MgSO4 for the Prevention of Cerebral Palsy in Preterm Infants

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Cerebral Palsy

- Affects 2 - 3 per 1,000 live births
- 80 times more likely in 24-27 week survivors
- 25% cannot walk
- 30% mentally retarded
- Prevalence rose 20% 1960 to 1986

MgS04 Exposure and CP
Nelson and Grether, Pediatrics 1995

• 75 VLBW control infants, without CP
• 42 VLBW infants with CP, survived to 3 yrs
• Amongst survivors without CP 36% had received MgSO4 prior to delivery
• Amongst survivors with CP only 7% had received MgSO4 prior to delivery
• OR 0.14 (95%CI 0.05 – 0.51)
• Neuroprotective benefit persisted independent of steroids or preeclampsia

Nelson KB, Grether  JK. Pediatrics 95:263, 1995
ACTOMAG Trial
Crowther et al, JAMA, 2003

- 1,062 women < 30 wks expected deliver within 24 hrs

- Randomised to:
  - MgSO4, 4g load, 1g/hr iv infusion
  - Placebo load and iv infusion

- 99% follow-up to 2 years of age
# ACTOMAG Trial
Crowther et al, JAMA, 2003

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MgSO4 (n=535)</th>
<th>Placebo (n=527)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>6.8%</td>
<td>8.2%</td>
<td>0.83 (0.54-1.27)</td>
</tr>
<tr>
<td>Gross motor dysfunction</td>
<td>3.4%</td>
<td>6.6%</td>
<td>0.51 (0.29-0.91)</td>
</tr>
</tbody>
</table>

Crowther CA et al. JAMA 290:2669, 2003
Hypothesis:
Maternal administration of MgSO4 will prevent cerebral palsy in the offspring of women at high risk for early preterm birth
BEAM – Study Design

• Randomised trial
• Placebo-controlled
• Double-masked
• 20 MFMU Network centres in US
• 1997 - 2004
BEAM – Study Design

• Eligibility:
  • Singleton or twin pregnancy
  • 24 0/7 to 31 6/7 weeks
  • PPROM
  • Advanced preterm labour (4-8cm)
  • Indicated preterm delivery

Rouse DJ et al. NEJM 359:895, 2008
BEAM – Study Design

Randomisation

IV MgSO4

Placebo

6g iv load

2g / hr iv infusion 12 hrs

Rouse DJ et al. NEJM 359:895, 2008
BEAM – Primary Outcome

• Composite outcome of:
  • Moderate or severe cerebral palsy at exam by certified pediatrician at 2 yrs OR
  • Death (stillbirth or infant death by 1 yr)

Rouse DJ et al. NEJM 359:895, 2008
## BEAM – Results
### Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>MgSO4 (n=1,096)</th>
<th>Placebo (n=1,145)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>1.9%</td>
<td>3.5%</td>
<td>0.55 (0.32-0.95)</td>
</tr>
<tr>
<td>Death</td>
<td>9.5%</td>
<td>8.5%</td>
<td>1.12 (0.85-1.47)</td>
</tr>
</tbody>
</table>

Rouse DJ et al. NEJM 359:895, 2008
# BEAM – Results

Cerebral Palsy*

<table>
<thead>
<tr>
<th></th>
<th>MgSO4</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(40 / 942)</td>
<td>(74 / 1,002)</td>
</tr>
<tr>
<td>Mild</td>
<td>2.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Severe</td>
<td>0.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Total</td>
<td>4.2%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

* *P = 0.004*

Rouse DJ et al. NEJM 359:895, 2008
# BEAM – Results

**Neonatal Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>MgSO4 (n=1,096)</th>
<th>Placebo (n=1,145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>1410</td>
<td>1424</td>
</tr>
<tr>
<td>5-min Apgar &lt;7</td>
<td>18.1%</td>
<td>18.5%</td>
</tr>
<tr>
<td>Hypotonicity</td>
<td>7.3%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Severe IVH</td>
<td>2.1%</td>
<td>3.2%</td>
</tr>
<tr>
<td>PVL</td>
<td>1.9%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

* = No significant differences for any variable

Rouse DJ et al. NEJM 359:895, 2008
BEAM – Results
Neonatal Outcomes

• Neonatal cord blood Mg levels checked on 1,507 infants
• No associations between cord blood Mg an delivery room resuscitation

Cochrane Meta-Analysis
Prenatal MgSO4 Exposure and CP

- Five Trials – 6,145 babies:
  - Cerebral Palsy: RR 0.68 (0.54-0.87)
  - Substantial GMD: RR 0.61 (0.44-0.85)
  - Death: RR 1.04 (0.92-1.17)

Doyle et al. Cochrane Database Syst Rev CD004661, 2009
• Conclusion:

The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth for the preterm fetus is now established.

Number needed to treat to prevent one case CP:
63 (95% CI: 43 – 87)

Doyle et al. Cochrane Database Syst Rev CD004661, 2009
• The available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants.
• In women at risk of early preterm imminent birth use magnesium sulphate for neuroprotection of the fetus when GA is less than 30 weeks, when birth is expected within 24 hours.
• Magnesium sulphate given before delivery reduces risk of CP in those infants born preterm.
• This effect greatest at early gestations and not associated with adverse outcomes.
How could MgSO4 be Neuroprotective?

- Protects against neuronal injury from asphyxia, trauma and glutamate activated calcium channels
- Cerebrovasodilator, improving cerebral blood flow
- Anti-oxidant effects
- Reduces pro-inflammatory cytokines

Volpe JJ. Biol Neonate 62:231, 1992
MgSO4 for Neuroprotection
Practical Issues

• Who to treat?
• When to treat?
• What dose to use?
• Contraindications?
• Monitoring?
MgSO4 for Neuroprotection

Who to Treat?

• Any very preterm patient at imminent risk of delivery within the next 24 hours:
  • PPROM with contractions
  • Preterm labour with cervix >4cm dilated
  • Indicated preterm delivery, such as severe preeclampsia or IUGR
• Readministration not recommended
• **DO NOT DELAY CORTICOSTEROIDS**
MgSO4 for Neuroprotection

When to Treat?

• Greater than 24 0/7 weeks gestation
• Less than 32 0/7 weeks gestation
  • No information on role outside these ages
  • Beneficial effect of MgSO4 appeared best at earlier gestational ages:
    • NNT for <32 wk group 56
    • NNT for < 30 wk group 46
• Ideally 4 hours before planned preterm birth

MgSO4 for Neuroprotection

What Dose to Use?

- **BEAM:** 6g load, 2g/hr
- **ACTOMAG:** 4g load, 1g/hr
- **PREMAG:** 4g load

- **BEAM** – Higher incidence maternal side effects:
  - 65% flushing
  - 15% nausea / vomiting
  - 4% infusion stopped due to adverse event

Rouse DJ et al. NEJM 359:895, 2008
MgSO4 for Neuroprotection
What Dose to Use?

- 4g loading dose with 1 g/hr infusion likely less side effects and likely as effective
- 100mls infused by pump over 30 mins
- 25mls per hr infused by pump for next 24 hrs
- If resource limitations an issue, may consider just 4g loading dose, without infusion
MgSO4 for Neuroprotection
Contraindications?

• Absolute contraindication:
  • Myasthenia gravis

• Relative contraindications:
  • Myocardial compromise (negative inotrope)
  • Respiratory compromise (respiratory depressant)
  • Concomitant use of Ca channel blockers
  • Reduced maintenance infusion if renal compromise
MgSO4 for Neuroprotection

Monitoring?

During 4g loading dose:

- Continuous fetal HR monitoring
- Maternal RR, HR and BP every 15 mins for 1 hour
- Check patellar reflexes after loading
  - Hold infusion if reflexes absent
- Observe for development of side effects
MgSO₄ for Neuroprotection

Monitoring?

During 1g/hr infusion:

• Continuous fetal HR monitoring
• Maternal RR, HR and BP hourly
• Hold if RR < 10-12 minute
  • Calcium gluconate 1g over 10 mins available
• Check patellar reflexes every 2-4 hours
  • Hold infusion if reflexes absent
• Observe for development of side effects
• No indication for serum Mg levels if asymptomatic
MgSO4 for Neuroprotection

Toxicity

MgSo4 concentrations (mmol/L) and side effects:

- **0.8 – 1.0**: Normal plasma concentration
- **1.7 – 3.5**: Therapeutic range preeclampsia
- **2.5 – 5.0**: ECG changes
- **4.0 – 5.0**: Reduced deep tendon reflexes
- **> 5.0**: Loss deep tendon reflexes
- **> 7.5**: Respiratory and CNS depression
- **> 12.0**: Cardiac arrest
MgSO4 for Neuroprotection

Conclusions

• Consider administering MgSO4 to any patient at imminent risk preterm delivery 24-32 wks

• 30% reduction in incidence of CP proven

• Need to treat 63 patients to prevent one case of CP

• MgSO4 has current widespread acceptance to prevent eclampsia, with NNT of 100
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