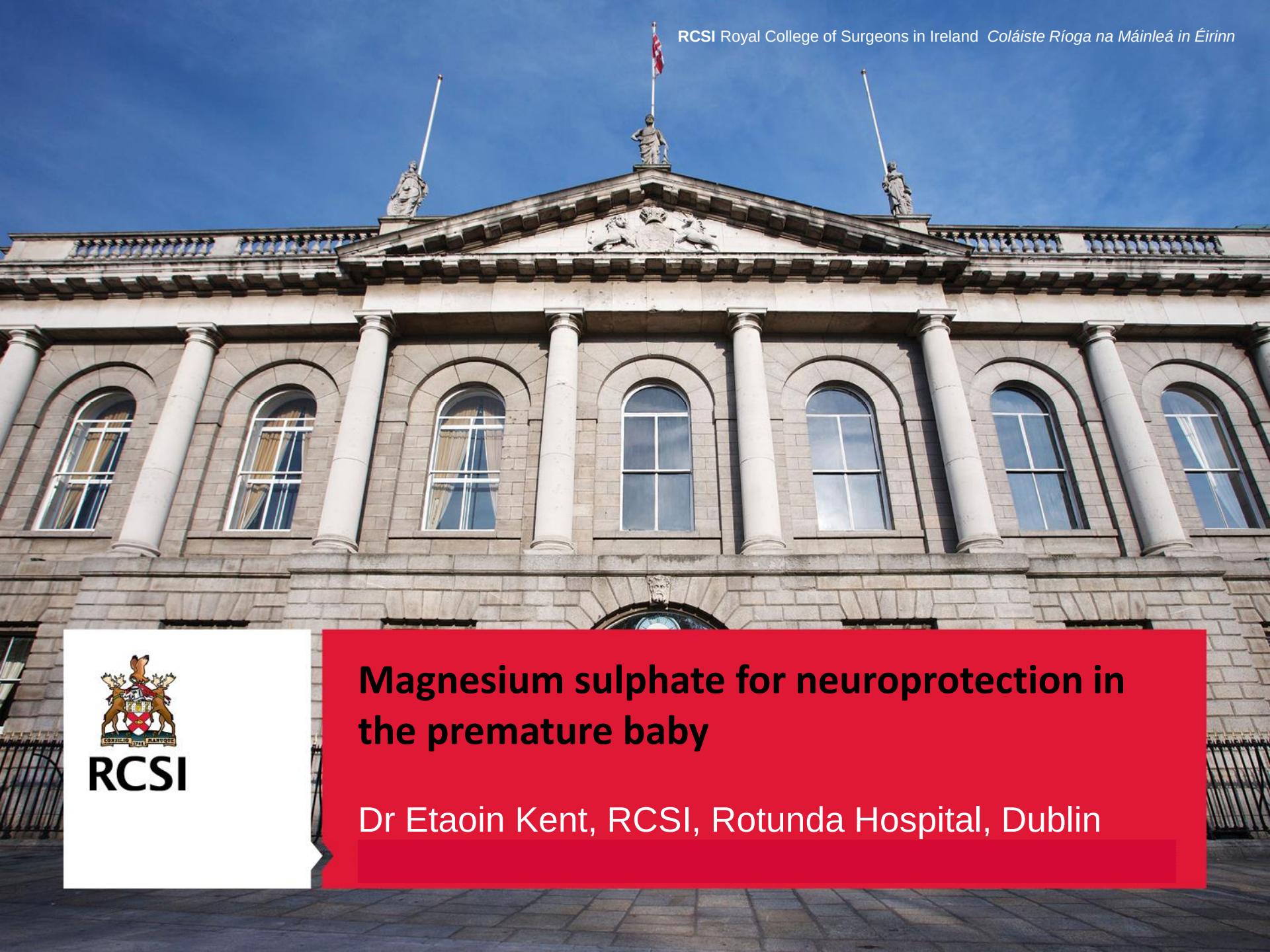


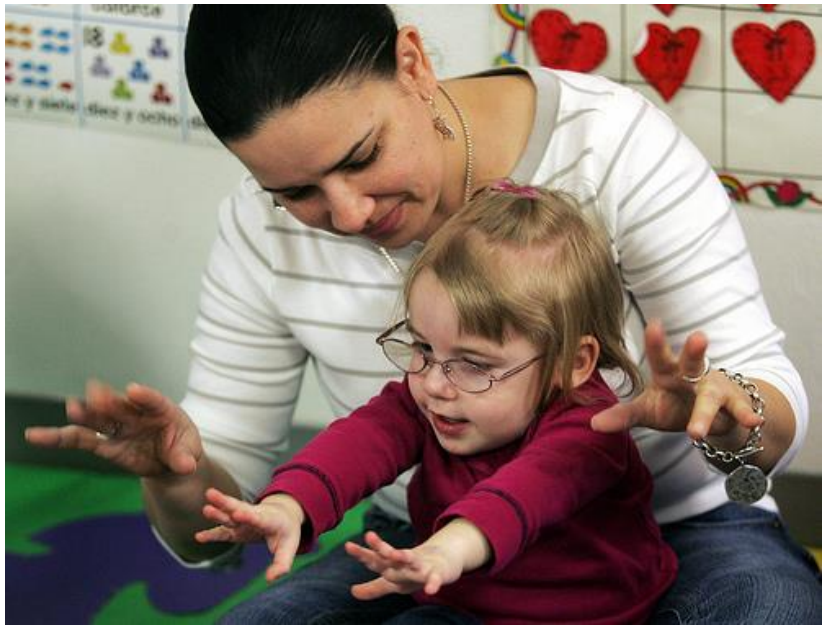
RCSI

Magnesium sulphate for neuroprotection in the premature baby

Dr Etaoin Kent, RCSI, Rotunda Hospital, Dublin

Cerebral Palsy

- Group of disorders characterised by abnormalities of movement/posture
- Non-progressive
- May be associated with cognitive impairment
- Caused by damage to the developing fetal or infant brain
- Prevalence approx. 3.6 per 1,000
- Significant economic burden



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Cerebral Palsy

- Increasing prevalence of preterm birth
  - Improved survival rates
  - Prevalence of cerebral palsy increasing
- Rates of cerebral palsy inversely proportional to gestational age at delivery
  - 22-27 wks: 14.6%
  - 28-31 wks: 6.2%
  - 32-36 wks: 0.7%
  - Term: 0.1%

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Background

- Case control studies suggested link between in utero exposure to $MgSO_4$ and reduced rates of CP
- Patients given $MgSO_4$ as tocolytic or for eclampsia prophylaxis

Kuban et al, 1992

Nelson et al, 1995

- Conflicting results from subsequent studies

- Several RCTs commenced to evaluate potential utility of $MgSO_4$ as a neuroprotective agent

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Mechanism of Neuroprotection

- Exact mechanism of action unknown

- Number of possible biological actions:
  - Reversal of hypoxic/ischaemic brain injury through blockage of NMDA receptor on oligodendrocytes
  - Protection against free radical injury
  - Vasodilatory activity
  - Reduction of vascular instability
  - Anti-apoptotic activity

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Evidence for Benefit

- Randomised Controlled Trials
  - ACTOMAG, Crowther et al, JAMA, 2003
  - PREMAG, Marret et al, BJOG, 2007
  - BEAM, Rouse et al, NEJM, 2008

- Cochrane review, Doyle et al, 2009

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Cochrane Review

Trial characteristics of the five randomised controlled trials contributing to the meta-analysis of Doyle *et al.*

Study	Gestation	Inclusion	Exclusion	Women	Fetuses	Regimen	Follow-up
Mittendorf[4] (MagNET)*	25-33 weeks	Singleton or twins, preterm labour.	Non-reassuring fetal status, infection or preeclampsia	149	165	4g load only (neuroprotection arm)	18 months
Crowther[5] (ACTOMgSO4)*	< 30 weeks	Singleton or twins. Delivery expected within 24 hours.	Second stage of labour, received magnesium sulphate this pregnancy.	1062	1255	4g load; 1g/hour maintenance	24 months
Marret[6] (PREMAG)*	< 33 weeks	Singleton, twins, triplets. Delivery expected within 24 hours.	Fetal abnormality, emergency caesarean delivery, contraindication to magnesium.	573	688	4g load only	24 months
Rouse[7] (BEAM)*	24-31 weeks	Singleton or twins. High risk for preterm delivery, preterm PROM, preterm labour (4-8cm), indicated delivery.	Delivery anticipated < 2 hours, major abnormality, PROM < 22 weeks, hypertension, preeclampsia.	2241	2444	6g load; 2g/hour maintenance	24 months
Duley[8] (MAGPIE)	All gestation	Preeclampsia and uncertainty whether magnesium sulphate indicated.	Myasthenia, hepatic coma, CI to magnesium.	1544	1593	4g load; 1g/hour maintenance, OR 5g IM four-hourly	18 months

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ACTOMAG Trial

Crowther et al, JAMA, 2003

- Multicentre RCT: 16 hospitals in Aus/NZ
- 1062 women
- Inclusion Citeria:
  - Gestation <30 wks
  - Delivery planned or expected within 24 hours
- Dosing: $MgSO_4$ 4g loading dose followed by 1g/hr infusion vs placebo
- Continued until delivery or for 24 hours

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ACTOMAG Trial

Crowther et al, JAMA, 2003

- Primary Outcomes:
  - Total paediatric mortality up to 2 years
  - CP at 2 years corrected
  - Combined outcome of death or CP at 2 years

- 99% follow up

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ACTOMAG Trial

Crowther et al, JAMA, 2003

Outcome	$MgSO_4$ (n=535)	Placebo (n=527)	RR (95% CI)
CP	6.8%	8.2%	0.83 (0.54-1.27)

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ACTOMAG Trial

Crowther et al, JAMA, 2003

Outcome	$MgSO_4$ (n=535)	Placebo (n=527)	RR (95% CI)
CP	6.8%	8.2%	0.83 (0.54-1.27)
Death or CP	19.8%	24.0%	0.83 (0.66 – 1.03)

RCSI

ACTOMAG Trial

Crowther et al, JAMA, 2003

Outcome	$MgSO_4$ (n=535)	Placebo (n=527)	RR (95% CI)
CP	6.8%	8.2%	0.83 (0.54-1.27)
Death or CP	19.8%	24.0%	0.83 (0.66 – 1.03)
Gross motor dysfunction	3.4%	6.6%	0.51 (0.29-0.91)

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Premag Trial

Marret et al, BJOG, 2007

- RCT: 18 centres in France
- Inclusion criteria:
  - < 33wks
  - delivery planned or expected within 24 hours

- 4g $MgSO_4$ over 30 mins vs placebo

- 564 women/688 infants

- Primary Outcome:
  - Severe white matter injury
  - Total mortality before discharge
  - Combined outcome

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Premag Trial

Marret et al, BJOG, 2007

- Reduction in all primary end points in $MgSO_4$ group – non-significant
- Secondary Outcomes: 2008, 2 year follow up
- Outcomes: Death, motor dysfunction, cerebral palsy, cognitive dysfunction
- Reduced rates of all secondary endpoints
- Significant reduction in combined outcome of death or gross motor dysfunction
    - OR 0.62; 0.41 – 0.93

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Beam Trial

Rouse et al, NEJM, 2008

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

Hypothesis:

Maternal administration of $MgSO_4$ will prevent cerebral palsy in the offspring of women at high risk for early preterm birth

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BEAM – Study Design

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

- Randomised trial
- Placebo-controlled
- Double-masked

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BEAM – Study Design

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

- Randomised trial
- Placebo-controlled
- Double-masked
- 20 MFMU Network centres in US
- 1997 - 2004

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BEAM – Study Design

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

- Eligibility:
  - Singleton or twin pregnancy
  - 24 0/7 to 31 6/7 weeks

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BEAM – Study Design

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

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

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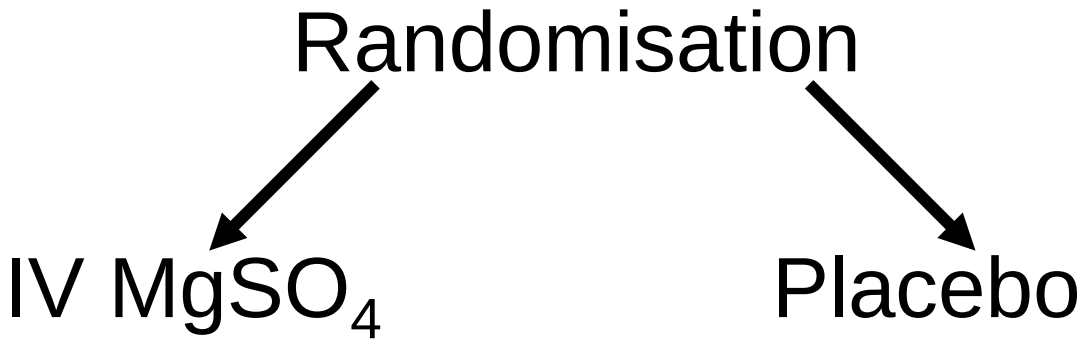
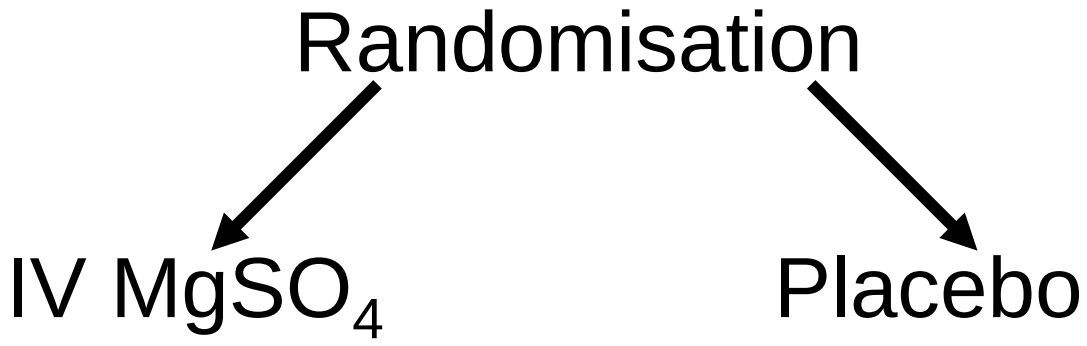
BEAM – Study Design



BEAM – Study Design



6g IV load

2g/hr IV infusion 12 hrs

BEAM – Primary Outcome

National Institute of Child Health and Human Development (NICHD)

- Composite outcome of:
  - Moderate or severe cerebral palsy at 2 yrs

    OR
  - Death (stillbirth or infant death by 1 yr)

- 2241 women
- 95.6% follow up

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BEAM – Results

Primary Outcome

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

	$MgSO_4$ (n=1,096)	Placebo (n=1,145)	RR (95% CI)
CP	1.9%	3.5%	0.55 (0.32-0.95)

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BEAM – Results

Primary Outcome

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

	$MgSO_4$ (n=1,096)	Placebo (n=1,145)	RR (95% CI)
CP	1.9%	3.5%	0.55 (0.32-0.95)
Death	9.5%	8.5%	1.12 (0.85-1.47)

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BEAM – Results

Cerebral Palsy*

	$MgSO_4$ (40 / 942)	Placebo (74 / 1,002)
Mild	2.2%	3.7%

* p =0.004

BEAM – Results

Cerebral Palsy*

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

	$MgSO_4$ (40 / 942)	Placebo (74 / 1,002)
Mild	2.2%	3.7%
Moderate	1.5%	2.0%

* p =0.004

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BEAM – Results

Cerebral Palsy*

	$MgSO_4$ (40 / 942)	Placebo (74 / 1,002)
Mild	2.2%	3.7%
Moderate	1.5%	2.0%
Severe	0.5%	1.6%
Total	4.2%	7.3%

* p =0.004

BEAM – Results

Neonatal Outcomes*

	$MgSO_4$ (n=1,096)	Placebo (n=1,145)
Birthweight (g)	1410	1424
5-min Apgar <7	18.1%	18.5%
Hypotonicity	7.3%	7.1%
Severe IVH	2.1%	3.2%
PVL	1.9%	2.3%

* = No significant differences for any variable

BEAM – Results
Neonatal Outcomes

National Institute of Child Health and Human Development (NICHD)

National Institute of Neurological Disorders and Stroke

- Neonatal cord blood Mg levels checked on 1,507 infants

- No associations between cord blood Mg and level of delivery room resuscitation

Johnson et al J Pediatr 2012

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THE COCHRANE COLLABORATION®

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D

Cochrane Database of Systematic Reviews 2009, Issue 1.
Art. No.: CD004661. DOI: 10.1002/14651858.CD004661.pub3.

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Cochrane Meta-Analysis
Prenatal $MgSO_4$ Exposure and CP

- Five Trials – 6,145 babies:

Doyle et al. Cochrane Database Syst Rev CD004661, 2009

RCSI

Cochrane Meta-Analysis
Prenatal $MgSO_4$ Exposure and CP

- Five Trials – 6,145 babies:

Cerebral Palsy RR 0.68 (0.54-0.87)

Doyle et al. Cochrane Database Syst Rev CD004661, 2009

RCSI

Cochrane Meta-Analysis
Prenatal $MgSO_4$ 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)

Doyle et al. Cochrane Database Syst Rev CD004661, 2009

RCSI

Cochrane Meta-Analysis
Prenatal $MgSO_4$ 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

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Cochrane Meta-Analysis
Prenatal $MgSO_4$ Exposure and CP

- Conclusion:

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

Doyle et al. Cochrane Database Syst Rev CD004661, 2009

RCSI

Cochrane Meta-Analysis
Prenatal $MgSO_4$ Exposure and CP

- 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

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ACOG Committee Opinion 2010

- The available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants

ACOG Committee Opinion #455. Obstet Gynecol 115:669, 2010

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Australian National Health and Medical Research Council Guideline 2010

- 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

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RCOG Committee Opinion 2011

- 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.

MgSO4 for Neuroprotection

Practical Issues

- Eligible patients
- Gestational Age
- Dosing regimen
- Optimal timing
- Adverse effects
  - Maternal monitoring
  - Fetal monitoring
- Contraindications

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Eligible Patients

- Consider administration in patients in whom preterm delivery is anticipated within subsequent 12 hours
  - Preterm labour with evidence of cervical dilatation
  - Preterm prelabour rupture of the membranes with regular uterine contractions
  - Severe preeclampsia/HELLP with planned delivery within the subsequent 12 hours
  - Severe intrauterine growth restriction with planned delivery with the subsequent 12 hours
  - Any other medical or obstetric condition necessitating preterm delivery

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Gestational Age

- Inclusion criteria varied between trials

- *Costantine et al, Obstet Gynecol, 2009*
  - Meta-analysis evaluating outcomes at different gestations
  - NNT before 32-34 weeks: 56
  - NNT before 28 weeks: 46

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Gestational Age

- *Rouse et al, NEJM*
  - Subanalysis of patients recruited <28 weeks
  - Greater risk reduction in CP
    - RR 0.45 (95% CI 0.23-0.87)

- **Recommendation**
  - **Consider administration in patients at imminent risk of PTD < 32 weeks**
  - **Emphasis on those delivering < 28 weeks**

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Dosing regimen

Loading dose

or

Loading dose + infusion

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Dosing Regimen

- Benefits with each different regimen
- Only study with statistically significant benefit – BEAM study – 6g loading/2g/hr infusion
- Cochrane review: Analysis limited to studies with loading dose and infusion
  - Reduction in CP
  - RR 0.68 (95% CI 0.52-0.91)

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Dosing Regimen

- No definite evidence regarding minimum effective dose
- BEAM: Higher incidence of maternal side effects

Recommendation:

- **4g loading dose over approx 20 mins followed by infusion of 1g/hr**
- **Limited resources/limited time: reasonable to administer loading dose only**

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Optimal Timing of Administration

- Mode of action: Adequate fetal levels of magnesium sulphate at time of delivery

- Animal studies:
  - Sustained infusion of $MgSO_4$
  - Crosses fetal blood-brain barrier within 2 hours
  - Concentrations increased in fetal forebrain after 4 hours

Hallak et al, AJOG, 1993

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Optimal Timing of Administration

- Study of fetal serum concentrations of $MgSO_4$ in patients undergoing FBS
  - Elevated levels of $MgSO_4$ in fetal serum at 1 hour and 3 hours post administration
  - Levels increased between 1 and 3 hours
  - Fetal serum magnesium concentrations correlated with maternal magnesium concentrations

Hallak et al, Obstet Gynecol, 1993

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Optimal Timing of Administration

Recommendation

- Further research necessary to define optimal timing
- Aim to commence magnesium sulphate approximately 4 hours prior to delivery
- If not possible to achieve a 4 hour window prior to delivery, magnesium sulphate should still be administered, as it is likely that benefit will be seen when administered within this time

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Adverse Effects

- Maternal side effects
  - Common:
    - Flushing, sweating
    - Vomiting
    - Headaches
    - Palpitations
  - Serious adverse effects:
    - Respiratory depression
    - Respiratory or cardiac arrest
    - Death

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Adverse Effects

- *Conde-Agudelo et al, AJOG 2009*
  - Systematic review of trials of $MgSO_4$ for neuroprotection
  - 70.7% reported side effects of flushing, nausea, vomiting, sweating
  - No increase in serious maternal events – death, cardiac respiratory arrest, pulmonary oedema, severe PPH, CS rates

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Monitoring

- While receiving magnesium sulphate patients require the following observations:
  - Assessment of maternal pulse rate, blood pressure, respiratory rate and deep tendon reflexes prior to commencement
  - Hourly assessment of maternal pulse, blood pressure, respiratory rate, deep tendon reflexes
  - Hourly urine output monitoring

- Discontinue magnesium sulphate if:
  - Respiratory rate drops to less than 12 breaths per minute
  - Diastolic BP drops more than 15mmHg below baseline
  - Deep tendon reflexes are absent
  - Urine output decreases to less than 100mls over 4 hours

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Monitoring

- Monitoring of serum magnesium levels only necessary if there is maternal renal compromise
- Calcium Gluconate 1g IV over 10 mins may be administered as an antidote to magnesium sulphate if there is significant maternal toxicity

- Fetal Monitoring
  - Continuous CTG monitoring recommended while patient receives magnesium sulphate

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Contraindications

- **Non reassuring fetal heart rate tracing:**
  - Delivery should not be delayed to facilitate administration of magnesium sulphate
- **Use of calcium channel blockers:**
  - Potential leading to hypotension and neuromuscular blockade
  - More intensive monitoring of maternal haemodynamic status.
- **Renal Insufficiency:**
  - Monitoring of maternal serum levels of magnesium with appropriate dose adjustment of rate of infusion with impaired renal function
- **Maternal Myasthenia Gravis**

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MgSO4 for Neuroprotection
Conclusions

- Consider administering $MgSO_4$ to any patient at imminent risk preterm delivery < 32 wks
- 30% reduction in incidence of CP proven
- $MgSO_4$ has current widespread acceptance to prevent eclampsia, with NNT of 100
- Need to treat 63 patients to prevent one case of CP

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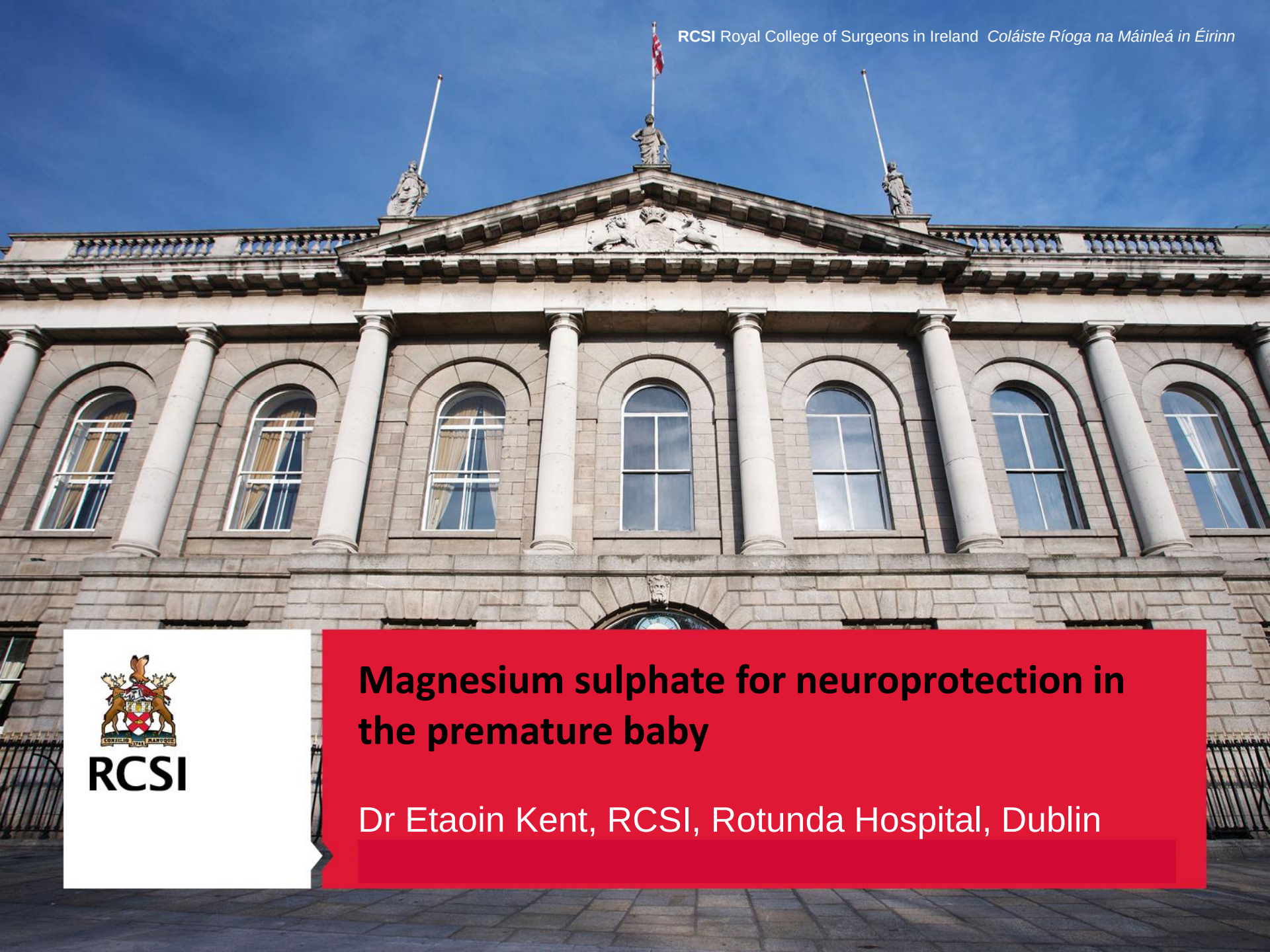

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