Magnesium Sulfate for the Prevention of Cerebral Palsy

Dwight J. Rouse, MD

Brown University ~ Warren Alpert School of Medicine

Cerebral Palsy

- Related group of disorders
- Abnormal control of movement and posture
- Activity limitation
- Non-progressive damage or dysfunction developing fetal or infant brain

Cerebral Palsy

- Leading cause of chronic childhood disability
- Tragic and profound consequences
- 800,000 Americans
- $1M per person (2003)
- Preterm birth a leading risk factor (50X)

Neonatal Survival

< 1000 gms

1960 -- < 5%

1996 -- 80%

CP if Born Preterm: Stable

- Finland
- < 1000 gms
  - 1996-1997: 110/1000 survivors
  - 1999-2000: 120/1000 survivors

Tommiska V, et al. Pediatrics 2007; 119: 29

CP if Born Preterm: Decreasing

- Northern Alberta
- 20-27 Weeks
  - 1992-1994: 110/ 1,000 live births
  - 2001-2003: 22/1000 live births

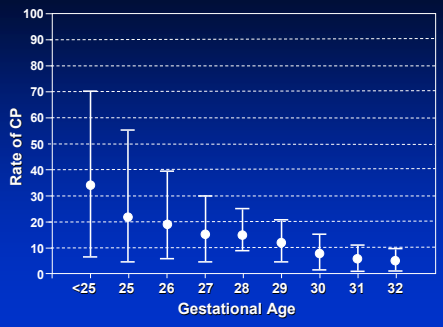
Robertson CMT, et al. JAMA 2007; 297:2733

CP if Born Preterm: Increasing

- Nova Scotia
- 24-30 weeks gestation
  - 1993: 44/1,000 live births
  - 2002: 100/1000 live births

Vincer, MJ, et al. Pediatrics 2006;118: e1621

Cerebral Palsy and Gestational Age



Murphy et al. BMJ 1997

Cerebral Palsy & Prematurity

Infants < 2500 gms at birth (5.3% of survivors) - 47% of CP

Infants < 1000 gms at birth (0.2% of survivors) - 8% of CP

Cummins et al., J Peds 1993

Cerebral Palsy & Prematurity

1986-1991

- < 2500 gms
  - 52% of CP
- < 1500 gms
  - 33% of CP

Winter S, Pediatrics 2003;110:1220

Nelson and Grether

- Case-Control Study (Pediatrics 1995)
  - Magnesium sulfate ↓↓ cerebral palsy
    - Potential mechanisms
      - Improve vascular stability
      - Prevent hypoxic damage
      - Mitigate cytokine / excitatory amino acid damage

Randomized Clinical Trial

Hypothesis

Maternally-administered $MgSO_4$ will prevent cerebral palsy in the offspring of women at high risk of early preterm birth

Rouse DJ, et al.
NEJM 2008;359:895

Study Design

- Randomized
- Placebo-controlled
- Double masked

Eligibility

- 24 weeks to 31 weeks, 6 days
  - Ruptured membranes
  - Advanced preterm labor (4-8 cm)
  - Indicated preterm delivery
- Singletons and twins

Exclusion Criteria

- Delivery anticipated within 2 hrs
- Cervical dilation > 8 cm
- Membrane rupture < 22 weeks
- Obstetrician unwillingness to intervene for fetal benefit
- Fetal anomalies or demise
- Hypertensive disorders
- Severe maternal disease
- Receipt of $MgSO_4$ within 12 hrs
- Candidate for tocolysis

Randomization

6 gm load

2 gm / hr X 12 hours

Primary Study Outcome

Composite

- Moderate or severe cerebral palsy at 2 year examination

or

- Stillbirth or infant death

Cerebral Palsy

- Neurological assessment for diagnosis
- Gross and fine motor assessment to determine severity

Cerebral Palsy
Diagnosis

Centrally certified pediatrician or pediatric neurologist

Cerebral Palsy
Diagnosis

At least 2 of 3

1) 30% delay in gross motor development
2) Abnormal
   - Muscle tone
   - Deep tendon reflexes
   - Coordination
   - Movement
3) Absence of protective reflexes
   Persistence of primitive reflexes

Cerebral Palsy
Severity

Moderate or severe

- Gross Motor Function Classification 2-5
  - Unable to walk without assistance
- Fine motor
  - Unable to grasp and release small objects

Palisano R, et al. Dev Med Child Neurol 1997;39:214-23

Sample Size

- Primary outcome rate: 14%
  - 6% death
  - 8% cerebral palsy
- 30% effect size
- 80% power, $\alpha = 0.05$
- 10% loss to follow-up
- N = 2,200

Statistical Analysis

- Intent to treat
- Analysis by pregnancy

Results

Recruitment

- December, 1997 through May, 2004
- 2,241 women
- 2-year follow-up:

  95% $MgSO_4$

  96% Placebo

Protocol Adherence

- 98% study drug loading dose
- 97% maintenance infusion
- 1.4% open label $MgSO_4$

Baseline Characteristics

	$MgSO_4$ (n = 1,096)	Placebo (n = 1,145)
Gestational age - wks	28.3 ± 2.5	28.2 ± 2.4
PPROM	86.4%	86.9%
Advanced preterm labor	10.6%	10.0%
Indicated delivery	3.0%	3.1%
Twin gestation	8.4%	9.7%
$MgSO_4$ prior to enrollment	18.3%	19.0%

Maternal Outcomes

	$MgSO_4$ (n = 1,096)	Placebo (n= 1,145)
Gestational age at delivery – wks	29.8 ± 3.1	29.7 ± 3.1
Corticosteroids	97%	98%
Chorioamnionitis	12%	12%
Cesarean delivery	38%	39%

Neonatal Outcomes

Outcome	$MgSO_4$ (n = 1,174)	Placebo (n= 1,244)
Birthweight - gm	1410 ± 567	1424 ± 577
5-minute Apgar < 7	18.1%	18.5%
Hypotonicity	7.3%	7.1%
Severe IVH	2.1%	3.2%
PVL	1.9%	2.3%

Primary Outcome

	$MgSO_4$ (N = 1,041) %	Placebo (N = 1,095) %	RR (95% CI)
CP or death	11.3	11.7	0.97 (0.77-1.23)
CP	1.9	3.5	0.55 (0.32-0.95)
Death	9.5	8.5	1.12 (0.85-1.47)

Primary Outcome: Major Malformations Excluded

	$MgSO_4$ (N= 997) %	Placebo (N = 1,063) %	RR (95% CI)
CP or death	10.0	11.0	0.91 (0.71-1.17)
CP	1.8	3.2	0.56 (0.32-0.99)
Death	8.3	8.1	1.03 (0.77-1.37)

Primary Outcome: Randomization < 28 Weeks

	$MgSO_4$ (N = 424) %	Placebo (N = 480) %	RR (95% CI)
CP or death	19.1	20.8	0.92 (0.71-1.19)
CP	2.8	6.0	0.47 (0.24-0.91)
Death	16.5	15.4	1.07 (0.79-1.44)

Cerebral Palsy

	$MgSO_4$ %	Placebo %
Mild	2.2	3.7
Moderate	1.5	2.0
Severe	0.5	1.6
Total	4.2	7.3

P = 0.004

Is there a toxic MgS04 dose?

Mg Dose Quartile (gm)	OR for Death	95% CI
1st (0-29)	1.45	0.80-2.62
2nd (29.1 -31.3)	0.57	0.28 –1.17
3rd (31.4- 44.10	1.16	0.61- 2.18
4th (44.2- 201)	1.01	0.48- 2.10

Excluding major malformations, adjusted for GA, race, and chorioamnionitis

Is there a toxic cord blood magnesium concentration?

Cord Mg (meq/L)	OR for Death	95% CI
1st (0-1.7)	Reference	--
2nd (1.8-2.6)	0.83	0.45-1.52
3rd (2.7-3.3)	1.61	0.86-2.99
4th (3.4-5.4)	0.82	0.36-1.84

Excluding major malformations, adjusted for GA, race, and chorioamnionitis

Crowther Trial

- 1,062 women randomized before 30 weeks
- $MgSO_4$
  - 4 gm load
  - 1 gm / hr
- 99 percent follow-up

Crowther CA, et al. JAMA 2003; 290:2669-76

Crowther Trial

Outcome	$MgSO_4$ (n = 535) %	Placebo (n = 527) %	RR (95% CI)
Death	13.8	17.1	0.83 (0.64-1.09)
CP or death	19.8	24.0	0.83 (0.66-1.03)
Substantial gross motor dysfunction	3.4	6.6	0.51 (0.29-0.91)

Marret Trial

- 573 women randomized before 33 weeks
- $MgSO_4$
  4 gm IV
- Universal follow-up of 688 infants

Gynécologie Obstétrique Fertilité 2008;36:278

Marret Trial

Outcome	$MgSO_4$ (n = 352) %	Placebo (n = 336) %	OR (95% CI)
Death	9.7	11.3	0.74 (0.42-1.32)
CP or death	16.1	20.2	0.65 (0.42-1.03)
Gross motor dysfunction	17.6	21.8	0.65 (0.41-1.02)

Other Randomized Trials

Magpie

1,544 women with severe pre-eclampsia

- < 37 weeks gestation
- $MgSO_4$ 4 gm IV load
- 1 IV gm/hr or 5 gm IM q 4°
- 2/3 of children selected for follow-up
- 73% assessed

Br J Obstet Gynaecol 2007;114:289-99

Other Randomized Trials

Magnet

149 women

- Neuroprotective Arm: 57 women
- Tocolysis Arm: 92 women

Lancet 1997;350:1517-8

Cochrane Meta-Analysis

Five Trials

6,145 babies

- Cerebral Palsy: RR 0.68, 0.54-0.87
- Substantial Gross Motor Dysfunction: RR 0.61, 0.44-0.85
- Death: RR 1.04, 0.92-1.17

Cochrane Meta-Analysis

Neuroprotective Trials (4)

4,446 babies

- Combined CP or Death RR 0.85, 0.74-0.98

Cochrane Meta-Analysis

Conclusion

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

NNT = 63

Conde-Aguedo and Romero

We found persuasive evidence that magnesium sulfate administered to women at high risk of preterm birth before 34 weeks of gestation reduces the risks of cerebral palsy in their children.

AJOG 2009; June; 595

Conde-Aguedo and Romero

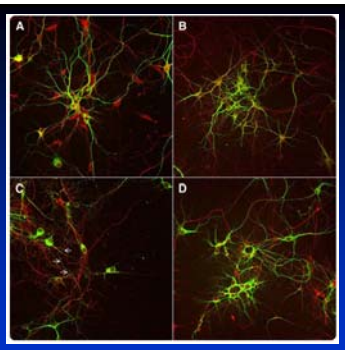
- **NNT < 34 weeks: 52**
- **Prevent one case of CP: $10,291**

AJOG 2009; June; 595

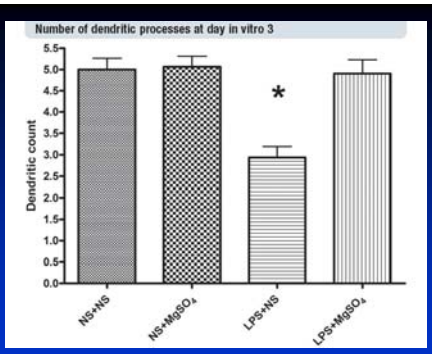
Neuroprotective Mechanisms

- **Active area of inquiry**
  - **UPENN-Mouse model of inflammation**
  - **LPS injected into peritoneum**
  - **+/- MagS04**
- **No effect**
  - **Pro-inflammatory cytokine expression**
  - **Cell death markers**
  - **Prooligodendrocyte, astrocyte development**

Burd et al. AJOG 2010; 2002:292.e1-9



Burd et al. AJOG 2010; 2002:292.e1-9



Burd et al. AJOG 2010; 2002:292.e1-9

Matrix metalloproteinase-9 (MMP9)

- May break down blood-brain barrier
  - Cytokine mediated cell injury
- Addition of MagS04
  - To cord plasma
    - ↓ed MMP9 by 25%
  - To HUVEC line
    - ↓ed MMP9 by 32%

Dolinsky et al. AJOG 2009, December, S171, #450

Considerations

$MgSO_4$

- Inexpensive
- Easy to administer
- Safe
- Used regularly

Considerations

- To prevent one case of moderate or severe cerebral palsy
  - Treat 63
  - Treat 30 (<28 weeks)
- To prevent one eclamptic convulsion
  - Treat 100

Conclusion

$MgSO_4$ protects the survivors of early preterm birth against cerebral palsy.

Conclusion

Widespread administration of magnesium sulfate prior to early preterm birth would safely prevent as many as 1000 cases of handicapping cerebral palsy in the United States alone.

There is no reason for us not to avail ourselves of this opportunity.

Magnesium Sulfate Before Anticipated Preterm Birth for Neuroprotection

The available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.

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