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Magnesium Sulfate for Fetal Neuroprotection

Background

A number of randomized controlled trials and meta-analyses have recently been published on the use of magnesium sulfate (MagSO4) before anticipated preterm birth for neuroprotection (1,2,3,4,5,6). The evidence from these trials is somewhat weak, but a benefit in preventing cerebral palsy (CP) in survivors of preterm birth (PTB) is demonstrated. The number needed to treat to prevent one case of CP is 46. There are several potential mechanisms of perinatal brain injury where there is biologic plausibility for the utility of MagSO4 (7).

The American Congress of Obstetricians and Gynecologists (ACOG) has published a Committee Opinion on this topic, cautiously endorsing its use for this purpose (8). However, they go on to caution that institutions electing to use MagSO4 for this purpose develop specific guidelines in accordance with one of the protocols used in the above mentioned trials. While most of our very preterm labor patients are delivered at an institution with a level III neonatal intensive care unit, we do manage the transports, and the need to institute MagSO4 for neuroprotection becomes an issue for us. It should be noted that there was no evidence that MagSO4 reduced the frequency of delivery within 48 hours when compared to placebo, so it is not recommended that it be used as a primary tocolytic agent.

In a 2014 report from Duke ELBW infants (78.3%) were exposed to Mg during MagSO4 compared with 50.6% and 60.8% before and after, respectively. (14) Incidence of SIP on protocol was 30.4% vs 12.9% off protocol ($P = 0.03$). GA was strongly associated with SIP ($P < 0.01$). Antenatal Mg dose was also associated with SIP/death regardless of epoch (odds ratio 9.3 (1.04–104.6)), but increased SIP/death was limited to those 25 weeks gestation.

A focused review from Providence Alaska Medical Center in Anchorage raised similar questions in very premature fetuses < 25 wks EGA and suggested using the lowest dose possible for the shortest duration possible until further data is available.

Summary of the Evidence

The largest randomized controlled trials (RCT) and meta-analyses are summarized here:

1. Crowther C, et al. ((2003) RCT. n = 1255. Subjects were included if PTB anticipated within 24 hours at less than 30 weeks gestation. The protocol employed a loading dose of 4g and a maintenance dose of 1 g/h for up to 24 hours. The relative risk (RR) for CP in survivors was 0.83 (CI 0.64-1.03).
2. Marret S, et al. (2007) RCT. n = 688. Included all women in PTL <33 weeks. A single loading dose of 4 g was given. RR for CP: 0.70 (CI 0.41-1.19).

3. Rouse DJ, et al. (2008) RCT. n = 2241. Women at high risk of PTB (87% PPROM) at <32 weeks included. Loading dose 6g, maintenance dose 2 g/h for 12 hours. RR for CP: 0.55 (0.32-0.95).
4. Doyle LW, et al. (2009) meta-analysis. n = 6145. RR for CP: 0.69 (0.54-0.87).
5. Conde-Agudelo A, et al. (2009) meta-analysis. n = 5357. RR for CP: 0.69 (0.55-0.88).
6. Costantine MM, et al. (2009) meta-analysis. n = 5235. RR for CP: 0.70 (0.55-.089).

Guideline for Use of MagSO4 for Fetal Neuroprotection

A. Indications:

1. Women with preterm labor (defined as regular at least every 5 minutes uterine contractions accompanied by cervical change, and/or positive fetal fibronectin (fFN), and/or transvaginal ultrasound cervical length <1.5 cm) at or less than 32 weeks gestation, with either a singleton or twin pregnancy, who are expected to deliver within the next 24 hours.
2. Women with preterm premature rupture of membranes (PPROM) (documented by usual clinical criteria of pooling and ferning, and confirmed if necessary by oligohydramnios on ultrasound or a positive dye test), at or less than 32 weeks gestation, upon diagnosis, either in active labor or not.

B. Exclusions:

1. Women with a short cervix on ultrasound not anticipated to deliver within 24 hrs.
2. Women with preterm contractions without cervical change, or women with a negative fFN.
3. Women who are being induced preterm for severe preeclampsia who would receive MagSO4 for a more prolonged period, and possibly at a different dose.
4. Women who have not delivered within 12 hours of admission for preterm labor or PPROM.
5. Please note the management changes for fetuses ≤ 25 wks EGA below

C. Procedures:

1. A mainline IV of lactated ringers or saline solution should be running.
2. A Foley catheter should be inserted for accurate intake and output (may be omitted if provider so orders and accurate I&O able to be obtained).
3. An oxygen saturation monitor should be in place.
4. External fetal monitoring should be continuous (as able) during the time of the infusion.
5. A loading dose of MagSO4 6 g IV over 20 minutes should be given.
6. A maintenance dose of MagSO4 of 2 g/h should be continued for 12 hours.

7. Other orders for tocolysis, antenatal corticosteroids, and group B strep prophylaxis as per provider orders.
8. The infusion should be stopped at 12 hours if delivery has not occurred.
9. If delivery is again considered imminent (resumption of active labor and cervix >4 cm dilated) within 12 hours after the infusion has been discontinued, a repeat 6 g bolus is suggested and the infusion may be resumed at 2 g/h. The total length of maternal exposure should be less than 24 hours, even if MagSO4 is given in divided doses.
10. If tocolysis is necessary, consider NSAIDs as first line agents, followed by nifedipine as the next line agent.

Fetuses ≤ 25 wks EGA

1. Apply all above, except use a 4 gm MagSO4 bolus and run at 1 gm/hr for 12 hrs.

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