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Magnesium sulphate versus lytic cocktail for eclampsia (Review)

Duley L, Gülmezoglu AM, Chou D

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[Intervention Review]

Magnesium sulphate versus lytic cocktail for eclampsia

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ABSTRACT

Background

Eclampsia, the occurrence of a seizure in association with pre-eclampsia, is a rare but serious complication of pregnancy. A number of different anticonvulsants have been used to control eclamptic fits and to prevent further seizures.

Objectives

The objective of this review was to assess the effects of magnesium sulphate compared with lytic cocktail (usually chlorpromazine, promethazine and pethidine) when used for the care of women with eclampsia. Magnesium sulphate is compared with diazepam and with phenytoin in other Cochrane reviews.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (July 2010) and the Cochrane Central Register of Trials (*The Cochrane Library* 2010, Issue 2).

Selection criteria

Randomised trials comparing magnesium sulphate (intravenous or intramuscular administration) with lytic cocktail for women with a clinical diagnosis of eclampsia.

Data collection and analysis

Two review authors (L Duley and D Chou) assessed trial quality and extracted data.

Main results

We included three small trials (total 397 women) of average quality in the review. Magnesium sulphate was associated with fewer maternal deaths (risk ratio (RR) 0.14, 95% confidence interval (CI) 0.03 to 0.59; 3 trials, 397 women) and was better at preventing further seizures (RR 0.06, 95% CI 0.03 to 0.12; 3 trials, 397 women) than lytic cocktail. Magnesium sulphate was also associated with less respiratory depression (RR 0.12, 95% CI 0.02 to 0.91; 2 trials, 198 women), less coma (RR 0.04, 95% CI 0.00 to 0.74; 1 trial, 108 women), and less pneumonia (RR 0.20, 95% CI 0.06 to 0.67; 2 trials, 307 women). There was no clear difference in the RR for any death of the baby (RR 0.35, 95% CI 0.05 to 2.38, random effects; 2 trials, 177 babies).

Authors' conclusions

Magnesium sulphate, rather than lytic cocktail, for women with eclampsia reduces the RR of maternal death, of further seizures and of serious maternal morbidity (respiratory depression, coma, pneumonia). Magnesium sulphate is the anticonvulsant of choice for women with eclampsia; the use of lytic cocktail should be abandoned.

PLAIN LANGUAGE SUMMARY

Magnesium sulphate versus lytic cocktail for eclampsia

Magnesium sulphate performs better than lytic cocktail in preventing maternal deaths, further fits, respiratory depression, coma and pneumonia for pregnant women with eclampsia.

Pre-eclampsia, also known as toxaemia, is a condition which leads to high blood pressure and protein in the urine. Eclampsia is when a pregnant woman with pre-eclampsia has one or more seizures (fits). Eclampsia is a serious threat to the life of both mother and baby. We identified three randomised trials, involving 397 women with eclampsia who were randomly assigned to treatment with magnesium sulphate or a lytic mixture of chlorpromazine, promethazine and pethidine that lowers blood pressure and is a sedative. Both drugs could be given either by intravenous or intramuscular injection. Although the trials were small and of average quality, the review found that magnesium sulphate was better than lytic cocktail at preventing maternal deaths, further seizures, and breathing problems and coma for the mother. Magnesium sulphate is also relatively cheap and easy to use. The adverse effects of magnesium sulphate come largely from its smooth muscle relaxant activity; respiratory depression is dose dependent and, with monitoring of the woman's clinical condition, uncommon.

BACKGROUND

The aim of this review is to summarise the evidence about the differential effects of magnesium sulphate when compared with lytic cocktail (chlorpromazine, promethazine and pethidine) for the care of women with eclampsia. This review should be viewed in conjunction with Cochrane reviews where magnesium sulphate is compared with diazepam (Duley 2003c) and with phenytoin (Duley 2003b).

Description of the condition

Pre-eclampsia ('toxaemia') is defined as raised blood pressure (hypertension) accompanied by proteinuria (protein in the urine) (NHBPEP 2000). Eclampsia is the occurrence of a seizure (fit) in association with pre-eclampsia. When severe, pre-eclampsia and eclampsia can involve the woman's liver, kidneys, clotting system, or brain. Rare but serious complications include stroke, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) and disseminated intravascular coagulation (DIC). These complications are associated with an increased risk of maternal death. As pre-eclampsia and eclampsia can affect the placenta, risks for the baby are also increased. The most common problems are those related to poor intrauterine growth and premature birth, leading to an increase in perinatal mortality (Ananth 1995; Roberts 2005). Perinatal mortality is particularly high following eclampsia (Collab Trial 1995; Douglas 1994).

Maternal mortality in parts of Africa and Asia is 100 to 200 times greater than it is in Europe and North America. In western countries the average lifetime risk of dying from pregnancy-related causes is between one in 4000 to one in 1000, whereas women in low-income countries have a risk between one in 15 and one in 20. There is no other public health statistic for which the disparity between high- and low-income countries is so wide. Eclampsia remains a major cause of maternal mortality and morbidity. Between 10% to 15% of maternal deaths occur in low- and middle-income countries, and 30% of maternal deaths in Africa are associated with pre-eclampsia or eclampsia (Duley 1992; Khan 2006), as are 15% of direct obstetric deaths in the UK (Lewis 2007) and USA (MMWR 2003). In low- and middle-income countries most deaths associated with hypertension during pregnancy are due to eclampsia (Duley 1992). In high-income countries around half the deaths are associated with eclampsia, and half with pre-eclampsia. In low- and middle-income countries the case fatality is around 4% (Collab Trial 1995), whilst in high-income countries it appears to be lower (Knight 2007).

Pre-eclampsia and eclampsia are part of a spectrum of conditions known as the hypertensive disorders of pregnancy: this includes women with pre-eclampsia, eclampsia, pre-existing hypertension, and pre-existing hypertension with superimposed pre-eclampsia or eclampsia. The definitions and classification of the hypertensive disorders of pregnancy are discussed more fully in the generic protocol, "interventions for treating pre-eclampsia and its consequences" (Duley 2009).

The terminology of pre-eclampsia and eclampsia is misleading, as it implies a progression from mild disease to more severe, that pre-eclampsia precedes eclampsia, and that eclampsia is the most severe end of the spectrum. This is not the case, as some women have normal blood pressure at the time of their first fit, and some women become very sick and may even die without developing eclampsia. About one-quarter of cases of eclampsia occur without signs or symptoms suggestive of imminent eclampsia, such as headache and proteinuria (Andersgaard 2006; Douglas 1994; Igberase 2006). Nevertheless, women with severe pre-eclampsia are at particularly high risk of developing eclampsia.

Incidence of pre-eclampsia and eclampsia

Pre-eclampsia usually occurs during the second half of pregnancy and complicates 2% to 8% of all pregnancies (WHO 1988). Eclampsia is rare in Europe, with two to three cases reported per 10,000 births (Knight 2007; Kullberg 2002). In low- and middle-income countries, eclampsia is more common, with the incidence estimated as 16 to 69 cases per 10,000 births (Frias 2003). An estimated 1.5 million to 8 million women develop pre-eclampsia worldwide per year, of whom 150,000 may develop eclampsia (Villar 2003).

Eclampsia can occur in pregnancy, during labour, or after the birth. Where the incidence is high, a greater proportion of women with eclampsia have the onset before the birth. In high-income countries, where incidence of eclampsia is lower, a greater proportion of women have postpartum onset (Andersgaard 2006; Douglas 1994; Igberase 2006; Onuh 2004). Gestation is also a factor, as women with eclampsia preterm are at least three times more likely to have their first seizure in the antepartum period than women who have eclampsia at term (Andersgaard 2006; Douglas 1994). Postpartum eclampsia is usually close to the time of birth, but may be days or even several weeks later (Collab Trial 1995; Sibai 2005).

Aetiology and pathophysiology

Despite a growing understanding of the pathophysiology of pre-eclampsia, the underlying cause remains unclear. Factors that appear to have a role include maternal age, parity, obesity, maternal immune response, genetic predisposition, and maternal vascular disease (such as diabetes, chronic hypertension and autoimmune disease) (Duckitt 2005). Diet and nutrition may also have a role. Whether an individual woman will develop pre-eclampsia probably depends on which of these factors she has, and how they interact.

Pre-eclampsia is thought to occur as a result of inadequate blood supply to the placenta, related either to abnormal implantation, or to increased demand from the placenta (for example, in a multiple pregnancy). So, although pre-eclampsia is usually diagnosed in the second half of pregnancy, the antecedents are present much earlier. Current thinking is that inadequate blood supply to the placenta leads to the release of unknown factors or materials into the maternal circulation which activate or injure the endothelial cells, resulting in endothelial dysfunction (abnormal functioning of cells lining blood vessels) (Roberts 2002). Endothelial dysfunction results in widespread vasoconstriction and activation of platelets and the coagulation system. Injured endothelial cells allow leakage of fluid out of the blood vessels and into surrounding tissues, causing oedema and a reduction in the circulating blood volume. There is then inadequate blood flow to many of the woman's organs, especially the kidneys, liver, and brain. It is the vasoconstriction, micro clots, and reduced circulating blood volume that result in the clinical manifestations of pre-eclampsia. For a more detailed review of the aetiology and pathophysiology of pre-eclampsia, *see* Meher 2005.

The aetiology and pathophysiology of eclampsia are also incompletely understood. Although there are similarities between eclampsia and hypertensive crisis, the two conditions are not identical (Redman 1984). Some women (around 6%) develop eclampsia with no apparent disturbance of blood pressure (Douglas 1994). Hence, although control of blood pressure is important, it will not necessarily prevent or treat eclampsia. Eclampsia is associated with cerebral oedema and cerebral vasospasm; and women with eclampsia may have cerebral oedema or cerebral ischaemia (Belfort 1992; Katz 2000; Sibai 2005).

Risk factors for eclampsia include a family history, little or no antenatal care, being less than 20 years old, having had four or more previous pregnancies, and two or more signs and symptoms of imminent eclampsia (such as headache, epigastric pain, hyperreflexia, visual disturbances and severe hypertension). In low- and middle-income countries, the majority (around 90%) of women with eclampsia have had limited access to care (Igberase 2006; Onuh 2004).

Prevention of eclampsia

Primary prevention of eclampsia is preventing women from developing pre-eclampsia. Once the woman has pre-eclampsia, prevention is preventing progression to eclampsia. Screening for pre-eclampsia is an important part of antenatal care, and is based on the clinical history and examination (Milne 2005; NICE 2008). Various diagnostic tests have been advocated to identify women at particularly high risk of developing pre-eclampsia. So far none have proved to be of good predictive value, and so they are not recommended for clinical practice (Meads 2008).

Current strategies for prevention of pre-eclampsia can be broadly classified as antenatal surveillance, modification of lifestyle, nutritional supplementation, and pharmacological therapy (*see* Meher 2005). Cochrane reviews of strategies for preventing pre-eclampsia include: lifestyle advice, such as altered dietary salt (Duley 2005) and exercise (Meher 2006); the use of nutritional supplementation, such as calcium (Hofmeyr 2007), magnesium (Makrides 2001), zinc (Mahomed 2007), marine oils (Makrides 2006), vitamins C and E (Rumbold 2008); and pharmacologic agents such as antiplatelet agents (Duley 2007) and nitric oxide (Meher 2007).

Once women have pre-eclampsia, a Cochrane Review now provides robust evidence that magnesium sulphate halves the risk of eclampsia and probably reduces the risk of maternal death (Duley 2003b).

Description of the intervention

The only definitive treatment for pre-eclampsia or eclampsia is to end the pregnancy. The aim of interventions for women with eclampsia is to prevent further seizures, to minimise and treat any complications, and, if not delivered, to optimise the timing of birth for the baby. Other relevant Cochrane Reviews cover drug treatment for very high blood pressure (Duley 2006), plasma volume expansion (Duley 1999), and the timing of delivery for women before 34 weeks' gestation (Churchill 2002). Currently, standard care for women with eclampsia is to use an anticonvulsant drug to control the immediate fit, and to continue maintenance treatment to prevent further seizures. This review compares a policy of using magnesium sulphate to a policy of using lytic cocktail for the care of women with eclampsia.

Magnesium sulphate

Magnesium sulphate was introduced for care of women with eclampsia in the 1920s following reports of its use for control of convulsions due to tetanus (Duley 1996). Based on publication of several case series, it became standard care in several parts of the world, particularly in North America. Initially, magnesium sulphate was given in very low doses (Duley 1996), although it is now administered in relatively high doses. Common regimens are an initial intravenous loading dose of 4 grams (Dinsdale 1988; Pritchard 1955; Zuspan 1978): followed by maintenance intravenous infusions of 1 gram per hour (Dinsdale 1988; Zuspan 1978); or by 10 grams by intramuscular injection and then 5 grams intramuscularly every six hours (Eastman 1945). Alternative regimens for magnesium sulphate are the topic of a separate Cochrane Review (Duley 2008).

Lytic cocktail

Lytic cocktail is a mixture of drugs used for women with eclampsia; these are usually chlorpromazine, promethazine and pethidine (meperidine). First introduced in India (Menon 1961), this combination of drugs was thought to lower blood pressure and sedate the central nervous system. Lytic cocktail was once standard treatment in India and some other parts of the developing world, but is no longer in widespread use.

How the intervention might work

Magnesium sulphate

The mode of action for magnesium sulphate in control of eclamptic seizures and prevention of recurrent convulsions is still not clearly understood. Magnesium sulphate is not a traditional anticonvulsant, but nevertheless is better than the traditional anticonvulsant drugs at control of eclamptic seizures. This anticonvulsant activity may be mediated by magnesium's role as an N-methyl-D-aspartate (NMDA) antagonist (Euser 2009). Stimulation of NMDA receptors by neurotransmitters such as glutamate may lead to seizures when neuronal networks are over-activated. Magnesium may prevent and control eclamptic seizures by inhibiting NMDA receptors. Other possible mechanisms are that magnesium sulphate may lead to cerebral vasodilatation with subsequent reduction of cerebral ischaemia (Belfort 1992), and it may block some of the neuronal damage associated with ischaemia (Goldman 1988; Sadeh 1989). The pathway for blocking neuronal damage may also be through NMDA inhibition.

Magnesium is also a calcium antagonist, and a smooth muscle relaxant. It may affect the cerebral endothelium which forms the blood brain barrier. Lowering intracellular calcium may limit paracellular transport of vascular contents, such as ions and proteins, effectively decreasing the factors which promote cerebral oedema and seizure activity (Euser 2009).

The calcium antagonist activity of magnesium sulphate has led to the belief that it also lowers systemic blood pressure, but this has not been supported by evidence from randomised trials (MAGPIE 2002). Magnesium sulphate does not appear to be an antihypertensive drug (Abalos 2007).

The adverse effects of magnesium sulphate come largely from its action as a smooth muscle relaxant. The most serious are respiratory depression, and respiratory and cardiac arrest. However, the adverse effects follow a dose response. Deep tendon

reflexes are lost at a serum magnesium level of 10 mEq/L, with respiratory depression occurring at 15 mEq/L and cardiac arrest at > 15 mEq/L. This dose-response relationship means that clinical monitoring should ensure that toxicity and adverse effects are avoided. Provided deep tendon reflexes are present, toxicity and adverse effects will be avoided. Monitoring of serum magnesium levels is therefore not necessary, and clinical monitoring of tendon reflexes and respiration rate will ensure safe administration. As magnesium is excreted almost exclusively in the urine, women with impaired renal function will quickly have raised serum magnesium levels and be at risk of significant adverse effects if the dose is not reduced. Measuring hourly urine output should, therefore, be included in the clinical monitoring. If toxicity does develop, calcium gluconate is an effective antidote.

Lytic cocktail

Each individual component of lytic cocktail has sedative effects on the central nervous system. Chlorpromazine is an antipsychotic agent with central nervous system depressant effects. Given as an intramuscular injection, onset of action is in approximately 15 minutes. Chloropromazine is metabolised by the liver and excreted in urine. Adverse effects reported include cardiac arrhythmias and seizures (Baldessarini 2006).

Promethazine is an H_1 histamine antagonist with moderate sedative and anti-emetic properties. Intramuscular injection is the preferred mode of administration, as intravenous use has been associated with severe tissue damage. Given as an intramuscular injection, onset of action is in approximately 20 minutes. Promethazine is metabolised by the liver and excreted in urine and faeces as inactive metabolites. Toxic effects include hallucinations, incoordination, and seizures (Skidgel Randal 2006).

Pethidine (meperidine) is an opioid analgesic and produces generalised central nervous system depression. When given with chlorpromazine and/or promethazine this potentiates its sedative effects. It is metabolised by the liver into active and inactive metabolites. The active metabolite, normeperidine, has half the analgesic effect and two to three times the central nervous system effects of pethidine (meperidine). Normeperidine can accumulate and in high doses may cause seizures (Gutstein 2006).

When these drugs are combined, as in lytic cocktail, they potentiate and augment each other. Also a well-documented side effect of chlorpromazine is that it may cause seizures, as may pethidine in high doses and promethazine. This is a serious potential adverse effect for women with eclampsia.

OBJECTIVES

The aim was to compare the differential effects of magnesium sulphate and lytic cocktail given either by the intramuscular or the intravenous route, for the care of women with eclampsia. The comparison was in terms of maternal mortality, recurrence of seizures, other serious morbidity that could lead to death, and use of health service resources. For women who were entered into the trials before delivery, additional outcomes were those related to labour, delivery, and mortality and morbidity of the baby.

METHODS

Criteria for considering studies for this review

Types of studies

All adequately randomised trials comparing magnesium sulphate with lytic cocktail for treatment of women with eclampsia or its complications. This includes women who are antepartum, intrapartum and postpartum.

Cluster-randomised studies designs are unlikely to be relevant to most interventions for treatment of women with pre-eclampsia, and are therefore, unlikely to be identified. If such studies have been conducted, we have not automatically excluded them; rather, the relevant review authors have considered and justified whether or not it is appropriate to include them.

We planned to exclude studies with a quasi-random design, such as allocation by alternation, day of week, or hospital numbers as they have a greater potential for bias (Higgins 2008). We have also excluded studies with a crossover design.

Types of participants

Women with a clinical diagnosis of eclampsia at randomisation irrespective of whether they were before or after delivery, had a singleton or multiple pregnancy, or whether an anticonvulsant had been given before trial entry. If women with pre-eclampsia had also been entered into the trial, we have included data only for women with eclampsia in this review.

Types of interventions

Any randomised comparison of magnesium sulphate (intravenous or intramuscular administration for the maintenance regimen) with lytic cocktail for women with eclampsia. We included all routes of administration, as well as any combination of drugs known as 'lytic cocktail', regardless of the constituents or of how they were administered.

Types of outcome measures

The most important outcome is maternal death but as this is relatively rare, even for women with eclampsia, we also included other measures of serious morbidity which could lead to death.

Primary outcomes

For the woman

1. Death: before discharge from hospital; up to six weeks postpartum; beyond six weeks postpartum.
2. Recurrence of seizures.
3. Stroke.
4. Any serious morbidity: defined as at least one of stroke, renal failure, liver failure, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), disseminated intravascular coagulation, pulmonary oedema (fluid in the lungs), and cardiac arrest; or as reported in the trial.

For the child

1. Death: stillbirths (death in utero at or after 20 weeks' gestation); perinatal deaths (stillbirths plus deaths in first week of life); death before discharge; neonatal deaths (death in the first 28 days after birth); deaths after 28 days.

2. Preterm birth: defined as birth before 37 completed weeks' gestation.
3. In a special care nursery for more than seven days.

Secondary outcomes

For the woman

1. Kidney failure.
2. Liver failure.
3. HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome.
4. Disseminated intravascular coagulation.
5. Pumonary oedema (fluid in the lungs).
6. Cardiac arrest.
7. Death or serious morbidity (any of 1 to 6, above).
8. Use of antihypertensive drugs.
9. Abruption of the placenta or antepartum haemorrhage.
10. Elective delivery: induction of labour or caesarean section.
11. Labour greater than eight hours.
12. Caesarean section.
13. Postpartum haemorrhage, defined as blood loss of 500 ml or more.
14. Serious adverse effects: respiratory depression, need for calcium gluconate.
15. Stopped treatment due to toxicity or adverse effects.
16. Side effects: flushing, local skin reaction at site of injection, reduced respirations, absent tendon reflexes.
17. Use of hospital resources: intensive care (admission to intensive care unit, length of stay), need for ventilation, need for dialysis, transfer to another hospital for a higher level of care.
18. Postnatal depression.
19. Breastfeeding, at discharge and up to one year after delivery.
20. Women's experiences and views: childbirth experience, physical and psychological trauma, mother-infant interaction and attachment.

For the child

1. Severity of preterm birth: very preterm birth (before 32 to 34 completed weeks) and extremely preterm birth (before 26 to 28 completed weeks).
2. Death before discharge from hospital or in a special care nursery for more than seven days.
3. Respiratory distress syndrome.
4. Infection.
5. Necrotising enterocolitis.
6. Retinopathy of prematurity.
7. Intraventricular haemorrhage.
8. Small-for-gestational age: defined as growth less than 3rd centile, or lowest growth centile reported.
9. Apgar score at five minutes: low (less than seven), very low (less than four), or lowest reported.
10. Use of hospital resources: admission to special care nursery, length of stay, endotracheal intubation, use of mechanical ventilation.
11. Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay and cerebral palsy.
12. Side effects associated with the intervention: respiratory depression shortly after birth.

Economic outcomes

1. Costs to the health service resources: short-term and long-term for both mother and baby.
2. Costs to the woman, her family, and society.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (July 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL and MEDLINE, 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.

In addition, we searched CENTRAL (*The Cochrane Library* 2010, Issue 2) using the search strategy detailed in Appendix 1.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Three review authors (L Duley (LD), AM Gulmezoglu (AMG), D Chou (DC)) independently assessed for inclusion all potentially eligible studies identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

For previous versions of this review two review authors (LD, AMG) extracted data from each report. For this update, during which we also updated the methods according to the generic protocol (Duley 2009), two review authors (DC, LD) extracted data from each report. We resolved all discrepancies by discussion. There was no blinding of authorship or results. We entered data into Review Manager software (RevMan 2008) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide clarification or further information.

Assessment of risk of bias in included studies

At least two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We resolved any disagreement by discussion, or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We described 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 assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear.

We excluded studies with inadequate sequence generation.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear

(3) Blinding (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, 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 was reported, or supplied by the trial authors, we re-included missing data in the analyses. We assessed methods as:

- adequate;
- inadequate;
- unclear.

For outcomes up to the time of discharge from hospital, if data for more than 20% of participants were missing, we excluded that outcome or study from the analysis. For longer-term follow up, attrition is likely to be greater, and we included studies provided there was reasonable reassurance about potential for bias.

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- adequate (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);
- inadequate (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.

(6) Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias: for example, if the trial stopped early due to some data-dependent process, or if there was an extreme baseline imbalance.

We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we have presented results as a summary risk ratio (RR) with 95% confidence intervals.

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

Although cluster-randomised trials of interventions for treatment of pre-eclampsia are unlikely, if we identified them and they met all other eligibility criteria, we included them along with individually randomised trials. If included, we adjusted their sample sizes or standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC.

If we identify both cluster-randomised trials and individually randomised trials, we would plan to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We would also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis.

Crossover trials

We excluded crossover trials, as for eclampsia the important clinical outcomes are at birth, and beyond.

Dealing with missing data

For included studies, we noted levels of attrition. We explored 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 carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Where important data or information about the study design were missing, whenever possible we contacted trial authors to ask if they could provide it.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. When we identified substantial heterogeneity (above 50%), we explored it by prespecified subgroup analysis.

Assessment of reporting biases

Where we suspected reporting bias (*see* 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data could introduce serious bias, we have explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Data synthesis

We performed statistical analyses using Review Manager (RevMan 2008) software, with results presented as RR and risk difference (RD). From 1/RD we calculated the number needed to treat for benefits, and for harmful or adverse effects. For each measure we have given the 95% confidence intervals. We used the fixed-effect model for calculating RR. If there was clear heterogeneity between the studies in any one outcome, we used a random-effects model. We explored possible factors in the heterogeneity, including quality of the concealment of allocation, clinical factors as determined by the prespecified subgroup analyses, and the play of chance.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses based on:

1. whether the woman had delivered before trial entry: not delivered at trial entry, postpartum at trial entry, unclear or mixed;
2. whether the woman received anticonvulsants before trial entry: anticonvulsant before trial entry, no anticonvulsant before trial entry, unclear or mixed;
3. gestation at trial entry: at least 32 to 34 weeks, less than 32 to 34 weeks, unclear or mixed.

We planned to use the primary outcomes in these subgroup analyses. Data were not presented by gestation at trial entry, and so this subgroup analysis was not possible.

We planned an additional subgroup analysis based on route for the maintenance regimen of magnesium sulphate:

4. allocated maintenance regimen: by intravenous route, intramuscular route, unclear or mixed.

Outomes related to adverse effects and toxicity were used for this subgroup analysis.

For fixed-effect meta-analyses we planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. For random-effects meta-analyses we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We carried out sensitivity analysis to explore the effect of trial quality, including only studies which have been assessed as having adequate control of the potential for bias.

RESULTS

Description of studies

This review includes three trials with data from 397 women with eclampsia randomised to magnesium sulphate or lytic cocktail in the treatment of eclampsia. All three studies were conducted in India. The largest trial enrolled 199 women, the smallest 91 women. The majority of women were antepartum. No trials reported data stratified by delivery status at time of randomisation or whether women had received an anticonvulsant prior to trial entry.

Nifedipine was administered to all women in one study for blood pressure control (India 1994).

The women who received magnesium sulphate in these trials had either 4 g or 6 g as a loading dose, and then maintenance therapy was the intramuscular regimen. For most women duration of treatment was 24 hours. Women were monitored using respiratory rate, urine output and tendon reflexes. Serum magnesium levels were determined in one study (India 1994) every 12 hours, but clinical management was used. One study (India 1988) did not provide details of treatment regimens beyond stating the name of the regimen (Pritchard's or Menon's).

Two trials (India 1994; India 1995) reported fetal and neonatal mortality. No other outcomes for the baby were reported.

Risk of bias in included studies

Randomisation procedures were not described by one study (India 1988). One study (India 1995) is only available as an abstract, and there is no information about concealment of allocation or how outcome was assessed. We obtained some additional information about the interventions and outcomes for this study by recording data from the conference poster presentation.

Allocation

For one study (India 1994) the randomisation procedure is described, although it is unclear whether there was any central record of the envelopes, or whether the envelopes were to be used in a particular sequence. Information regarding allocation concealment was not provided by the other studies.

Blinding

Once women were randomised, the allocated treatments could not be blinded in any of these studies. The trials do not report who assessed outcome. It is however unlikely that any subsequent bias will have substantially influenced the results as the main outcomes reported were objective. The strength and consistency of the data across the three studies suggest they represent true effects.

Incomplete outcome data

The studies included in this review did not adequately address incomplete outcome data. In one study (India 1994), one woman was excluded because of an uncertain diagnosis. In another (India 1988) data for postpartum women and multiple gestations are not clearly explained. In the third study (India 1995) outcome for the baby is only reported for those with birthweight greater than 1 kg. The only outcome reported for the babies was death.

Effects of interventions

This review includes three trials (397 women) comparing magnesium sulphate with lytic cocktail for women with eclampsia.

Outcome for the women

Maternal death

Magnesium sulphate is associated with fewer maternal deaths than lytic cocktail (RR 0.14, 95% confidence interval (C)I 0.03 to 0.59; three trials, 397 women).

Recurrence of seizures

Magnesium sulphate is associated with a substantial reduction in the RR of recurrence of seizures, when compared with lytic cocktail (RR 0.06, 95% CI 0.03 to 0.12; three trials, 397 women). This means that, on average, for every two women treated with magnesium sulphate rather than lytic cocktail one recurrence of seizures will be prevented (number needed to treat (NNT) 2; 95% CI 2 to 3).

Cerebrovascular accident

One trial (108 women) reported the risk of cerebrovascular accident (stroke), there was no clear difference in RR between the two groups (RR 0.22, 95% CI 0.01 to 4.54).

Any serious morbidity - composite outcome

None of the trials reported this composite outcome.

Other serious morbidity

There were no clear differences between the two groups in the RR of any measure of other serious morbidity:

- renal failure: RR 0.64, 95% CI 0.22 to 1.85; two trials, 307 women;
- oliguria: RR 0.50, 95% CI 0.10 to 2.59; one trial, 90 women;
- HELLP syndrome: RR 3.35, 95% CI 0.14 to 80.6; one trial, 108 women;
- coagulopathy: RR 0.39, 95% CI 0.08 to 1.95; one trial, 199 women.
- coma: RR 0.04, 95% CI 0.00 to 0.74; one trial, 108 women;
- respiratory depression: RR 0.12, 95% CI 0.02 to 0.91; two trials, 198 women;
- pneumonia: RR 0.20, 95% CI 0.06 to 0.67; two trials, 307 women;
- cardiac arrest: RR 0.26, 95% CI 0.03 to 2.34; two trials, 307 women.

Use of hospital resources

There was no difference in the need for ventilation when comparing women treated with magnesium sulphate rather than lytic cocktail (RR 0.20, 95% CI 0.01 to 4.05; one trial, 90 women).

For women randomised before delivery

Treatment with magnesium sulphate rather than lytic cocktail is not associated with any clear difference in the RR of caesarean section, or of postpartum psychosis:

- caesarean section: RR 0.83, 95% CI 0.49 to 1.41; two trials, 183 women;
- postpartum psychosis: RR 1.00, 95% CI 0.15 to 6.79; one trial, 90 women.

No other outcomes related to the delivery were reported.

Outcome for the child

Death

Two trials (177 infants) reported stillbirths and neonatal deaths; neither reported perinatal mortality. There was significant heterogeneity between the two trials for stillbirths and for any baby death, so we used a random-effects analysis for these data. Overall, there was no clear difference in the RR of any death of the baby for women allocated magnesium sulphate rather than lytic cocktail (RR 0.35, 95% CI 0.05 to 2.38 random effects; two trials, 177 babies). This

result should be interpreted with caution, however, as it represents the average effect across the two trials and results in the individual studies may depart substantially from this average value.

For women allocated magnesium sulphate rather than lytic cocktail, the relative risk of stillbirth was 0.33 (95% CI 0.01 to 7.16 random effects), and of neonatal death was 0.37 (95% CI 0.14 to 1.00).

Neonatal morbidity

No trials included in this review reported preterm birth or any measure of neonatal morbidity (respiratory distress, retinopathy of prematurity, intraventricular haemorrhage, necrotising enterocolitis, infection, small-for-gestational age, or adverse effects attributable to maternal treatment),

Use of health service resources

No trials reported admission to a special care baby unit, or any other measure of use of health service resources for the baby.

Long-term outcome

No trials reported outcome beyond discharge from hospital.

Subgroup analysis

Data are not available to perform subgroup analysis by whether or not the woman was delivered prior to trial entry or whether she received anticonvulsants prior to trial entry. All trials used intramuscular magnesium sulphate for the maintenance regimen, so subgroup analysis by mode of maintenance was not possible.

Sensitivity analysis

Formal sensitivity analysis was not performed, as none of the three trials included in this review met the criteria for adequate control of the potential for bias.

DISCUSSION

Summary of main results

The three trials included in this review were small and of average quality. Nevertheless, taken together they show that magnesium sulphate is substantially better than lytic cocktail for reducing maternal deaths, recurrent seizures, coma, respiratory depression and pneumonia. There is no clear difference in the effect on mortality for the baby, and morbidity for the baby is not reported.

The number of women in this review is relatively small, and the risk of further fits for women allocated lytic cocktail rather than magnesium sulphate was surprisingly high. Whilst this may in part be due to the play of chance, and/or reflect bias in the concealment of allocation or ascertainment of outcome, it is likely that at least some of this effect is real. Lytic cocktail almost certainly increases the risk of women having a seizure, as seizures are a well-documented side effect of chlorpromazine, one of the constituents of lytic cocktail, and are also associated with the other two common constituents. The effect on recurrence of seizures was also consistent across the three studies, and is reflected in other related measures of serious morbidity such as coma, respiratory depression and pneumonia.

Overall completeness and applicability of evidence

All trials in this review reported maternal death and recurrence of seizures. Reporting of other measures of maternal morbidity varies. Data on outcome for the child are incomplete, only two studies reporting baby death and no study reporting any measures of neonatal morbidity.

The three trials in this review were conducted in India. Nevertheless, there is no reason to expect that their results would not be applicable in other countries.

Quality of the evidence

The trials in this review were of average quality due to significant concerns regarding methodology in all three studies. One study was presented in abstract only (India 1995), and there is inadequate information about study quality.

Potential biases in the review process

The search strategy for this review was extensive, and not restricted to studies published in English. One of the problems in identifying potentially eligible studies is that they are likely to have been conducted in low- and middle-income countries, where eclampsia is more common. If such studies are published in journals not easy to access, or are unpublished, they may not have been identified by our search strategy. We would welcome information about any additional studies potentially eligible for this review (please send information to: l.duley@leeds.ac.uk).

Agreements and disagreements with other studies or reviews

This review should be viewed in conjunction with the Cochrane Reviews comparing magnesium sulphate with diazepam (Duley 2003c) and with phenytoin (Duley 2003b) for women with eclampsia.

Overall, there is now compelling evidence in favour of magnesium sulphate, rather than diazepam, phenytoin or lytic cocktail for the treatment of eclampsia. Lytic cocktail should never be used for women with eclampsia. Magnesium sulphate is the anticonvulsant of choice for women with eclampsia (Langer 2008; Neilson 1995; Roberts 2002; Robson 1996; Sheth 2002), and this use is endorsed by national and international guidelines (RCOG; WHO 2007). Magnesium sulphate is relatively affordable, and should be made available for the care of women with eclampsia, particularly in low- and middle-income countries (Langer 2008; Sheth 2002).

The fifth Millennium Development Goal (MDG) calls for a reduction by three-quarters between 1990 and 2015 in the maternal mortality ratio. Universal implementation of magnesium sulphate for treatment of women with eclampsia would be a substantial step towards achieving this goal (Langer 2008).

Ensuring more women with eclampsia receive appropriate treatment with magnesium sulphate will require dedicated, focused and co-ordinated action at several levels. There is a need for governments, donors and international agencies concerned with women's health, such as the World Health Organization (WHO), United Nations Population Fund (UNFPA), the International Federation of Gynecology and Obstetrics (FIGO) and the International Confederation of Midwives (ICM) to, as a priority, increase support for effective care for women with eclampsia

(Langer 2008; Lumbiganon 2007) This support should include advocacy and funding to help ensure magnesium sulphate is registered and available for care of women with eclampsia in all middle- and low-income countries. In addition governments, together with national associations of obstetricians and midwives, should ensure appropriate training of all relevant health professionals (including obstetricians, midwives, emergency-room doctors, anaesthetists, nurses, medical officers and pharmacists) in the management of women with eclampsia and in the use of magnesium sulphate.

AUTHORS' CONCLUSIONS

Implications for practice

Lytic cocktail should be withdrawn from clinical practice. Magnesium sulphate is relatively cheap and easy to use. It should be made available for treatment of all women with eclampsia.

Magnesium sulphate is the drug of choice for treatment of women with eclampsia, both whilst they have a seizure (Duley 2003b; Duley 2003c), and to prevent recurrence of further seizures (Duley 2003a). Duration of treatment should not normally exceed 24 hours. The intravenous or intramuscular route can be used for maintenance therapy. If the intravenous route is used, the dose should not exceed 1 g/hour. Clinical monitoring of respiration, urine output and tendon reflexes is essential. Serum monitoring is not necessary and should not be used.

Implications for research

Magnesium sulphate is now the gold standard against which any new anticonvulsants for women with eclampsia should be compared in properly designed randomised trials.

The evidence supporting use of magnesium sulphate comes from trials which recruited women in secondary and tertiary level hospitals. Questions which merit further research include: whether a loading dose of magnesium sulphate should be given to women at primary care level before transfer to hospital; the minimum effective dose; and the optimal mode of administration and duration of treatment.

Any future trials should be of adequate size, and report mortality, serious morbidity and use of health service resources for both the woman and the baby.

Eclampsia can be distinguished from other forms of seizures in that it is better controlled by magnesium sulphate than by either diazepam or phenytoin (both conventional anticonvulsants), which may offer opportunities to explore the pathogenesis of eclampsia.

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Duley 2001

Duley L, Gulmezoglu AM. Magnesium sulphate versus lytic cocktail for eclampsia. *Cochrane Database of Systematic Reviews* 2000, Issue 3. [DOI: 10.1002/14651858.CD002960]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

India 1988

Methods	Please see bias table below.
Participants	199 women with eclampsia.
Interventions	$MgSO_4$: modified Pritchard's regimen. After the loading dose administered, the IM maintenance dose was administered every 6 hours instead of 4. Lytic cocktail: Menon's regimen. No further information given.
Outcomes	Women: maternal mortality, maternal morbidity, coma > 72 hours, oliguria, anuria, acute renal failure, DIC, respiratory infection, abruptio placentae, atonic PPH, vulval hematoma, postpartum psychosis, cardiac arrest, shock, UTI, bed sore, thrombophlebitis. Babies: stillbirth, neonatal death, Apgar score < 7, < 4, RDS, meconium aspiration syndrome, septicaemia, hyperbilirubinemia, intracranial haemorrhage, bronchopnuemonia, diarrhoea.
Notes	

India 1988 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as "randomly allocated to two treatment regimens." No further information given.
Allocation concealment?	Unclear risk	No information given.
Blinding? All outcomes	High risk	Blinding of the 2 treatment regimens was not possible. Outcome assessment was by the attending clinician, but outcomes used were largely objective, reducing potential for bias.
Incomplete outcome data addressed? All outcomes	Unclear risk	Data are presented as percentages only.

India 1994

Methods	Please see bias table below.
Participants	91 women with eclampsia.
Interventions	$MgSO_4$: 4 g IV (20% solution) + 8 g IM (50% solution) loading dose, then 4 g 4 hourly until 24 hours after delivery. If recurrent fits, 1.5 g IV. Lytic cocktail: pethidine. promethazine and chlorpromazine 'as described by Menon'.
Outcomes	Women: further fits, death, aspiration, respiratory depression, difficulty with BP control, sudden hypotension, oliguria, postpartum psychosis, caesarean section, induction of labour. Babies: stillbirth, neonatal death, asphyxia, 'permanent sequelae'.
Notes	All women had nifedipine for BP control. $MgSO_4$ new intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were stratified into groups of 8 with "1 in 2 chance" of being in either treatment group. Randomisation scheme is not discussed.
Allocation concealment?	Low risk	"Presealed, prenumbered, opaque envelopes."
Blinding? All outcomes	High risk	Blinding of the two treatment regimens was not possible. Outcome assessment was by the attending clinician, but outcomes used were largely objective, reducing potential for bias.
Incomplete outcome data addressed? All outcomes	High risk	1 woman with uncertain diagnosis was excluded from the analysis. Babies without audible fetal heart tones were excluded. For the purpose of data extraction, these were considered stillbirths.

India 1995

Methods	Please see bias table below. 'Randomly allocated'. No other information.
Participants	108 women with eclampsia.
Interventions	$MgSO_4$: 4 g IV + 10 g IM loading dose, then 5 g 4 hourly up to 24 hours after delivery. Lytic cocktail: 100 mg pethidine + 25 mg chlorpromazine IV and 50 mg chlorpromazine + 25 mg promethazine IM loading dose. 100 mg pethidine in 1 litre 20% dextrose over 24 hours, 25 mg promethazine 4 hourly, 50 mg chlorpromazine 8 hourly for 48 hours.
Outcomes	Women: further fits, death, pneumonia, stroke, coma > 24 hours, respiratory failure, cardiac failure, renal failure, HELLP. Babies: stillbirth and neonatal death (for babies with birthweight > 1 kg).
Notes	Published as abstract only. Additional data taken from conference poster presentation. $MgSO_4$ new intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'Randomly allocated'. No other information.
Allocation concealment?	Unclear risk	Not described.
Blinding? All outcomes	High risk	Blinding of the 2 treatment regimens was not possible. Outcome assessment was by the attending clinician, but outcomes used were largely objective, reducing potential for bias.
Incomplete outcome data addressed? All outcomes	Unclear risk	Data presented in abstract only.

BP: blood pressure
DIC: disseminated intravascular coagulopathy
HELLP: haemolysis elevated liver enzymes and lowered platelets
IM: intramuscular
IV: intravenous
MgSO4: magnesium sulphate
PPH: postpartum haemorrhage
RDS: respiratory distress syndrome
UTI: urinary tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
India 1997	Not a randomised trial. Study was designed as 4-arm quasi-randomised study, then converted to 2-arm quasi-randomised trial and subsequently published as a case series. Participants: 100 women with eclampsia. Interventions: magnesium sulphate (16 women), lytic cocktail (28 women), diazepam (16 women), phenytoin (40 women).

Study	Reason for exclusion
India 2001a	Not a randomised trial. Retrospective case control study of 120 women with eclampsia. 55 received magnesium and nifedipine, 42 magnesium sulphate and a sedative (pethidine or diazepam).
India 2001b	Described as a series of 90 women with eclampsia. 32 received phenytoin, 34 Menon's (modified) regime and 24 magnesium sulphate. The study is unlikely to be randomised trial, the authors do not indicate that it was randomised and there is imbalance in the number of patients for each arm.

DATA AND ANALYSES

Comparison 1. Magnesium sulphate versus lytic cocktail

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	3	397	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.59]
2 Recurrence of convulsions	3	397	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.03, 0.12]
3 Stroke	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.54]
4 Renal failure	2	307	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.22, 1.85]
5 Oliguria	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.10, 2.59]
6 HELLP syndrome	1	108	Risk Ratio (M-H, Fixed, 95% CI)	3.35 [0.14, 80.36]
7 Coagulopathy	1	199	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.95]
8 Coma > 24 hours	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.74]
9 Respiratory depression	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.91]
10 Pneumonia	2	307	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.67]
11 Cardiac arrest	2	307	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.34]
12 Mechanical ventilation	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.05]
13 Caesarean section	2	183	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.49, 1.41]
14 Postpartum psychosis	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.79]
15 Death of the fetus or infant (subgroups by stillbirth, perinatal and neonatal death)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Stillbirth	2	177	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.16]
15.2 Neonatal death	2	153	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.14, 1.00]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
15.3 Perinatal death	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16 Any death of the fetus or infant	2	177	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.05, 2.38]

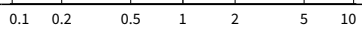
Analysis 1.1. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 1 Maternal death.

Study or subgroup	Magnesium sulphate n/N	Lytic cocktail n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
India 1988	0/101	8/98		57.88%	0.06[0,0.98]
India 1994	0/45	2/45		16.77%	0.2[0.01,4.05]
India 1995	1/51	4/57		25.35%	0.28[0.03,2.42]
Total (95% CI)	**197**	**200**		**100%**	**0.14[0.03,0.59]**
Total events: 1 (Magnesium sulphate), 14 (Lytic cocktail)					
Heterogeneity: Tau^2=0; Chi^2=0.84, df=2(P=0.66); I^2=0%					
Test for overall effect: Z=2.68(P=0.01)					

magnesium sulphate lytic cocktail

Analysis 1.2. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 2 Recurrence of convulsions.

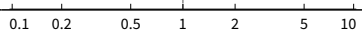
Study or subgroup	Magnesium sulphate n/N	Lytic cocktail n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
India 1988	2/101	61/98		56.91%	0.03[0.01,0.13]
India 1994	1/45	11/45		10.11%	0.09[0.01,0.68]
India 1995	3/51	38/57		32.98%	0.09[0.03,0.27]
Total (95% CI)	**197**	**200**		**100%**	**0.06[0.03,0.12]**
Total events: 6 (Magnesium sulphate), 110 (Lytic cocktail)					
Heterogeneity: Tau^2=0; Chi^2=1.5, df=2(P=0.47); I^2=0%					
Test for overall effect: Z=7.13(P<0.0001)					



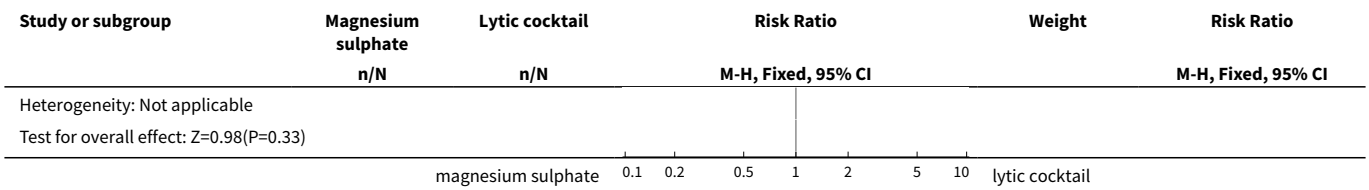
magnesium sulphate lytic cocktail

Analysis 1.3. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 3 Stroke.

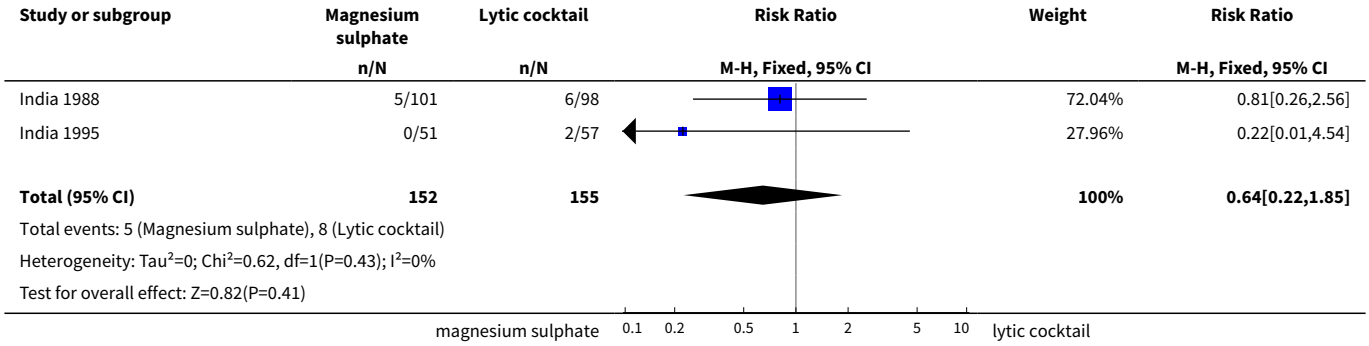
Study or subgroup	Magnesium sulphate n/N	Lytic cocktail n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
India 1995	0/51	2/57		100%	0.22[0.01,4.54]
Total (95% CI)	**51**	**57**		**100%**	**0.22[0.01,4.54]**
Total events: 0 (Magnesium sulphate), 2 (Lytic cocktail)					



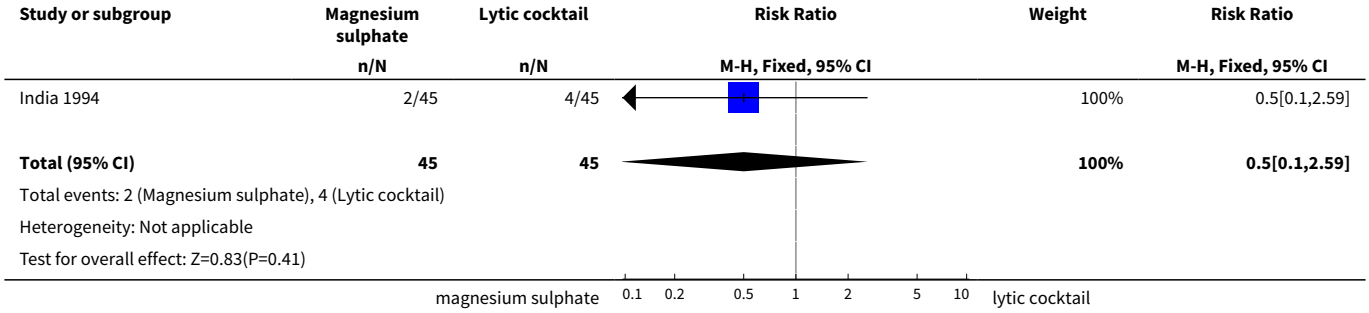
magnesium sulphate lytic cocktail



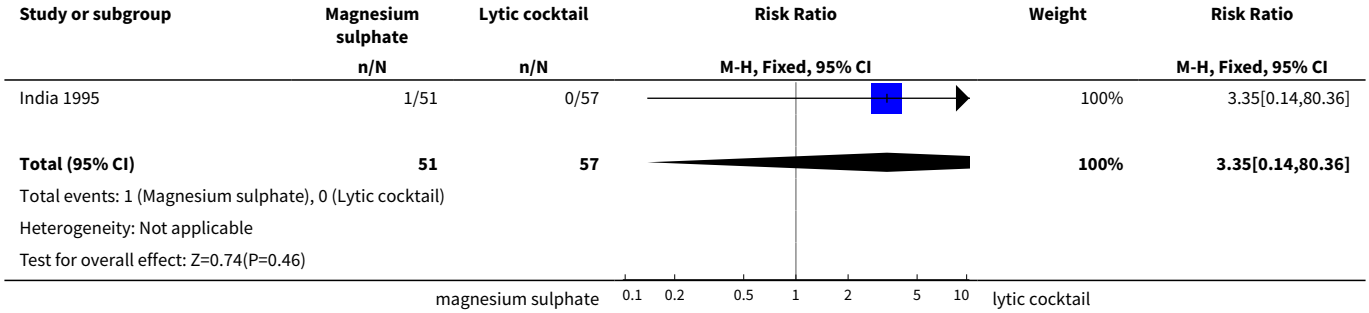
Analysis 1.4. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 4 Renal failure.



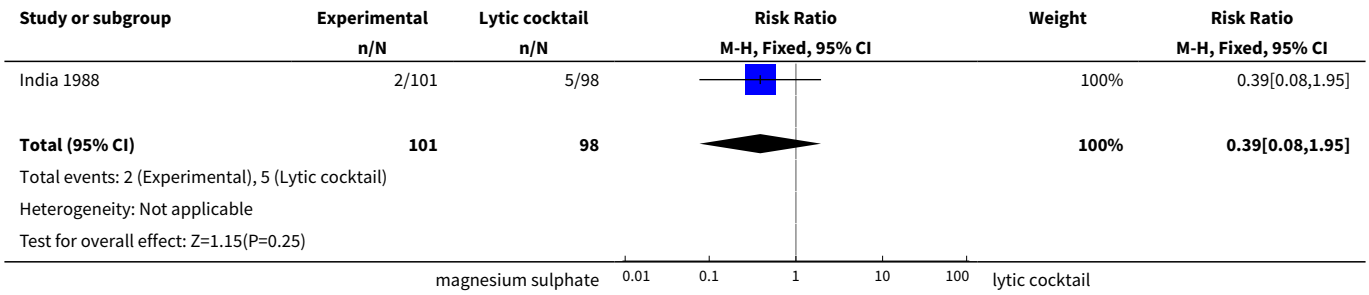
Analysis 1.5. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 5 Oliguria.



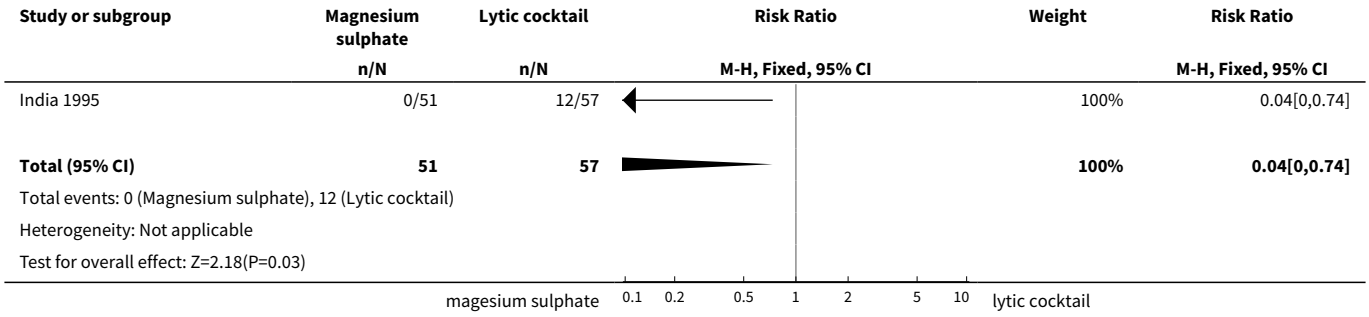
Analysis 1.6. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 6 HELLP syndrome.



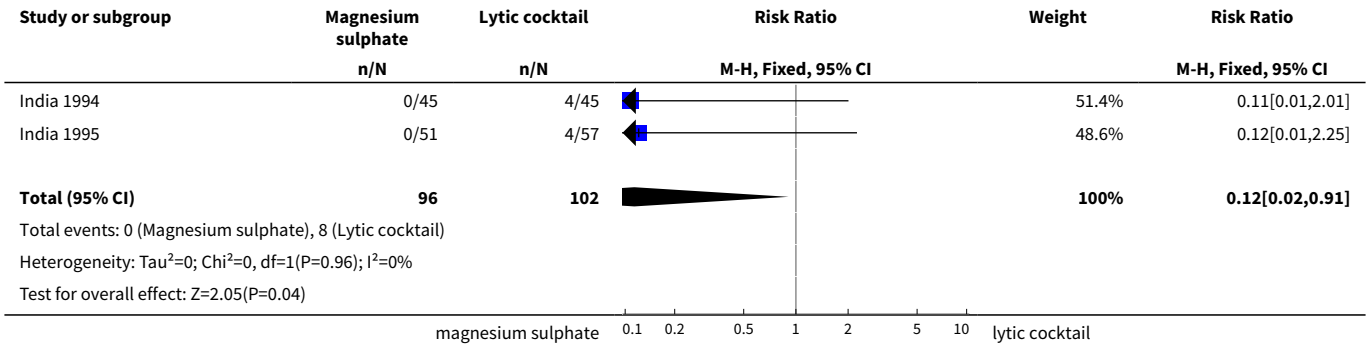
Analysis 1.7. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 7 Coagulopathy.



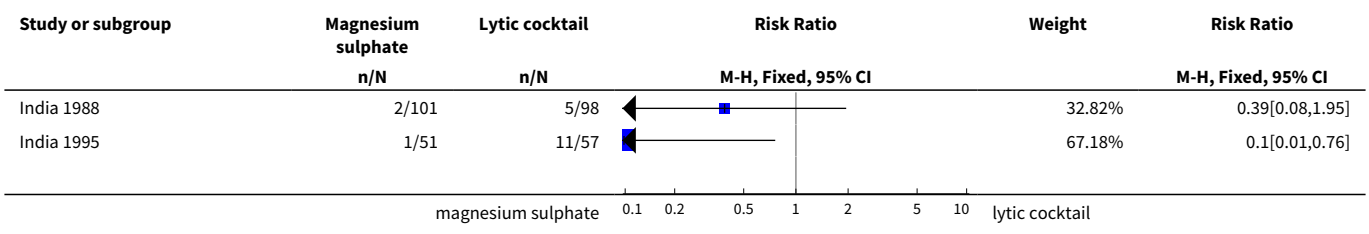
Analysis 1.8. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 8 Coma > 24 hours.

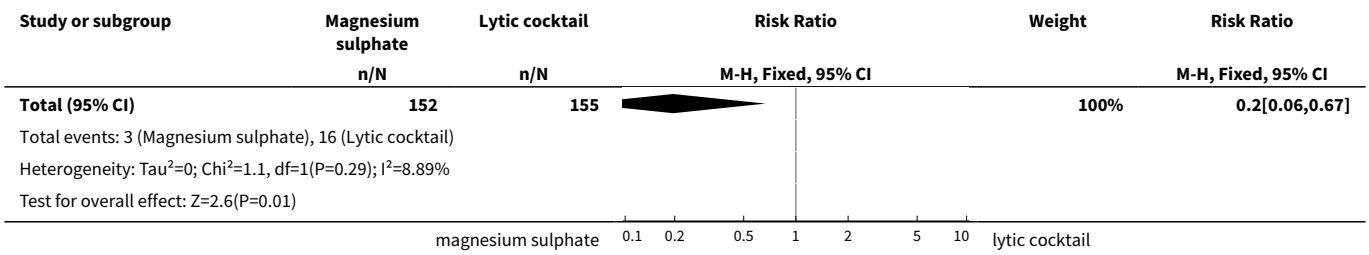


Analysis 1.9. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 9 Respiratory depression.

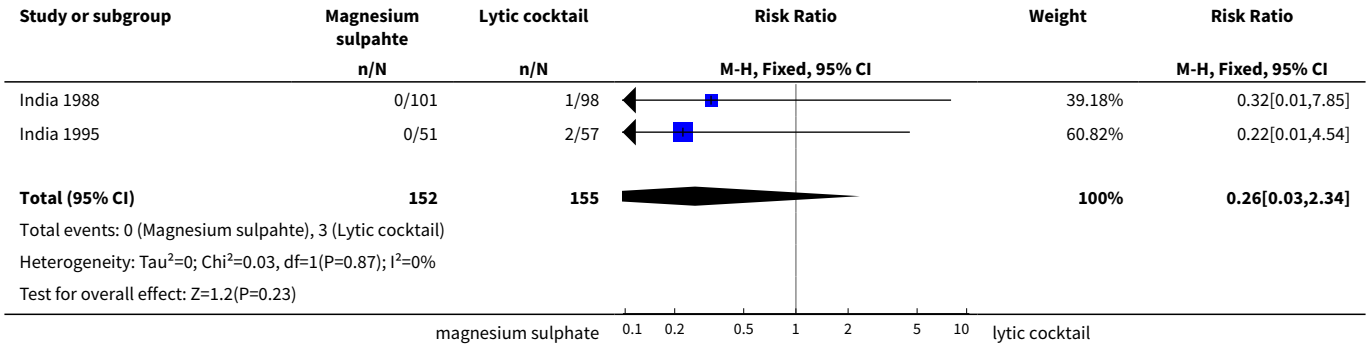


Analysis 1.10. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 10 Pneumonia.

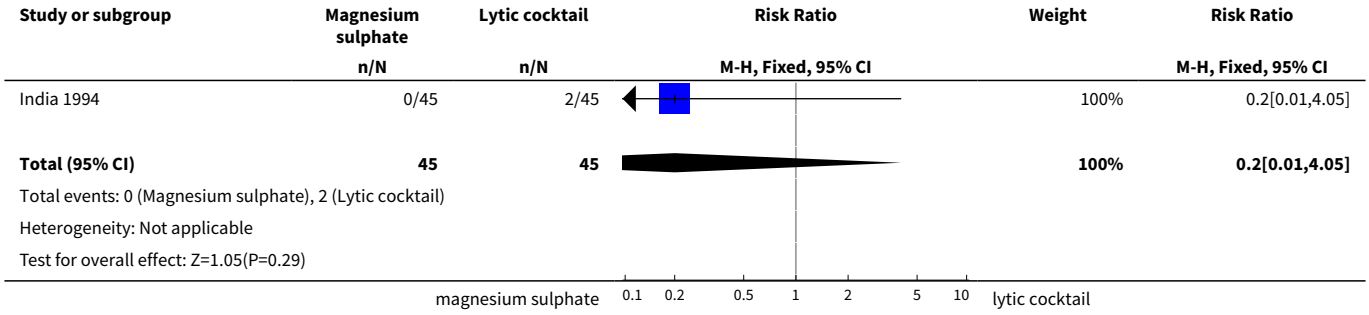




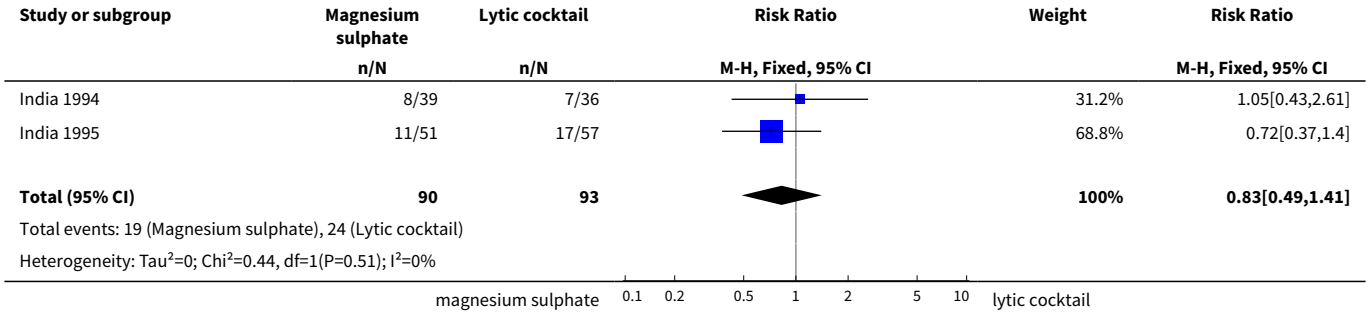
Analysis 1.11. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 11 Cardiac arrest.

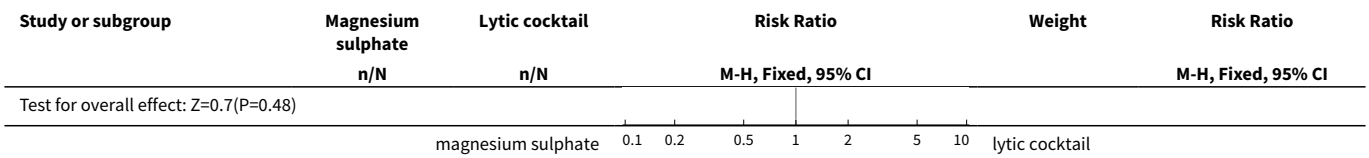


Analysis 1.12. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 12 Mechanical ventilation.

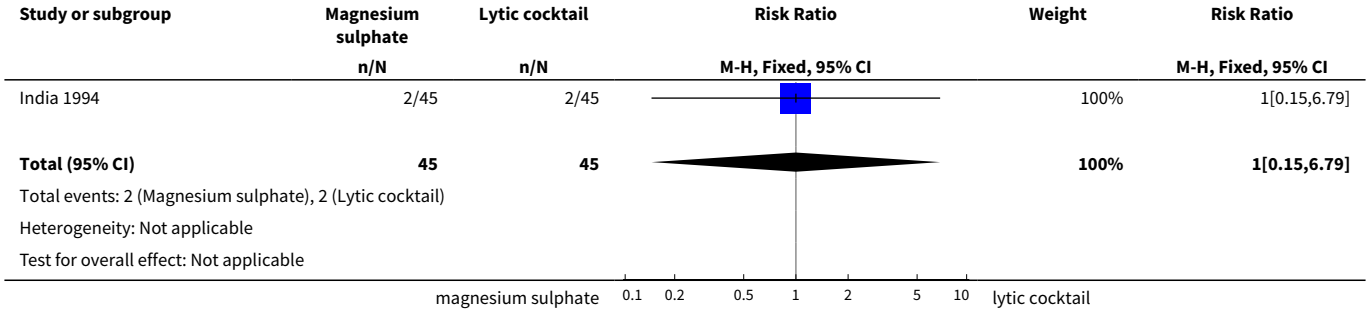


Analysis 1.13. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 13 Caesarean section.

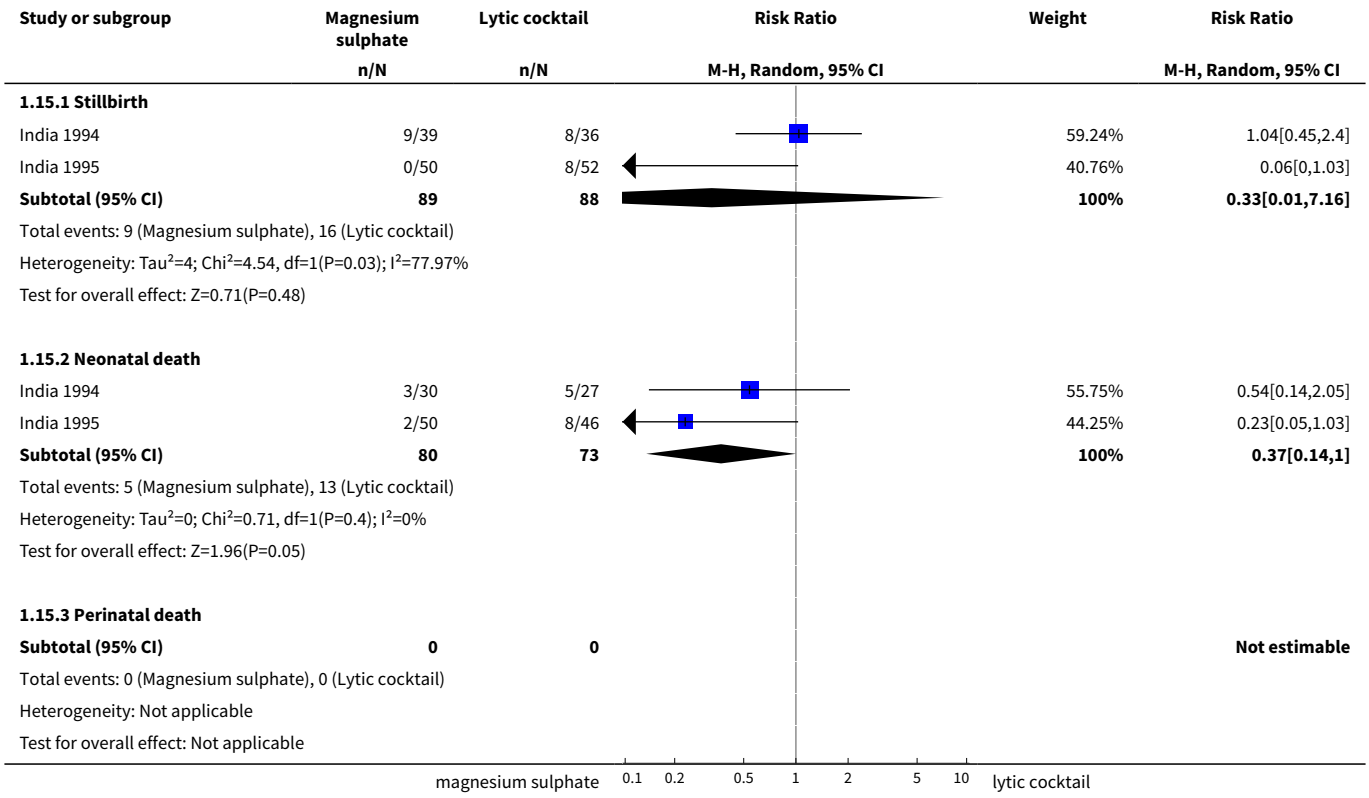




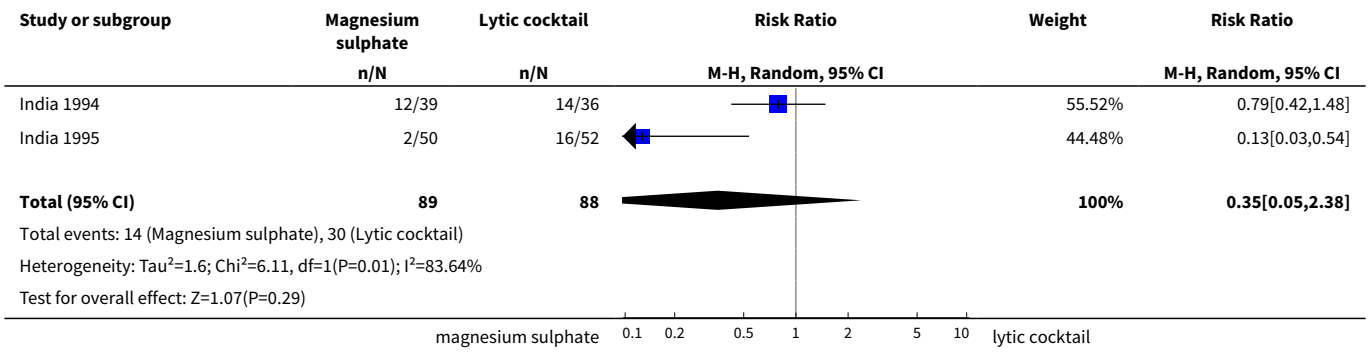
Analysis 1.14. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 14 Postpartum psychosis.



Analysis 1.15. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 15 Death of the fetus or infant (subgroups by stillbirth, perinatal and neonatal death).



Analysis 1.16. Comparison 1 Magnesium sulphate versus lytic cocktail, Outcome 16 Any death of the fetus or infant.



APPENDICES

Appendix 1. CENTRAL search strategy

#1. PREGNAN* AND HYPERTENS*
#2. ECLAMP*
#3. LYTIC NEAR COCKTAIL
#4. CHLORPROM*
#5. #1 OR #2
#6. #4 0R #3
#7. #5 AND #6

WHAT'S NEW

Date	Event	Description
15 March 2011	Amended	Contact details amended.

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 1, 2001

Date	Event	Description
28 July 2010	New citation required but conclusions have not changed	New author helped update the review.
28 July 2010	New search has been performed	Search updated; one new study included (India 1988). No change in conclusions.
17 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the design. Two review authors (L Duley (LD) and D Chou (DC)) conducted data extraction for this update. LD entered the data, which was checked by DC. LD and DC drafted the text with comments and input from Metin Gülmezoglu.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- UNDP/UNFPA/WHO/World Bank (HRP), Switzerland.
- Resource Centre for Randomised Trials, UK.

External sources

- Medical Research Council, UK.
- UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Department of Reproductive Health and Research, WHO, Switzerland.

(DC)

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Chlorpromazine [administration & dosage]; Drug Combinations; Eclampsia [*drug therapy]; Magnesium Sulfate [adverse effects] [*therapeutic use]; Meperidine [administration & dosage]; Promethazine [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy