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Review Article

Facts about Magnesium Sulfate: Time to Revise the Safety Concern in Obstetric Use

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Abstract

Magnesium sulfate ($MgSO_4$) is the agent most commonly used for treatment of eclampsia and prevention of eclampsia in patients with severe pre-eclampsia. Another commonly practiced off-label use of this drug is in preventing preterm labor in pregnant women where the duration of the treatment might be more than one week. It is usually given either by intramuscular or intravenous route. After administration, about 40% of plasma magnesium is bound with protein. The unbound magnesium ion diffuses into the extravascular extracellular space and then diffuses into bone. It also crosses the placenta and fetal membranes and then diffuses into the fetus and amniotic fluid. Magnesium is almost exclusively excreted in the urine; 90% of the dose is excreted during the first 24 hours after an intravenous infusion of $MgSO_4$. The clinical effect and toxicity of $MgSO_4$ can be linked to its concentration in plasma. A concentration of 1.8–3.0 mmol/L has been suggested for treatment of eclampsia. The actual magnesium dose and concentration needed for prophylaxis have never been estimated. Maternal toxicity is rare when $MgSO_4$ is carefully administered and monitored. Deep tendon reflexes, respiratory rate, urine output and serum concentrations are the most common variables for monitoring the toxic effect. Currently the United States (US) Food and Drug Administration (FDA) is advising health care professionals against using $MgSO_4$ injection for more than 5–7 days to stop preterm labor in pregnant women (off-label use). Administration of $MgSO_4$ injection to pregnant women for more than 5–7 days may lead to low calcium levels and bone problems in the fetus, including osteopenia and fractures. The harmful effect in the fetus with the shortest duration is not established. In light of this new safety information, the drug label for $MgSO_4$ injection, USP 50% has also been changed, including changing the pregnancy category to D from A and denoting the effect as "New teratogenic effects". Similarly, the manufacturers of other $MgSO_4$ injection products have made similar changes to their drug labels. In this review, the currently available knowledge of the pharmacokinetics of $MgSO_4$ and its clinical usage for women with pre-eclampsia and eclampsia, its off-label use and safety concern regarding the warning announced by the FDA will be outlined.

***Key words**: Magnesium sulfate; Eclampsia; Pre-eclampsia; Preterm labor; Teratogenic effects*

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Introduction

Magnesium sulfate ($MgSO_4$) has been used in obstetrics for decades.[1] Although a variety of tocolytics are used in clinical practice, $MgSO_4$ remains one of the most commonly used tocolytic agents. This drug has been evaluated and used for its tocolytic properties for nearly 50 years.[2,3] It is approved to prevent seizures in pre-eclampsia (a condition in which the pregnant woman develops hypertension and proteinuria) and for control of seizures in eclampsia. Both pre-eclampsia and eclampsia are life-threatening complications that can occur during pregnancy. Pre-eclampsia can lead to eclampsia, seizures, stroke, multiple organ failure and

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death of the woman and/or baby. Many practitioners use long courses of $MgSO_4$, sometimes for months. $MgSO_4$ is usually given through a vein until contractions have slowed and the mother's cervix has stopped thinning (effacing) or opening (dilating). Most recently, prevention of cerebral palsy in preterm infants has become another indication for administration of $MgSO_4$ to the mother.[4,5]

$MgSO_4$ is not a benign drug. It has been associated with significant adverse drug reactions, overdose (primarily from medication administration errors) and the potential for increased blood loss at delivery. Several minor side effects including feeling of warmth, flushing, nausea and vomiting, muscle weakness, somnolence, dizziness and irritation at the injection site may occur. Serious side effects are rare, but there may be loss of the patellar reflex (typically occurring at a serum concentration of 8–10 mEq/L) and respiratory depression (when serum magnesium level >13 mEq/L).[6,7] Magnesium is used as a tocolytic and may increase the rates of cesarean delivery, and peripartum infection and/or hemorrhage. Neonatal depressive effects may also be of concern.[8]

Physiological role of $MgSO_4$

Several studies have reviewed the molecular and cellular physiology of magnesium in details in health and pregnancy.[9-15] Magnesium, a divalent cation, is the fourth most common cation in the human body after sodium, potassium and calcium. It is the second most common intracellular cation after potassium. Intracellular magnesium is found predominantly in bone (53%) and in myocytes (27%)[9] and is localized in the nucleus, microsomes, and mitochondria.[10] Only 1% of total body magnesium is found extracellularly[11], with serum magnesium accounting for 0.3% of the total body magnesium content.[9] Approximately 62% of serum magnesium circulates in ionized form.[9] The normal serum magnesium level is 0.75–0.95 mmol/L (1.8–2.3 g/dL).[10] Serum magnesium levels decline in pregnancy, likely due in part to hemodilution.[13,14] In addition to serving as a cofactor for numerous reactions, including energy metabolism and nucleic acid synthesis, magnesium is implicated in regulation of adenylate cyclase, transmembrane ion flux, muscle contraction and neuronal activity, as well as controlling vasomotor tone, cardiac excitability and neurotransmitter release.[14] $MgSO_4$ is known to reduce spontaneous and induced myometrial contractions.[2,16] Magnesium is believed to effect contractility by competing with calcium in the sarcoplasmic reticulum, reducing the availability of calcium to participate in actin–myosin interaction and in myometrial repolarization. Magnesium is thought to act through both intra- and extracellular mechanisms resulting in decreased intracellular calcium availability by blocking channel-dependent influx of extracellular calcium and also by blocking agonist stimulated release of intracellular calcium via inositol 1,4,5-triphosphate receptor/channels.[17,18] In vitro, $MgSO_4$ has been demonstrated to reduce spontaneous myometrial contractions at a concentration of 2–3 mmol/L (4–6 mEq/L), but suprapharmacologic level (8–16 mEq/L) is required to inhibit agonist-mediated cyclic uterine activity.[17-19]

$MgSO_4$ therapy in pre-eclampsia

Though the use of $MgSO_4$ is widespread and effective, its mechanism of action in pre-eclampsia remains unclear. Several possible mechanisms of action have been proposed. Its mechanism of action is likely multifactorial, encompassing both vascular and neurological mechanisms. Being a calcium antagonist, its effect on vascular smooth muscle to promote relaxation and vasodilatation may have a role in lowering total peripheral vascular resistance. In addition, $MgSO_4$ may have an effect on the cerebral endothelium to limit vasogenic edema by decreasing stress fiber contraction and paracellular permeability via calcium-dependent second messenger systems such as myosin light chain kinase. $MgSO_4$ may also act centrally to inhibit N-methyl-D-aspartate (NMDA) receptors, providing anticonvulsant activity by increasing the seizure threshold.[6]

Pharmacology and clinical pharmacology of $MgSO_4$

$MgSO_4$ has been evaluated and used for its tocolytic properties for nearly 50 years.[2,3] Typically a 4–6 g loading dose over 15–30 minutes is followed by a continuous infusion of 2 g/hr, and this infusion may be increased up to 4–5 g/hr as needed in the absence of significant clinical side effects or oliguria. Dosage of $MgSO_4$ must be carefully adjusted according to individual requirement and response and administration of the drug should be discontinued as soon as the desired effect is obtained.

Both intravenous (IV) and intramuscular (IM) administrations are appropriate. IM administration of

the undiluted 50% solution results in therapeutic plasma levels in 60 minutes, whereas IV doses will provide a therapeutic level almost immediately. The rate of IV injection should generally not exceed 150 mg/minute (1.5 mL of a 10% concentration or its equivalent), except in severe eclampsia with seizures.

Solutions for IV infusion must be diluted to a concentration of 20% or less prior to administration. The diluents commonly used are 5% dextrose solution and 0.9% sodium chloride solution. Deep IM injection of the undiluted (50%) solution is appropriate for adults, but the solution should be diluted to a 20% or less concentration prior to such injection in children.

$MgSO_4$ in eclampsia

In severe pre-eclampsia or eclampsia, the total initial dose is 10–14 g of $MgSO_4$. Intravenously, a dose of 4–5 g in 250 mL of 5% dextrose solution or 0.9% sodium chloride solution may be infused. Simultaneously, IM doses of up to 10 g (5 g or 10 mL of the undiluted 50% solution in each buttock) are given. Alternatively, the initial IV dose of 4 g may be given by diluting the 50% solution to a 10 or 20% concentration; the diluted fluid (40 mL of a 10% solution or 20 mL of a 20% solution) may then be injected intravenously over a period of 3–4 minutes. Subsequently, 4–5 g (8–10 mL of 50% solution) is injected intramuscularly into alternate buttocks every four hours, depending on the continuing presence of the patellar reflex and adequate respiratory function. Alternatively, after the initial IV dose some clinicians administer 1–2 g/hr by constant IV infusion. Therapy should continue until paroxysms cease. A serum magnesium level of 6 mg/100 mL is considered optimal for control of seizures. A total daily (24 hour) dose of 30–40 g should not be exceeded. In the presence of severe renal insufficiency, the maximum dosage of $MgSO_4$ is 20 gm/48 hrs and frequent serum magnesium concentrations must be obtained.

$MgSO_4$ affects the central nervous system (brain and spinal cord) of the mother. If too much $MgSO_4$ is given, the mother's reflexes will be slowed. Reflexes are usually checked about every 2–4 hours while the mother is on this medication. It also affects the central nervous system of the fetus. If this medication has been given to the mother in large doses and the baby is born before the drug is cleared off from the mother's body, the baby may have temporary problems with breathing right after birth. These problems can be quickly reversed with medicine.[20-31]

Review of several studies regarding the effect of $MgSO_4$ on mother and newborn

Several studies have been carried out on pregnant women to observe the side effects of $MgSO_4$ on the mother as well as on the newborn. The FDA identified 18 cases reported in FDA's Adverse Event Reporting System describing skeletal abnormalities in neonates exposed to $MgSO_4$ in-utero.[20,21,23,32] $MgSO_4$ was administered to mothers for tocolysis in pregnancy. The average duration of in-utero exposure to $MgSO_4$ was 9.6 weeks (range 8–12 weeks) and the estimated average total maternal dose administered was 3,700 grams. The published case series describes neonates developing skeletal abnormalities related to osteopenia; some developed multiple fractures involving the ribs and long bones.[32] The osteopenia and fractures were transient and resolved in cases when the outcome was reported. Based on these literature cases, it is plausible that bone abnormalities in neonates are associated with prolonged in-utero exposure to $MgSO_4$. Osteopenia and fractures may result from hypermagnesemia, which in turn causes hypocalcemia in the developing fetus.[20,21,23,32]

FDA also reviewed published epidemiologic studies.[20,22,24,25,27,28,30] One of these studies found a statistically significant increase in bone abnormalities in neonates with in-utero exposure to $MgSO_4$ for >7 days, compared to those exposed for <3 days.[28] Another study found a significant difference at birth in the serum values of magnesium, calcium, phosphorus and osteocalcin (a marker of bone formation) between neonates unexposed to $MgSO_4$ and those exposed in-utero to $MgSO_4$ for more than 1 week; there was no difference in radius bone mineral content in the two groups.[25] In these studies, the neonatal bone abnormalities described in association with in-utero $MgSO_4$ exposure beyond 5–7 days included radiographic findings of radiolucent transverse metaphyseal bands of long bones such as the humerus. Most of the epidemiological studies reviewed were based on retrospective reviews of charts in individual hospitals; none of the reviewed studies involved large electronic health care databases. The long-term clinical significance of altered laboratory parameters and/or radiographic findings suggestive of bone abnormalities found in these studies is unclear because long-term follow-up data

are not available in many of these studies. In one study, 11 babies who had shown bone abnormalities at birth manifested no radiographic bone abnormality at 1 and 3 years of age.[24]

In the past, $MgSO_4$ was thought safe for babies whose mothers were prescribed this drug. However, doctors are debating the significance of one 1997 study that challenges this view.[32] In the University of Chicago a study was conducted in 1997 and found an increased number of neonatal deaths in women who were prescribed $MgSO_4$ for preterm labor in comparison to those women who were given another preterm labor drug (ritodrine, terbutaline, indomethacin or nifedipine). A second group of women with advanced cervical dilation, but not eligible for preterm labor drugs received either a 4 gm dose of $MgSO_4$ or a placebo (saline). The women who received $MgSO_4$ dose or doses had a higher rate of neonatal deaths (8 deaths out of 75 pregnancies) than the control group (1 death out of 75 pregnancies). The difference was statistically significant.[32] More studies are needed before definite conclusions can be made. In addition, because of the significant risk of developing eclampsia, the benefits of a woman being on $MgSO_4$ may outweigh the risks to her and also to the baby.

A retrospective cohort study was carried out between January 2000 and February 2009 over 6654 women with pre-eclampsia who were treated with IV $MgSO_4$ beginning with a 6 gm dose, followed by 2–3 gm/hr infusion. Total 88 (6%) infants were diagnosed with hypotonia. As maternal serum magnesium concentrations increased before birth, values of 1-minute and 5-minute Apgar scores became low and incidence of intubation in the delivery room, admission to special care nursery and hypotonia significantly increased.[33]

Another retrospective study was conducted from 1995 to 2003 in pregnant women who received tocolytic $MgSO_4$. Cases (n=78) who received $MgSO_4$ for >48 hrs were compared to controls (n=77) who received it ⩽48 hrs for maternal side effects and neonatal outcome. The median neonatal magnesium level was significantly higher in cases 3.3 versus 2.6 mg/dL (p=0.016); however, neonatal mortality and morbidity rates were similar in both groups. Abnormal bone mineralization was encountered in 3 neonates (cases).[22]

More than 40 years ago, Lipsitz and English[34] reported a case series of six infants who had hyporeflexia, hypotonia and respiratory depression which were attributed to $MgSO_4$ given to the mother. Lipsitz later reported a larger case series including 37 infants in which he found a trend toward lower Apgar scores in association with maternal $MgSO_4$ therapy.[35] Stone and Pritchard[36] were unable to confirm changes in Apgar scores in 118 infants born of women given $MgSO_4$ for prevention of eclampsia. Donovan and colleagues[37] reported decreased muscle tone in 20 newborn infants associated with maternal magnesium levels. Chesley[38] found cord blood magnesium levels 70–96% of magnesium levels in the mother with a progressive increase in fetal levels as the duration of maternal $MgSO_4$ therapy lengthened. Most of the literatures available till now have dealt with the information on the neonatal effects of $MgSO_4$. In 2008, Rouse and colleagues[4] randomized $MgSO_4$ infusions or placebo in 2241 women delivered between 24 and 31 weeks gestation to find out the effects of $MgSO_4$ on perinatal death and/or cerebral palsy at 2 years of age. $MgSO_4$ therapy was not found to be associated with perinatal death, neonatal hypotonia or any other neonatal morbidities. However, such therapy was associated with a significant reduction in cerebral palsy, especially in infants born between 24 and 27 weeks gestation.

A systematic review was done on maternal and infant outcomes following $MgSO_4$ therapy and addressed the issue of drug safety.[39] This review included studies from both developed and developing countries. Findings indicated that the use of $MgSO_4$ for pre-eclampsia reduced the risk of progression of the disease and found that the use of the drug among patients with eclampsia was associated with lower risks of maternal death, recurrent seizures and major morbidity. Other clinical reviews and toxicology studies also indicate that the drug is safe for indicated purposes in recommended dosages according to standardized protocol for administration and monitoring.[40-42]

Recent updates on prolonged use of $MgSO_4$ issued by FDA

$MgSO_4$ is approved to prevent seizures in pre-eclampsia and for control of seizures in eclampsia. Both pre-eclampsia and eclampsia are life-threatening complications that can occur during pregnancy. Pre-eclampsia can lead to eclampsia, seizures, stroke, multiple organ failure and death of the woman and/or

baby. FDA warns professionals against using $MgSO_4$ injection for more than 5–7 days to stop preterm labor in pregnant women. This use of the drug is off-label, which means that it is not an FDA-approved use of the drug. Administration of $MgSO_4$ injection in pregnant women longer than 5–7 days may lead to low calcium levels and bone problems in the developing baby or fetus, including thin bones called osteopenia and fractures. The shortest duration of treatment that can result in harm to the baby is not known. In light of this new safety information about low calcium levels and bone problems in the developing baby, the following information is added to the drug label for $MgSO_4$ injection, USP 50%. A new warning states that continuous administration of $MgSO_4$ injection beyond 5–7 days in pregnancy for the treatment of preterm labor can cause low calcium levels and bone changes in the baby. By changing the pregnancy category to D from A, a new teratogenic effects section conveys that there is potential harm to developing babies. This section also includes the concerns described under the new warning. Pregnancy category D means there is positive evidence of human fetal risk, but the potential benefits from using the drug in pregnant women may be acceptable in certain situations despite its risks. Pregnancy category A means that adequate and well controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters. A new Labor and Delivery section emphasizes that continuous administration of $MgSO_4$ injection to treat preterm labor is not approved and that the safety and efficacy of use of $MgSO_4$ are not established. The manufacturers of other $MgSO_4$ injection products have made similar changes to their drug labels.

Facts about $MgSO_4$ injection

Magnesium is an essential mineral present in the human body in large amounts, mostly in bones. People obtain most of the magnesium in their bodies through diet. High or low levels of magnesium can affect the nervous system which includes brain, spinal cord and nerves. The metabolism and distribution of other minerals in the body such as calcium and potassium are often linked to levels of magnesium. The continuous administration of $MgSO_4$ injection to treat preterm labor is not FDA-approved, which means the safety and effectiveness of this use are not established.[43]

Conclusion

Maternal mortality in the developing world is receiving increasing attention and it is a key emphasis of the millennium development goals (MDGs). The World Health Organization (WHO) reports that hemorrhage/ bleeding, infections, unsafe abortions and eclampsia are common causes of maternal mortality, especially in developing countries. Severe pre-eclampsia and eclampsia-related deaths are common causes of preventable maternal deaths. Ninety nine percent of these deaths occur in low and middle income countries like Bangladesh. WHO has recommended the use of $MgSO_4$ as a safe and low-cost drug to manage severe pre-eclampsia and eclampsia. Studies have demonstrated that the drug significantly lowers the possibility of seizures in women with severe pre-eclampsia or eclampsia, prevents progression from severe pre-eclampsia to eclampsia and generally lowers maternal mortality. Furthermore, magnesium has been used as the standard drug for tocolysis during treatment of premature labor as off-label use and other drugs have been compared to it. Due to the warning issued by the FDA and also categorization of it as a teratogenic drug, the drug needs to be used cautiously and the risk assessment should be solely based on the benefits. Strict monitoring of drug scheduling and dose adjustment is highly recommended when it is absolutely indicated.

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