Magnesium Sulfate for Neuro-Protecton

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Magnesium Sulfate ?

Magnesium therapy, as an anticonvulsant was introduced into obstetric practice in the US over 100 years ago

No unanimity on the prophylactic use of magnesium for preeclampsia or to prevent recurrent seizures in women with eclampsia until recently

Magnesium Sulfate ?

Collaborative Eclampsia Trial

- 1687 women treated in 27 hospitals in 9 countries
- Magnesium Vs diazepam
  - Magnesium group had 52% lower risk of recurrent seizures
- Magnesium Vs phenytoin
  - Magnesium group had 67% lower risk of recurrent seizures

Magnesium Sulfate ?

Collaborative Eclampsia Trial

- Magnesium group (mothers)
  - Lower maternal mortality (NS)
  - Less likely to be intubated and ventilated
  - Less likely to develop pneumonia
  - Less likely to be admitted to ICU
- Magnesium group (neonates)
  - Less likely to be intubated or admitted to NBICU
- Eclampsia Collaborative Trial Lancet 1995;345:1455

Magnesium Sulfate: Can We Prevent Eclampsia ?

Magpie Trial

10,141 women from 175 hospitals in 33 countries

Eligibility: antepartum or ≤ 24 hours postpartum, BP 140/90, 1+ proteinuria

Randomized to 4 gram bolus of magnesium sulfate or placebo and then 1 gram per hour

Magnesium Sulfate ?

Magpie Trial

Women on Magnesium

- 58% lower risk of eclampsia consistently regardless of severity of preeclampsia at study entrance
- Less maternal mortality
- Lowered risk of abruptio placenta
- Less renal failure, liver failure or coagulopathy
- 30% of women received nifedipine, no adverse events noted
- Magpie Trial Lancet 2002;359:1877

Magnesium Sulfate

Used as a tocolytic agent

- 6 gram loading dose and then 2 grams per hour increasing by 1 gram per hour up to 4 grams per hour or until contractions are < 1/10 min

Magnesium sulfate tocolysis: Time to quit

- Cochrane systematic review (Cochrane Database Syst Review 2002;CD001060)
- Magnesium sulfate is ineffective as a tocolytic
- Grimes Obstet Gynecol 2006;108:986-9

Cochrane Systematic Review

2000 women in 23 trials

Magnesium sulfate is ineffective when compared with:

- No tocolytic
- Beta mimetics
- Calcium channel blockers
- Prostaglandin synthetase inhibitors
- Nitroglycerin
- Ethanol

Cochrane Systematic Review

Mg: Not only ineffective but harmful

The risk of fetal and pediatric death was increased significantly for infants exposed to magnesium
(RR 2.8, 95% CI 1.2-6.6)

Magnesium and total pediatric mortality (727 infants)

- Mittendorf (Lancet 1997;350:1517-8)
- Cox (AJOG 1990;163:767-72
- Scudiero (Obstet Gynecol 2000;96:178-82)

Scudiero
(Obstet Gynecol 2000;96:178-82)

Case control study: 14 years Chicago

Neonates
700-1249 grams
(27 – 31 weeks)

Multiple confounders were controlled for in this study

Total dose of magnesium > 48 grams
4 gram bolus and 2 grams / hour: exceed dose 24 hr

- **Perinatal mortality: OR 4.7; 95% CI (1.1 -20)**

Cerebral Palsy

Prevalence 2/1000 live births

Primary risk factor delivery < 34 weeks

Neonatal birth weight < 1500 grams

Other factors

- Chorioamnionitis
- APH
- Multiple pregnancy
- IVH
- Much less commonly perinatal asphyxia

MgSO4 and Cerebral Palsy

Link between Mg exposure and CP first noted in observational study

Subsequently a number of prospective trials have been undertaken

Prevalence is 3.6/1000 or 1/276 children

Lifetime costs for all people with CP in 2000 was 11.5 Billion Dollars

Nelson KB Pediatrics 1995;95263-9

Magnesium Sulfate MOA to Prevent CP

- Blocks NMDA receptors preventing the influx of Ca that causes cell death
- Vasoactive properties of Mg result in vasodilation with increased cerebral blood flow
- Inflammatory model of PTL, Mg has been shown to prevent neuronal injury from inflammatory cytokine
- Mg may have anti-apoptotic (programmed cell death) effects reducing neuronal loss

Association between Antenatal Mg in PTL and Adverse infant Outcomes (MAGNET)

PTL > 24 but < 34 weeks

- Tocolysis arm: PTL < 4cm, 4 gm bolus of Mg and 2-3 gm per hour (92) vs. other tocolytics
- Cerebral injury arm: > 4 cm, 4 gm Mg (57) [double blind] vs. saline
- Evaluation: 3 cranial US and follow up to 18 months for CP evaluation
- Adverse outcomes: IVH, PVL, CP , Death

Mittendorf AJOG 2002;186:1111-8

MAGNET

- Tocolytic arm: Mg (16/55, 29%) vs. Other tocolytics (9/51, 18%) [P=.18]
- Cerebral injury arm: Mg (11/30, 37%) vs. Saline (6/29, 21%) [P=.25]
- Combined: Mg (37/85, 32%) vs. 15/80, 19%) [P=.07]
- Cord Mg level and adverse outcomes < .60 mmol/L (6/42) vs. > .60 mmol/L (14/40) (P=.04)

MAGNET

10 infants with extremely adverse outcome (Grade III IVH, PVL, CP, Death vs. Less severe group (Grade 1 IVH)

- Extremely adverse: 31.9 gm Mg, BW 1430 gm
- Less severe: 2 gm Mg, BW 1803
- After statistical correction the BW became insignificant Mg remained significant

Effect of Magnesium Sulfate Given for Neuroprotection (ACTOMgSO4)

Prospective randomized double blind placebo control trial (Mg vs. isotonic saline)

16 tertiary hospitals in AU and NZ

1062 women (sing, twins, triplets, quad) < 30 weeks

- Planned or expected delivery within 24 hours
- 535 (633) Mg vs. 527 (629) to saline
- Mg: 4 gram load, 1 gram/hour to 24 hours (Mg given for neuroprotection not tocolytic)
- JAMA 2004;291:2669-2676

ACTOMgSO4

Primary outcomes

- Total pediatric mortality (stillbirth / neonatal / infant (up to 2 years)
- CP at age 2 years
- Combined CP and pediatric mortality

Maternal demographics, reason for PTB, birth wt, GA all similar

ACTOMgSO4

Total pediatric mortality

- Mg 13.8% vs.17.1%
  - (RR 0.83, 95% CI 0.64-1.09)

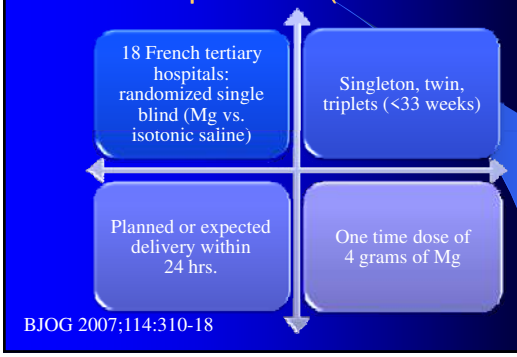
CP

- Mg 6.8% vs. 8.2%
  - (RR 0.83, 95% CI 0.54-1.27)

Death or CP

- Mg 19.8% vs. 24%
  - (RR 0.83,95% CI 0.66 – 1.03)

Effect of Magnesium Sulfate Given for Neuroprotection (PREMAG trial)



BJOG 2007;114:310-18

PREMAG trial

Outcomes

- Neonatal mortality prior to hospital discharge
- Abnormalities on neonatal cranial US
- Evidence of white matter injury

564 women

- 286 (354) Mg vs. 278 (341) placebo

PREMAG trial

Total mortality (stillbirth postnatal)

Mg 9.4% vs. 10.4% (OR 0.79, 95% CI 0.44-1.44)

Severe WMI

Mg 10% vs. 11.7% (OR 0.78, 95% CI 0.47-1.31)

Severe WMI and/or death

Mg 16.5% vs.17.9% (OR 0.86, 95% CI 0.55-1.34)

Effect of Magnesium Sulfate Given for Neuroprotection MFM Network BEAM Trial

Multicenter, placebo controlled, double blind trial, imminent delivery 24-31 weeks

6 gram Mg bolus followed by 2 grams/hr for up to 12 hrs. vs. placebo

Planned or expected delivery within 24 hrs

N ENGL J MED 2008;359:895-905

BEAM

Outcomes

- Stillbirth or infant death by 1 year of age
- Severe cerebral palsy at 2 years of age

Randomized 2241 women

- 1096 (1188) Mg vs. 1145 (1256) placebo

BEAM

- Moderate or severe CP or death
- Mg 11.3% vs. 11.7% RR 0.97 95% (CI 0.77-1.23)
- Moderate or severe CP alone
- Mg 1.9% vs. 3.5% RR 0.55 95% CI (0.32-0.95) P=0.03
- Death alone
- Mg 9.5% vs. 8.5% RR 1.12 95% CI (0.85-1.47)
- Death alone without anomalies
- Mg 8.3% vs. 8.1% RR 1.03 95% CI (0.77-1.37)

Meta-Analysis of Mg Exposure on Neuroprotection and Mortality in Preterm Infants

Primary outcome

- Death or CP by 18 – 24 m

Analysis

- BEAM
- ACTOMgSO4
- PREMAG
- Magpie
- MagNet

Constantine (Obstet Gynecol 2009;114:354-64

Meta-Analysis
Five RCT: 5235 Fetuses/Neonates

Study	GA Inclusion	Magnesium
Beam (2444)	24-31 weeks	6 gm bolus / 2gm/hr/12 hr Max 30 gm
ACTMgSO4 (1,255)	< 30 weeks	4 gm bolus/ 1 gm/hr/24hr Max 28 gm
PREMAG (688)	< 33 weeks	4 gm bolus Max 4 gm
Magpie (1593)	< 37 weeks	4 gm bolus/ 1 gm/hr/24hr Max 28 gm
MagNet (59) preventative (106) tocolytic	24-33 weeks	4gm Prev Max 4 gm Tocolytic 2-3 gm hr

Randomization Before 32-34 Weeks (5,235 Fetuses/Infants)

Primary Outcome	
Death or CP	RR 0.92, 95% CI 0.83 – 1.03
Death	RR 1.01, 95% CI 0.89 – 1.14
Death or Moderate to Severe CP	**RR 0.85, 95% CI 0.73 – 0.99**
CP of any Severity	**RR 0.70, 95% CI 0.55 – 0.89**
Moderate to Severe CP (only)	**RR 0.60, 95% CI 0.43 – 0.84**
NNT to prevent one case of CP at 18-24 months	**56 (95% CI 34-164)**

Randomization Before 30 Weeks (3,107 Fetuses/Infants)

Primary Outcome	
Death or CP	RR 0.91, 95% CI 0.81 – 1.03
Death of Moderate to Severe CP	**RR 0.84, 95% CI 0.71 – 0.99**
CP of any Severity	**RR 0.69, 95% CI 0.52 – 0.92**
Moderate to Severe CP (only)	**RR 0.54, 95% CI 0.36 – 0.80**
NNT to prevent one case of CP at 18-24 months	**46 (95% CI 26-187)**

Neuro-protection Studies Only

Primary Outcome	
Death or CP	**RR 0.86, 95% CI 0.75 – 0.99**
Death	RR 0.95, 955 CI 0.80 – 1.13
CP of any Severity	**RR 0.71, 95% CI 0.55 – 0.91**
Moderate to Severe CP (only)	**RR 0.85, 95% CI 0.73 – 0.99**
NNT to prevent one case of CP at 18-24 months	**52 (95% CI 30-184)**

Variations Among Studies

MgSO4 regimen varied among studies

- 4-6 gram bolus and then 4-30 grams
- MgSO4 as bolus or for 12 hours or for 24 hours

MgSO4 readily crosses the placenta and can be found in fetal serum in 1 hr. and AF in 3 hrs

Total dosage, infusions period, need for retreatment, and therapeutic window for neuroprotection is unknown

Who to Treat ?

Women with pregnancies at imminent risk for an early preterm delivery.

(< 34, < 32, < 30 weeks)

- Risk for CP
- NNT: < 32-34 / **56**: < 30 / **46**: < 28 / **29**

Probably needs to be on board for 4 hours prior to delivery

Review of Mg for Neuro-prophylaxis: Fact or Fiction

BEAM trial: Composite outcome, CP or death

- Death is a competing risk, if infant dies before first birthday cannot be assessed for CP
- Risk factors leading to death are also those which lead to CP
- No difference in moderate-severe CP and death between the Mg and placebo groups
- Mg group: decrease in CP but increased death, how many of 99 deaths needed to survive so CP outcome is NS (2)

Mg: Fact or Fiction

Meta-analysis: Studies were heterogeneous

Does statistical heterogeneity = clinical heterogeneity

- Should decision be based on RCT or meta-analysis : ASA for preeclampsia
- Meta-analysis: allows small studies or limited power to be combined, however they BEAM trial was adequately powered
- Combined outcomes from 4 trials vs. BEAM, 1 additional case from BEAM of CP or death to make results (NS)

MgSO4 for Neuro-protection

AJOG March 2011

GA: 23 – 31 6/7 weeks

- Load: 6 grams over 20 - 30 min
- Maintenance: 2 gm/hr up to 12 hrs. **30 gm**
- PTL again but < 6hr
- Restart Mg at 2gm/hr for up to 12 hours. **54 gm** > 6 hr
- 6 gm bolus + 2 gm/hr for up to 12 hr **60 gm**

KEMH Protocol Sept 2010

GA: < 30 weeks

- Load: 4 grams over 20 min
- Maintenance: 4 gm/hr up to 4 hours **8 gm**
- Do not retreat

UAMS Proposed Protocol

- **Gestational age of 24 – 34 week**
- **Imminent delivery (expected in the next 24 hours)**
- **Load 4 grams of Mg over 30 minutes then 1-2 grams per hour for up to 12 hours (this is to include the Mg given prior to and during transport)**
- **Planned delivery: Need to have Mg on board for 4 hours before the delivery; Give 4 grams of Mg (only – no hourly Mg maintenance) 4 hours before the planned birth (up to 34 wks)**

UAMS Proposed Protocol

- **After 12 hours of Mg, may switch to an alternative tocolytic (nifedipine or indocin) to complete steroids**
- **If patient were to be returned to labor and delivery with an imminent delivery and if has been > 24 hours since the Mg had been given and patient is < 32 weeks then may re-bolus with 4 grams of Mg. (one time only)**
- **If the patient has preeclampsia and the Mg is being used to prevent an eclamptic seizure , the Mg therapy may be extended as deemed appropriate by the Health Care team.**