sulfate and placebo. Birth weights were similar in both groups in both trials.

## RECOMMENDATIONS OF PROFESSIONAL ORGANIZATIONS

Neither the American College of Obstetricians and Gynecologists nor the Royal College of Obstetricians and Gynaecologists endorses use of magnesium sulfate tocolysis. For example, the American College of Obstetricians and Gynecologists notes that, “. . . all [tocolytic agents] have



demonstrated only limited benefit. Hence, there is no clear first-line tocolytic drug.” The Royal College states that, “In view of the current lack of evidence for any substantive benefit for the baby from tocolysis, and the possibility of hazard for the mother, the available evidence should be discussed with the woman and her partner and their preferences taken into account in determining her care.” The Scottish Programme for Clinical Effectiveness in Reproductive Health guideline specifically states “Magnesium sulfate is one of the most popular tocolytics in North America despite lack of clear tocolytic effects. . . .”

## HARMS

Risks of magnesium therapy range from unpleasant to fatal. Of most concern is the link between magnesium and total pediatric mortality.<sup>1</sup> Evidence comes both from randomized controlled trials<sup>7,8</sup> and an observational study.<sup>9</sup> The Magnesium and Neurologic Endpoints Trial was designed to test the ability of magnesium to prevent cerebral palsy, and the finding of increased total pediatric mortality (fetal, neonatal, and postneonatal) was unexpected.<sup>1</sup> However, in retrospect, the earlier randomized controlled trial at Parkland Hospital in Dallas also showed a significant increase in fetal and pediatric mortality associated with magnesium tocolysis.

A case-control study of perinatal mortality at the Chicago Lying-In Hospital from 1986 to 1999 found a statistically significant increase in risk of death with cumulative magnesium doses greater than 48 g.<sup>9</sup> The odds ratio of death with this dose was 4.7 (95% CI 1.1–20.0) compared with lower doses. Doses greater than 48 g occur with regimens such as a 4–6 g bolus followed by 2–4 g/h for 24 hours, used commonly for tocoly-

sis. Not all studies reveal that magnesium sulfate causes harm to the fetus or infant, and one study suggests a possible benefit.<sup>10</sup> However, the doses of magnesium used in this trial were lower than those commonly used for tocolysis (often greater than 50 g over 24 hours), and a narrow therapeutic window may exist between benefit and harm (Mittendorf R, Lee KS, Roizen NJ, Pryde PG. Magnesium sulfate for preterm neuroprotection [letter]. *JAMA* 2004;291:940–1).

One inventory lists 23 maternal complications of magnesium tocolysis. Respiratory arrest can result from accidental overdoses of magnesium. Pulmonary edema also can be life-threatening. In one study of pulmonary edema in pregnant women, the most common cause was the use of tocolytic agents, primarily intravenous magnesium sulfate. Other more common side effects include flushing, nausea, lethargy, chest tightness, and blurred vision.

## ALTERNATIVE TOCOLYTIC AGENTS

If tocolytics are desired, other agents are preferable to magnesium sulfate. The strongest evidence exists for calcium channel blockers, usually nifedipine. In a Cochrane systematic review of randomized trials, these drugs reduced the number of women giving birth within seven days (RR 0.76; 95% CI 0.60–0.97) and before 34 weeks of gestation (RR 0.83; 95% CI 0.69–0.99). Fewer women discontinued tocolytic therapy because of adverse drug reactions than with alternative agents (RR 0.14; 95% CI 0.05–0.36). In addition, statistically significant benefit has been seen for infants in terms of respiratory distress syndrome, necrotizing enterocolitis, intraventricular hem-

orrhage, and jaundice. In contrast, betamimetic drugs, such as terbutaline, have little benefit. These agents decrease the number of women giving birth within 48 hours (RR 0.63; 95% CI 0.53–0.75) but do not reduce births within seven days; they are often discontinued because of noxious side effects. Data are insufficient to assess the role of cyclooxygenase inhibitors, such as indomethacin. Randomized controlled trials have not confirmed the superiority of oxytocin receptor antagonists (atosiban) over betamimetic drugs or placebo.

## CONCLUSION

Magnesium sulfate is ineffective as a tocolytic (even in delaying labor for the short time needed to administer corticosteroids), potentially harmful to infants, and unpleasant for women. Hence, further use of this agent is inappropriate unless in the context of a formal clinical trial with institutional review board approval and informed consent for participants. Although inconsistent, evidence suggests that magnesium sulfate tocolysis may be associated with an excess of 1,900 to 4,800 fetal and neonatal deaths annually in the U.S., depending on the extent of its use and attributable mortality.<sup>1</sup> If so, 7% of infant mortality might be caused by this agent.<sup>1</sup> Should magnesium ultimately be found to be protective of the central nervous system of infants, that still would not justify its use for tocolysis, for which it has been found worthless.<sup>5</sup>

“Overgrazing” of ineffective and harmful practices on the “medical commons” is a stubborn problem in obstetrics. When we recount the inappropriate and unethical use of intravenous ethanol as a tocolytic agent three decades ago, resident



physicians today find it laughable. Few realize, however, that contemporary tocolysis with intravenous Epsom salt (magnesium sulfate) may seem equally ludicrous three decades from now. Tocolysis with magnesium sulfate is ineffective, and the practice should stop.

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