Different treatment regimens for magnesium sulphate for tocolysis in women in preterm labour for improving health outcomes (Protocol)

McNamara HC, Brown J, Crowther CA

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(Protocol)

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Different treatment regimens for magnesium sulphate for tocolysis in women in preterm labour for improving health outcomes

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A B S T R A C T

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review will assess the efficacy and safety of alternative magnesium sulphate regimens when used as single agent tocolytic therapy during pregnancy.

B A C K G R O U N D

Description of the condition

Preterm birth, defined as birth prior to 37 weeks estimated gestation (WHO 1992), is a leading cause of perinatal mortality (Beck 2010). Preterm infants are at significant risk of short-term and long-term morbidity (How 2006). The costs to individual families and to the community are great, and the burden on modern healthcare systems is significant. Spontaneous preterm labour contributes to 40% to 50% of all preterm birth (Goldenberg 2008). The prevention of spontaneous preterm labour using tocolysis has been a focus of obstetric research (Tsatsaris 2004).

Description of the intervention

Various pharmacological agents have been used in an attempt to arrest spontaneous preterm labour and therefore prolong pregnancy. Betamimetics (Neilson 2014), calcium channel blockers (King 2003), magnesium sulphate (Crowther 2002; update forthcoming) and oxytocin receptor antagonists (Papatsonis 2005) have each been the subject of Cochrane systematic reviews. Other drugs advocated for tocolysis include the prostaglandin inhibitor, indomethacin (Klauser 2012), selective COX-2 inhibitors, rofecoxib and celecoxib (Borna 2007; McWhorter 2004), progesterone (Borna 2008), nitrates and ethanol. Controversy remains as to which agent is preferable. A meta-analysis of 55 randomised controlled trials of tocolytic therapy (Haas 2012) found prostaglandin inhibitors and magnesium sulphate to have the highest probabil-
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Magnesium sulphate was first described for use as a tocolytic agent in 1977 (Steer 1977). An association between magnesium sulphate and uterine quiescence has long been established (Abarbanel 1945; Hall 1957). However, the mechanism of action of magnesium sulphate tocolysis remains incompletely defined. Evidence suggests the tocolytic effect of magnesium has both an intracellular and extracellular component (Lurie 2004). It is suggested that magnesium alters calcium uptake, binding and distribution in uterine smooth muscle cells, thereby reducing the frequency of cell depolarisation and inhibiting myometrial contraction (Lewis 2005). More recent evidence suggests the tocolytic effect of magnesium might have an anti-inflammatory component (Dowling 2012; Tam Tam 2011).

**Why it is important to do this review**

Magnesium sulphate has been trialled as a tocolytic agent in the context of threatened preterm labour for the prevention of preterm birth. Controversy exists regarding the benefits of magnesium sulphate therapy when given for tocolysis (Grimes 2006). There has been limited evaluation of the efficacy and safety of alternative regimens of magnesium sulphate when given for tocolysis. In order to determine the optimal dose, duration, route and timing of administration, evaluation of different regimens of magnesium sulphate given for tocolysis is warranted. Given its widespread availability and use in other obstetric contexts, further review of the safety profile of magnesium sulphate will be of value.

**OBJECTIVES**

This review will assess the efficacy and safety of alternative magnesium sulphate regimens when used as single agent tocolytic therapy during pregnancy.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All published, unpublished and ongoing randomised control trials comparing different magnesium sulphate regimens when administered to women as the only tocolytic therapy in the setting of threatened preterm labour will be included. Quasi-randomised trials will be included. Cross-over and cluster trials will be excluded. Conference abstracts will be included.

**Types of participants**

Women thought to be in preterm labour with a singleton or multiple pregnancy and administered magnesium sulphate for the prevention of preterm birth will be included. Women who have a planned preterm birth or preterm induction of labour will not be included.

**Types of interventions**

Intervention: intravenous or oral magnesium sulphate given alone for tocolysis.

Comparison: alternative dosing regimen of magnesium sulphate given alone for tocolysis.

Trials examining treatment regimens including magnesium sulphate co-administered with alternative tocolytic agents will not be included.

**Types of outcome measures**

Clinically relevant outcomes for trials of tocolysis for inhibiting preterm labour have been prespecified following consultation with the editors and authors of the individual reviews. Consensus was reached on a set of six ‘core’ outcomes, which are highlighted below. These will be included in all tocolysis reviews. In addition to these core outcomes, individual teams may include other outcomes as necessary.

**Primary outcomes**

**For the infant/child**

- Fetal, neonatal and infant death
- Birth less than 48 hours after trial entry
- Composite serious infant outcome (defined as death or chronic lung disease [oxygen requirement at 28 days of life or later]; intraventricular haemorrhage [grade three or four] or periventricular leucomalacia; major neurosensory disability [defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay/intellectual impairment [defined as developmental quotient or intelligence quotient less than two standard deviations below the mean])

**For the mother**

- Composite serious maternal outcome (defined as maternal death, cardiac arrest, respiratory arrest or admission to intensive care unit)
Secondary outcomes

For the infant

• Fetal death
• Neonatal death
• Preterm birth (less than 37 weeks)
• Very preterm birth (less than 34 weeks)
• Extremely preterm birth (less than 28 weeks)
• Birth less than 48 hours after trial entry
• Interval between trial entry and birth
• Gestational age at birth
• Apgar score less than seven at five minutes
• Active resuscitation at birth (assisted ventilation via an endotracheal tube)
• Use of respiratory support (mechanical ventilation or continuous positive airways pressure)
• Air leak syndrome
• Respiratory distress syndrome
• Chronic lung disease (need for supplemental oxygen at 28 days of life or later)
• Use of postnatal corticosteroids
• Intraventricular haemorrhage (IVH)
• Grade 3 or 4 IVH
• Periventricular leucomalacia (PVL)
• Necrotising enterocolitis
• Proven neonatal infection
• Hypocalcaemia, osteopaenia, or fracture(s)

For the child

• Cerebral palsy (mild, moderate or severe, evaluated separately)
• Developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below the mean)
• Legal blindness
• Sensorineural deafness requiring hearing aids

For the mother

• Death
• Cardiac arrest
• Respiratory arrest
• Antepartum haemorrhage
• Postpartum haemorrhage
• Need for blood transfusion
• Mode of delivery
• Any adverse effect(s) of therapy
• Hypotension
• Tachycardia
• Reduced or absent tendon reflexes

• Hypocalcaemia
• Pulmonary oedema
• Self-reported adverse effects or symptoms attributed to magnesium sulphate therapy (including discomfort at the infusion site, blurred vision, dizziness, headache, mouth dryness, muscle weakness, nausea or vomiting, drowsiness, sweating, flushing, other)
• Discontinuation of therapy
• Satisfaction with therapy

Health services outcomes

• Admission to intensive care unit for the mother
• Length of postnatal hospitalisation for the mother
• Admission to neonatal intensive care unit for the infant
• Length of stay in neonatal intensive care unit for the infant
• Length of neonatal hospitalisation for the infant

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group’s Trials Register. The Cochrane Pregnancy and Childbirth Group’s Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the ‘Specialized Register’ section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
Searching other resources
We will search the reference lists of retrieved studies.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies
Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult the third author.

Data extraction and management
We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult the third author. We will enter data into Review Manager software (RevMan 2014) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies
Two review authors will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)
We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:
- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)
We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:
- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)
We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:
- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)
We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:
- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)
We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.
We will assess methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ‘as treated’ analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.
Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Women will be the unit of analysis for maternal outcomes and where there is a multiple pregnancy the unit of analysis will be per infant for fetal, neonatal and child outcomes.

As infants from multiple pregnancies are not independent, we plan to use cluster trial methods in the analyses, where the data allow and where multiples make up a substantial proportion of the trial population, to account for non-independence of variables (Gates 2004).

Where a trial has multiple arms (more than two comparisons) and is included in the same meta-analysis the number of events and the sample size from one of the groups will be divided by the number of arms compared in the trial. This will ensure that no participants are double counted. If a subgroup analysis is being undertaken then the overall summary statistic will not be reported.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau², P and Chi² statistics. We will regard heterogeneity as present if an P is greater than 30% and either the Tau² is greater than zero, or there is a low P value (less than 0.10) in the Chi² test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are
estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials’ populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of $\tau^2$ and $I^2$.

**Subgroup analysis and investigation of heterogeneity**

We will perform comparisons for different types of regimens; including differences in route of administration, loading and maintenance doses, duration of treatment, timing of treatment and the possibility of repeat dosing.

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

Maternal and pregnancy characteristics are likely to affect health outcomes of both mother and child.

We plan to carry out subgroup analyses, where sufficient data are available, based on:

- significant factor(s) contributing to or precipitating preterm labour: including presence or absence of preterm rupture of membranes;
- multiple versus singleton pregnancy;
- gestational age at time of randomisation and treatment: less than 28 weeks, 28 weeks to less than 34 weeks, 34 weeks to less than 37 weeks or more than 37 weeks;
- use of antenatal corticosteroids for fetal lung maturation: in 50% or more of the study population or in less than 50% of the study population.

Subgroup analyses will only be performed with respect to primary outcomes examined.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test $I^2$ value.

**Sensitivity analysis**

Sensitivity analysis will be performed to investigate the effect of trial quality, as defined by allocation concealment and other risk of bias components, by excluding studies determined to be ‘high risk of bias’ for these components. Sensitivity analyses will be restricted to primary outcomes examined.

**ACKNOWLEDGEMENTS**

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group’s Statistical Adviser.

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Borna 2007
Different treatment regimens for magnesium sulphate for tocolysis in women in preterm labour for improving health outcomes

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**Doyle 2009**

**Duley 2010a**

**Duley 2010b**

**Duley 2010c**

**Duley 2010d**

**FDA 2013**

**Gates 2004**

**Glock 1993**

**Goldenberg 2008**

**Grimes 2006**

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**Hall 1957**

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**How 2006**

**James 2010**

**King 2003**

**Klauser 2012**
Larmon 1999

Lewis 2005

Lurie 2004

Lyell 2007

McWhorter 2004

Mittendorf 1997

Morales 1993

Nassar 2006

Neilson 2014

Papatsonis 2005

Pryde 2009

RevMan 2014

Schorr 1997

Steer 1977

Tam Tam 2011

Tsatsaris 2004

WHO 1992

* Indicates the major publication for the study

CONTRIBUTIONS OF AUTHORS

Helen McNamara wrote the first draft of the protocol, with Julie Brown and Caroline Crowther making comments and contributing to subsequent drafts.

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DECLARATIONS OF INTEREST

None known.

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