Effects and Safety of Magnesium Sulfate on Neuroprotection

A Meta-analysis Based on PRISMA Guidelines

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Abstract: To evaluate the evidence of effects and safety of magnesium sulfate on neuroprotection for preterm infants who had exposure in uteri.

We searched electronic databases and bibliographies of relevant papers to identify studies comparing magnesium sulfate (MgSO₄) with placebo or other treatments in patients at high risk of preterm labor and reporting effects and safety of MgSO₄ for antenatal infants. Then, we did this meta-analysis based on PRISMA guideline. The primary outcomes included fatal death, cerebral palsy (CP), intraventricular hemorrhage, and periventricular leukomalacia. Secondary outcomes included various neonatal and maternal outcomes.

Ten studies including 6 randomized controlled trials and 5 cohort studies, and involving 18,655 preterm infants were analyzed. For the rate of moderate to severe CP, MgSO₄ showed the ability to reduce the risk and achieved statistically significant difference (odd ratio [OR] 0.61, 95% confidence interval [CI] 0.42–0.89, P = 0.01). The comparison of mortality rate between the MgSO₄ group and the placebo group only presented small difference clinically, but reached no statistical significance (OR 0.92, 95% CI 0.77–1.11, P = 0.39). Summarily, the analysis of adverse effects on babies showed no margin (P > 0.05). Yet for mothers, MgSO₄ exhibited obvious side-effects, such as respiratory depression, nausea and so forth, but there exited great heterogeneity.

MgSO₄ administered to women at high risk of preterm labor could reduce the risk of moderate to severe CP, without obvious adverse effects on babies. Although there exist many unfavorable effects on mothers, yet they may be lessened through reduction of the dose of MgSO₄ and could be tolerable for mothers. So MgSO₄ is both beneficial and safety to be used as a neuroprotective agent for premature infants before a valid alternative was discovered.

(Permissions: BMD = Bayley mental development, BPD = Bayley psychomotor development, CI = 95% confidence interval, CNKI = China National Knowledge Infrastructure, CP = cerebral palsy, g = grams, ISCU = in special care baby unit, IVH = intraventricular hemorrhage, MgSO₄ = magnesium sulfate, NEC = necrotizing enterocolitis, OR = odds ratio, PVL = periventricular leukomalacia, RCTs = randomized controlled trials, wk = gestational weeks, WMI = white matter injury.

INTRODUCTION

Preterm infants, defined as infants who are born at more than 24 gestational weeks (wk) but <37 wk, are at high risk of dying in early life. If they fortunately survive, they are usually at great risk of neurological impairments, such as cerebral palsy (CP), gross motor dysfunction, deafness, blindness, developmental delay, and intellectual impairment.¹ Manuck et al² reported approximately 1 in 4 preterm children (<34 wk) had neurodevelopmental impairment at age 2 years. Among these, CP is the leading cause of neurologic impairment. CP is a nonprogressive neurological disorder affecting motor function, including a number of different morbid conditions that can arise at any time during brain development and may involve a disorder of motor function that is permanent but may change over time. Ninety-two percent of affected children can survive to 20 years old, contributing substantially to the burden of illness into adulthood.³

In recent decades, with the advances in medical and health conditions, such as the widespread use of surfactant and antenatal steroids, and improvements in ventilation management, the survival rate of preterm infants is sharply rising. Concomitantly, the number of infants with subsequent neurological impairments and disabilities is increasing, resulting in that more children require intensive postnatal medical care and costly developmental services.⁴⁵ So the therapy which can have a substantial effect on reducing the risk of neurological impairments is eagerly needed.

Luckily, magnesium sulfate (MgSO₄) shunts light upon such a head-scratching problem. In 1992, Kuban et al⁶ found MgSO₄ to be associated with a reduction in risk of intraventricular hemorrhage (IVH). A few years later, a case–control study demonstrated MgSO₄ had an effect in decreasing the risk of subsequent development of CP among preterm infants. Yet, 2 observational studies reported that prenatal use of MgSO₄ had no effects in reducing risk of IVH or CP.⁸⁹ Subsequently, researches regarding the association between MgSO₄ and CP mushroomed. To date, there have been 2 randomized control trials (RCTs) supporting that antenatal exposure to MgSO₄ could significantly decrease the risk of CP for preterm infants.¹⁰¹¹ However, a meta-analysis suggested there were no significant effects of antenatal MgSO₄ therapy on combined rates of mortality with CP, and there were higher rates of minor maternal side effects in the MgSO₄ group.¹² Regardless of MgSO₄’s uncertain neuroprotective effects, some study hold that it was its adverse effects on the mother, such as palpitations, hypotension, oliguria or renal failure, absent or reduced tendon reflexes, which may place gravida in life-
thwarting conditions, that restricted its use in clinics. As you witnessed, the issue concerning the effects and safety of MgSO4 used in clinics still remained controversial. Considering this, we sought to probe the correlation between MgSO4 and neuroprotective effects, as well as fetal and maternal adverse outcomes based on a large population.

MATERIALS AND METHODS

Search Strategy

We searched PubMed, China National Knowledge Infrastructure (CNKI), the Cochrane Library, and bibliographies of relevant papers published up to August 2015, without language limitations, using the keywords and combinations of the following search terms “magnesium sulfate” and “preterm labor/ labor/delivery” or “antenatal” and “neuroprotection” or “cerebral palsy.”

Study Selection Criteria

All published articles about women at risk of preterm labor given MgSO4 administered intravenously, intramuscularly or orally comparing with those using either placebo or tocolytic were included. And the reported outcomes should include primary outcomes or secondary outcomes.

Study Exclusion Criteria

Studies without a control group were excluded. Abstracts, reviews, protocols, letters, and comments were excluded because of the absence of details concerning study methods and results. Studies were surely ineligible if there was no information provided on any of the outcomes of focus, if data were not reported regarding the intention to deal with.

Data Extraction, Synthesis, and Analysis

If the abstract described a study that did not meet the eligible criteria, the study was not reviewed any further. Eligible articles were reviewed in details. The review of articles was undertaken independently by 2 reviewers (XZ and YX) who decided on which article was eligible. Any disagreements were resolved by discussing with a third reviewer (QT).

Two reviewers extracted data independently. The primary outcomes were death of preterm infants (neonatal, fetal, or later death during follow-up period), CP (moderate to severe, or mild), IVH (grade III–IV or any), periventricular leukomalacia (PVL), white matter injury (WMI). Secondary outcomes were infant outcomes (Apgar score <7 at 5 min, tracheal intubation, mechanical ventilation, neonatal convulsions/seizures, necrotizing enterocolitis (NEC), in special care baby unit (ISCU), need for supplemental oxygen at 36 wk, neurologic disability and developmental delay) and maternal complications (hypotension, absent or reduced tendon reflexes, muscle weakness, blurred vision, flushing, nausea or vomiting, sweating).

The diagnose of CP, neurologic disability, and developmental delay almost made by expert pediatricians at more than 18 months of corrected age. Whereby, 4 RCTs13–15 were did at 18 months of corrected age, 2 RCTs16,17 were did at 24 months of corrected age, the 2 cohort studies18,19 were did at school ages. Baseline data were depicted explicitly if possible.

Statistical analyses were conducted using the program “Review Manager 5.2.” We calculated a summary odds ratio (OR) and 95% confidence interval (CI) for dichotomous variables, using Mantel–Haenszel and fixed/random-effects mode.20 Statistical heterogeneity between trials was tested using the I² statistic. If substantial heterogeneity was found (I² > 25%), we used a random-effects Model. The OR was calculated as the ratio of the number of events using magnesium sulfate over that using placebo. If the 95% CI did not encompass 1.0 for OR or if the P value was <0.05, then the results were considered to be statistically significant. Homogeneity of tests among pooled results were performed using simple chi-squared test. Methodologic quality assessment of the trials was conducted based on the modified scoring system.21 Points were awarded on the basis of the quality of randomization, blinding, and follow-up. In addition, we also assessed concealment of allocation. The methodologic quality of included trials was assessed. The funnel plot was used to examine publication bias.22

Ethical Approval

The ethical approval was not necessary because our study was a meta-analysis that belongs to secondary researches.

RESULTS

This research generated 387 pieces of paper totally. However, 338 articles were excluded undoubtedly after screening the abstracts. Among the remaining 49 articles, 39 articles were excluded because of reviews, letters, comments, and unavailable data. The included 10 articles including 6 RCTs and 5 cohort studies (3 follow-up studies and 2 retrospective studies) were reviewed carefully. Because the article written by Mintendorf et al13 had 2 arms (tocolytic and neuroprotective), we considered it as 2 separate studies. Finally, 11 studies including 18,655 preterm infants were analyzed (Figure 1).

The characteristics of the included studies were exhibited in Table 1. The largest number of objectives was 10,110, more than 100 times of the smallest number. The earliest RCT started in 1995, the latest RCT ended in 2004, the duration of 6 RCTs ranged from 3 to 7 years. The 6 RCTs were conducted before 2004, while the 5 cohort studies were did in the lasted few years except 1.23 Apart from 2 RCTs13 and 2 retrospective studies,18,19 the rest were did in multicenters. The gestational ages at randomization were almost <34 wk except 1 was >37 wk.15 The dose of MgSO4 was 4 grams (g) bolus load only, or followed by an infusion of 1 to 3 g per hour (1–3 g/h) in 5 RCTs. While in one RCT and one retrospective study,24,25 the dose was 6 g bolus load, followed by an infusion of 2 g/h. Another retrospective study23 used 5 g bolus load, followed by an infusion of one g/h. Four RCTs applied saline in the control group, one RCT,13 and one retrospective study23 exploited tocolytic, the remaining RCT24 and one retrospective study22 did not report.

As to the quality assessment (Table 2), all RCTs described randomized assignment, allocation concealment, methods of blinding, and follow-up status, gaining a total score of 4 to 8 points. (2 RCTs were 4 points, 2 RCTs were 7 points, 2 RCTs were 8 points). Among these, 3 RCTs achieved satisfactory follow-up rate, in addition to 2 RCTs untold.

Seven studies evaluated the prevalence of CP between children who exposed to MgSO4 in uteri and those did not. For the rate of CP, MgSO4 seemingly showed the ability to reduce the risk of CP, but there was no statistically significant difference (OR 0.96, 95% CI 0.78–1.17, P = 0.66; Figure 2). As to the individual analysis of mild CP and moderate to severe CP, the former did not generate statistically significant difference (OR 0.76, 95% CI 0.53–1.11, P = 0.16), while the latter demonstrated obvious statistical difference (OR 0.61, 95% CI
0.42–0.89, \( P = 0.01 \)). Simultaneously, infant mortality was analyzed in details and no statistical significance was found (OR 0.92, 95% CI 0.77–1.11, \( P = 0.39 \); Figure 3). The rates of whole mortality, death <28 days or >28 days, death after discharge all showed a reduction in preterm infants who had exposure to MgSO\(_4\), but significant difference was not found (\( P > 0.05 \)). Moreover, there was no effect on the rates of death before discharge and still birth. In terms of IVH, IVH (III–IV), PVL, and WMI, there was no evidence showing whether MgSO\(_4\) would exert an effect on increasing or decreasing the risk (Table 3).

Researchers also performed a comparison of negative effects on neonates between the MgSO\(_4\) group and placebo group based on limited available data. The risk of Apgar score <7 at 5 min, need for oxygen at 36 wk, NEC and mechanic ventilation apparently went up for neonates in MgSO\(_4\) group, but no statistically significant difference was witnessed. Furthermore, neonatal seizures/convulsion, respiratory distress syndrome (RDS), ISCU, and tracheal intubation were dependently assessed by 2 studies, without achieving any statistical significance (Table 4).

When it came to the results of long-term outcomes for infants, MgSO\(_4\) seemingly could increased the risk of gross motor dysfunction, any neurological impairment and developmental delay, despite of no remarkable statistical significance (Table 5).

Finally, it is high time to mention the adverse effects of MgSO\(_4\) on pregnant women. Compared with women receiving placebo, the OR of respiratory depression for those exposed to MgSO\(_4\) was 1.62 (95% CI 1.12–2.34, \( P = 0.01, I^2 = 11\% \)). Besides, MgSO\(_4\) appeared to augment the hazard of tachycardia, flushing, and nausea/vomiting, but the heterogeneity among these studies was quite distinct (\( P < 0.05, I^2 > 90\% \); Table 6).

To evaluate the possibly exiting publication bias for the outcomes, funnel plot was demonstrated to find no evidence of asymmetry, suggesting that publication bias was not present (Figure 4).

**DISCUSSION**

The findings indicated that moderate to severe CP occurred significantly less frequently in the MgSO\(_4\) group, which was
| Study | Period | Location | Inclusion Criteria | Exclusion Criteria | Gestational Week | No. of Magnesium Sulfate (n) | No. of Control Group (n) |
|-------|--------|----------|-------------------|-------------------|------------------|--------------------------|------------------------|
| Mittendorf et al | MagNET 1995–1997 | Single center in the USA | Women with single or twin pregnancy in preterm labor at gestational ages >24 wk but <34 wk, with or without PROM, and cervical dilatation ≤4 cm | Mothers with triplet or higher order gestations any or with clinical features suggesting infection or preeclampsia | >24 wk but <34 wk | 4 g bolus followed by an infusion of 2–3 g/h (55) | Ritodrine, terbutaline, indomethacin, nifedipine (51) |
| Mittendorf et al | MagNET 1995–1997 | Single center in the USA | Women with single or twin pregnancy in preterm labor at gestational ages >24 wk, but <34 wk, with or without PROM, and cervical dilatation >4 cm | Mothers with triplet or higher order gestations any or with clinical features suggesting infection or preeclampsia | >24 wk but <34 wk | 4 g bolus, no maintenance (30) | Saline (29) |
| Crowther et al | ACTO MgSO4 1996/2–2000/9 | 16 tertiary hospitals (with 13 in Australia and 3 New Zeal) | Women with single, twin, triplet, or quadruplet pregnancy in preterm delivery at gestational ages <30 wk because of planned or expected birth within 24 h | Women in second stage of labor, or had received magnesium sulfate in this pregnancy, or have contraindications to magnesium sulfate | <30 wks | 4 g over 20 min IV (load), 1 g/h maintenance; until delivery or up to 24 h (629) | Saline (626) |
| Study            | Period                  | Location                  | Inclusion Criteria                                                                 | Exclusion Criteria                                                                 | Gestational Week | No. of Magnesium Sulfate (n) | No. of Control Group (n) |
|------------------|-------------------------|---------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------|-----------------------------|--------------------------|
| Marret et al17   | PREMAG 1997/7–2003/7    | 18 tertiary hospitals in French | Women with single, twin, triplet, or quadruplet fetuses in preterm delivery at gestational ages <33 wk if birth was expected or planned within 24 h | Fetus with severe malformations or chromosomal abnormalities and women with pregnancy associated vascular disease (preeclampsia, growth restriction, HELLP syndrome, retroplacental hematoma) or with at least 1 of the following criteria: hypotension, cardiac rhythm abnormalities, hydroelectrolyte abnormalities, renal insufficiency, ingestion during the last 24 h of calcium channel blockers, digitalins, or indomethacin, persistent signs of cardiovascular toxicity or tachycardia 1 h after cessation of tocolytic intake, myasthenia, or indication for emergency cesarean section | <33 wk           | 4 g over 30 min IV (load); no maintenance (362) | Saline (336) |
| Study          | Period       | Location                        | Inclusion Criteria                                                                 | Exclusion Criteria                                                                 | Gestational Week       | No. of Magnesium Sulfate (n) | No. of Control Group (n) |
|---------------|--------------|---------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------|-----------------------------|--------------------------|
| Rouse et al   | 1997/12–2004/5 | 20 centers in the USA           | Women with single or twin pregnancy in preterm labor at gestation ages of 24–31 wk and at high risk for spontaneous delivery because of PROM, advanced preterm labor with dilatation of 4–8 cm and intact membranes, or indicated preterm delivery anticipated within 2–24 h | Delivery anticipated within <2 h, cervical dilatation >8 cm, PPROM before 22 wk, unwillingness of the obstetrician to intervene for the benefit of the fetus, major fetal anomalies or death, maternal hypertension or preeclampsia, maternal contraindications to magnesium sulfate, and receipt of IV magnesium sulfate within the previous 12 h | >24 wk but <32 wk      | 6 g over 20–30 min IV (load); 2 g/h maintenance; Up to 12 h of treatment or resume if imminent labor | Not reported (1256)       |
| Altman et al  | Magpie Trial (1998/7–2001/11) | 175 secondary and tertiary hospitals in 33 countries | Women with singleton or multiple pregnancy with preeclampsia who had not given birth or were ≤24 h postpartum and uncertain about whether to use magnesium sulfate to prevent eclampsia, irrespective of whether they had received magnesium sulfate or other anticonvulsants previously | Women had hypersensitivity to magnesium, hepatic coma with a risk of renal failure, or myasthenia gravis | <37 wk                | 4 g over 10–15 min IV (load); 1 g/h maintenance (IV) or 5 g every 4 h (IM); up to 24 h | Saline (5055)            |
| Study                        | Period                  | Location                                                                 | Inclusion Criteria                                                                 | Exclusion Criteria                                                                 | Gestational Week       | No. of Magnesium Sulfate (n) | No. of Control Group (n) |
|-----------------------------|-------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------|----------------------------|--------------------------|
| Magpie Trial Follow-Up Study Collaborative Group | 1998/7–2001/11 | 125 centers in 19 countries across 5 continents | —                                                                                    | —                                                                                    | at 18 mo of age           | — (1635)                  | — (1648)                   |
| Doyle et al\(^1\)           | ACTO MgSO\(_4\) follow-up (2005–2011) | 14 centers in Australia and New Zealand | —                                                                                    | —                                                                                    | 2 or 6–11 y of age        | — (443)                   | — (424)                   |
| Chollat et al\(^1\)         | PREMAG follow-up (2009/12–2012/4) | 18 tertiary hospitals in French                                          | —                                                                                    | —                                                                                    | 7–14 y of age             | — (266)                   | — (257)                   |
| Rantonen et al\(^2\)        | Turku University Central Hospital | Retrospective analysis of mother treated antenatally for tocolysis with magnesium sulfate | Four mothers were treated for tocolysis antenatally with a combination therapy of magnesium sulfate and ritodrine | <33 wk                                                                             | 5 g/20 min IV (load); 1 g/h maintenance, until uterine contractions stopped or maternal heart rate was >140 beats/min (32) | Ritodrine (27)           |                          |
| Gibbins et al\(^2\)         | Women and Infants Hospital of Rhode Island in the USA | Women with single pregnancy at gestational ages <32 wk with 1 of the following diagnoses: preterm labor defined by contractions and cervical change; PPROM; or an obstetric or medical indication for delivery before 32 wk of gestation (eg. severe preeclampsia or fetal growth restriction) | Women who received betamethasone or dexamethasone at an outside institution          | <32 wk                                                                             | 6 g IV (load); 2 g/h maintenance (IV) until delivery, or stop if delivery is no longer deemed imminent (223) | Not reported (90)         |                          |

HELLP = hemolysis, elevated liver enzymes, low platelets; IM = intramuscular, IV = intravenous, PROM = premature rupture of membranes, wk = week of gestation, – = follow-up studies.


| Study | Method to Generate Randomization | Double Blind | Randomization | Adequate | Method of Concealment of Allocation | Adequate | Withdrawal or Follo-up, % | Total Score |
|-------|----------------------------------|--------------|---------------|-----------|------------------------------------|-----------|--------------------------|-------------|
| Mittendorf et al\(^1\)\(^3\) | RCT | No | No | Yes | Adequate | Yes | U | 4 |
| Mittendorf et al\(^1\)\(^3\) | RCT | Yes | Yes | Adequate | Adequate | Yes | U | 7 |
| Crowther et al\(^1\)\(^6\) | RCT | Yes | Yes | Adequate | Yes | 98.9 | U | 8 |
| Marret et al\(^1\)\(^7\) | RCT | No | Yes | Adequate | Yes | 98.43 | U | 7 |
| Rouse et al\(^1\)\(^0\),\(^2\)\(^4\) | RCT | Yes | Yes | Adequate | Yes | 95.6 | U | 8 |
| Altman et al\(^1\)\(^5\) | RCT | Yes | Yes | Adequate | Yes | 83.91 | U | 7 |

Points were awarded on the basis of the quality of randomization, double blinding, follow-up. In addition, concealment of allocation was assessed as follows: 2 points, adequate method (central randomization or drug containers or opaque, sealed envelopes that were sequentially numbered and opened sequentially only after they had been irreversibly assigned to the participant); 1 point, no concealment or randomization; 0 point, follow-up completion, <95% or unreported point, RCT = randomized controlled trials.

This study did not show more competence to detect clinically significant differences in many other maternal and neonatal outcomes, because the power was limited for less frequent outcomes such as maternal pulmonary edema, hypertension, postpartum hemorrhage, and infant development, including infant Bayley mental development (BMD) and Bayley psychomotor development (BPD)\(^2\)\(^7\) which were routinely used as the quantitative assessment of infant later development. One study\(^2\)\(^4\) providing relevant data implied that BMD <85 was diagnosed in 406 from 876 children in the MgSO\(_4\) group (46.34%) and in 427 from 919 children in the placebo group (46.46%), and the result was not statistically compelling (95% CI 0.83—1.20, \(P = 0.96\)). Simultaneously, the percentage of BPD <85 was 34.13% versus 34.27% in the MgSO\(_4\) group and placebo group, achieving no statistical significance (95% CI 0.82—1.21, \(P = 0.99\)). Additionally, one prevailing study noted that no substantial difference was found on any of the cognitive, academic, attention, executive function, and other neurosensory outcomes.\(^1\)\(^8\) Adverse effects may occur in women who become hypermagnesemic during MgSO\(_4\) treatment, such as an absent or reduced tendon reflexes, headache, itching or tingling, warmth over body, mouth dryness, muscular weakness, sleepiness, and dizziness. So maternal complications were analyzed, resulting in rising risk of any side effects, achieving no difference with inevitable heterogeneity (\(P < 0.0001\), \(I^2 = 98\%\)).

Equally, adverse effects could occur in neonates exposed to MgSO\(_4\) antenatally. Generally, we were prone to hypothesize that the risk of RDS, the need for resuscitation, neonatal seizures/convulsion, and Apgar score <7 at 5 min were certain to ascend on account of the elevated MgSO\(_4\) concentration in babies’ body. In light of this, the American Academy of Pediatrics and American Heart Association supported Neonatal Resuscitation Program lists MgSO\(_4\) among maternally administered medications.\(^2\)\(^9\) However, this meta-analysis offered indefinite evidences to associate fetal MgSO\(_4\) exposure with potentially possible adverse effects based on limited data (\(P > 0.05\)). Furthermore, a recent study aiming at investigating the association between umbilical cord blood MgSO\(_4\) concentration and resuscitation of infants showed that MgSO\(_4\) for neuroprotection had no effects on additional invasive delivery room resuscitation measures.\(^3\)\(^0\) Consequently, the detrimental outcomes of anteneonates cannot be attributed to the effects of MgSO\(_4\), for premature newborns were vulnerable to suffer from these hazards instinctively. Similarly, a study published in Lancet conveyed that MgSO\(_4\) did not appear to exert substantive harmful effects on mothers and babies in a short term.\(^1\)\(^2\) To verify whether there exited long-term effects, a follow-up study reported there were no serious maternal or perinatal complications ascribed to MgSO\(_4\).\(^2\)\(^5\)

### TABLE 2. Description of Quality Assessment of Included Studies

| Study | Method to Generate Randomization | Double Blind | Randomization | Adequate | Method of Concealment of Allocation | Adequate | Withdrawal or Follo-up, % | Total Score |
|-------|----------------------------------|--------------|---------------|-----------|------------------------------------|-----------|--------------------------|-------------|
| Mittendorf et al\(^1\)\(^3\) | RCT | No | No | Yes | Adequate | Yes | U | 4 |
| Mittendorf et al\(^1\)\(^3\) | RCT | Yes | Yes | Adequate | Adequate | Yes | U | 7 |
| Crowther et al\(^1\)\(^6\) | RCT | Yes | Yes | Adequate | Yes | 98.9 | U | 8 |
| Marret et al\(^1\)\(^7\) | RCT | No | Yes | Adequate | Yes | 98.43 | U | 7 |
| Rouse et al\(^1\)\(^0\),\(^2\)\(^4\) | RCT | Yes | Yes | Adequate | Yes | 95.6 | U | 8 |
| Altman et al\(^1\)\(^5\) | RCT | Yes | Yes | Adequate | Yes | 83.91 | U | 7 |

Points were awarded on the basis of the quality of randomization, double blinding, follow-up. In addition, concealment of allocation was assessed as follows: 2 points, adequate method (central randomization or drug containers or opaque, sealed envelopes that were sequentially numbered and opened sequentially only after they had been irreversibly assigned to the participant); 1 point, no concealment or randomization; 0 point, follow-up completion, <95% or unreported point, RCT = randomized controlled trials.

Consistent with a previous study\(^2\)\(^4\) and the number needed to treat to prevent one case of disabling CP estimated by one study varied from 30 to 60.\(^2\)\(^6\) While MgSO\(_4\) did not appear to be helpful in cutting down the mortality rate, which probably because various treatment regimens and durations may yield a difference in the outcomes. But when we excluded the trail using large dose,\(^2\)\(^7\) say 6 g/20—30 min IV (load) and followed by 2 g/h (maintenance), the OR of death was 0.82 (95% CI 0.63—1.09, \(P = 0.17\)). Similarly, excluding the trail using small dose,\(^2\)\(^2\),\(^2\)\(^4\) say more than 4 g IV (load), the OR of total mortality was 0.96 (95% CI 0.81—1.14, \(P = 0.66\)). This was in line with a study which suggested there was no difference in the rates of overall CP or death regardless of the total duration and doses of MgSO\(_4\).\(^2\)\(^7\)
TABLE 3. Primary Outcomes

| Outcome                        | No. of Studies | No. of Infants Exposing to MgSO₄ | OR    | 95% CI | P   | I², % |
|-------------------------------|----------------|----------------------------------|-------|--------|-----|-------|
| Overall CP                    | 7              | 2200/4043                        | 0.96  | 0.78–1.17 | 0.66 | 0     |
| Mild CP                       | 4              | 50/3504                          | 0.76  | 0.53–1.11 | 0.16 | 6     |
| Moderate to severe CP         | 4              | 45/3504                          | 0.61  | 0.42–0.89 | 0.01 | 0     |
| Death                         | 8              | 857/8555                         | 0.92  | 0.77–1.11 | 0.39 | 40    |
| <28 d                         | 2              | 92/970                           | 0.83  | 0.62–1.11 | 0.21 | 0     |
| >28 d                         | 2              | 46/970                           | 0.9   | 0.59–1.37 | 0.62 | 0     |
| Before discharge              | 2              | 93/858                          | 1.26  | 0.91–1.73 | 0.16 | 17    |
| After discharge               | 2              | 24/2264                          | 0.93  | 0.53–1.62 | 0.79 | 0     |
| Fatal death                   | 2              | 107/970                          | 1.35  | 0.65–2.78 | 0.42 | 80    |
| Still birth                   | 3              | 124/6514                         | 0.10  | 0.77–1.29 | 0.99 | 0     |
| IVH                           | 4              | 249/1022                         | 1.05  | 0.86–1.29 | 0.64 | 0     |
| IVH (III–IV)                  | 5              | 62/1156                          | 0.80  | 0.57–1.15 | 0.25 | 8     |
| PVL                           | 3              | 40/1069                          | 1.30  | 0.81–2.10 | 0.28 | 0     |
| WMI                           | 2              | 55/373                           | 0.81  | 0.54–1.21 | 0.30 | 0     |

*P < 0.05 was considered to be of statistical significance; if substantial heterogeneity was found I² > 50% was considered to be of substantial heterogeneity, a random-effects model was used. CI = confidence interval, CP = cerebral palsy, IVH = intraventricular hemorrhage, MgSO₄ = magnesium sulfate, OR = odds ratio, PVL = periventricular leukomalacia, WMI = white matter injury.
**TABLE 4. Neonatal Outcomes**

| Outcome                                | No. of Studies | Yes | No | OR | 95% CI   | P      | I², % |
|----------------------------------------|----------------|-----|----|----|----------|--------|-------|
| Apgar score <7 at 5 min                | 3              | 323/4737 | 263/4524 | 1.12 | 0.40–26.12 | 0.19   | 0     |
| Neonatal seizures/convulsion           | 2              | 47/4514  | 61/4434  | 0.75 | 0.51–1.10  | 0.15   | 0     |
| RDS                                    | 2              | 170/384  | 154/363  | 1.07 | 0.79–1.43  | 0.67   | 0     |
| ISCU                                   | 2              | 1026/24,477 | 863/2319 | 1.04 | 0.92–1.18  | 0.49   | 0     |
| Need for oxygen at 36 wk               | 3              | 483/5034 | 462/5049 | 1.07 | 0.92–1.25  | 0.35   | 0     |
| Tracheal intubation                    | 2              | 247/368  | 149/222  | 1.23 | 0.85–1.78  | 0.28   | 0     |
| NEC                                    | 3              | 45/1004  | 45/978   | 0.96 | 0.62–1.47  | 0.85   | 0     |
| Mechanic ventilation                   | 4              | 1168/5357 | 1101/5139 | 1.09 | 0.96–1.24  | 0.18   | 0     |

*P < 0.05 was considered to be of statistical significance; if substantial heterogeneity was found I² > 50% was considered to be of substantial heterogeneity, a random-effects model was used. CI = interval confidence, ISCU = in special care baby unit, MgSO₄ = magnesium sulfate, NEC = necrotizing enterocolitis, OR = odds ratio, RDS = respiratory distress syndrome.*

**TABLE 5. Long-Term Outcomes for Preterm Children**

| Outcome                             | No. of Studies | Yes | No | OR | 95% CI   | P      | I², % |
|-------------------------------------|----------------|-----|----|----|----------|--------|-------|
| Gross motor dysfunction             | 2              | 182/826 | 187/813 | 0.95 | 0.75–1.20 | 0.66   | 0     |
| Any neurologic impairment           | 3              | 216/2172 | 219/2158 | 0.92 | 0.73–1.16 | 0.49   | 29    |
| Blindness                           | 3              | 5/2603  | 4/2582  | 1.21 | 0.35–4.22 | 0.76   | 0     |
| Deafness                            | 3              | 10/2603 | 15/2582 | 0.70 | 0.16–3.01 | 0.64   | 51    |
| Developmental delay                 | 2              | 192/2131 | 193/2126 | 0.95 | 0.74–1.21 | 0.65   | 1     |

*P < 0.05 was considered to be of statistical significance; if substantial heterogeneity was found I² > 50% was considered to be of substantial heterogeneity, a random-effects model was used. CI = interval confidence, OR = odds ratio.*

**TABLE 6. Maternal Complications**

| Outcome                             | No. of Studies | Yes | No | OR | 95% CI   | P      | I², % |
|-------------------------------------|----------------|-----|----|----|----------|--------|-------|
| Respiratory depression              | 3              | 92/6612 | 57/6645 | 1.62 | 1.12–2.34 | 0.01   | 11    |
| Tachycardia                         | 2              | 95/5534 | 45/5520 | 2.12 | 1.47–3.06 | <0.0001 | 78    |
| Cesarean section                    | 2              | 133/316 | 106/305 | 1.36 | 0.98–1.88 | 0.06   | 0     |
| Flushing                            | 3              | 2045/6612 | 211/6645 | 19.86 | 11.44–34.50 | <0.00001 | 92    |
| Nausea/vomiting                     | 3              | 483/6612 | 90/6645 | 7.04 | 2.65–18.69 | <0.00001 | 93    |
| Stopping use of side effects        | 3              | 619/6612 | 266/6645 | 3.65 | 1.28–10.35 | 0.02   | 96    |
| Any side effects                    | 3              | 2519/6612 | 567/6645 | 12.77 | 5.38–30.31 | <0.0001 | 98    |

*P < 0.05 was considered to be of statistical significance; if substantial heterogeneity was found I² > 50% was considered to be of substantial heterogeneity, a random-effects model was used. CI = interval confidence, OR = odds ratio.*
CONCLUSIONS

In conclusion, the effect of MgSO4 in lowering the rate of moderate to severe CP in preterm infants was remarkable without affecting the neonatal and maternal adverse outcomes. Although there were side effects on mothers, yet they could be lessened or removed by reducing the dose. Thus, MgSO4 is beneficial and safe to be used as a special neuroprotective agent for premature infants before discovering a valid alternative.

REFERENCES

1. Wilson-Costello D, Friedman H, Minich N, et al. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics.* 2005;115:997–1003.
2. Manuck TA, Sheng X, Yoder BA, et al. Correlation between initial neonatal and early childhood outcomes following preterm birth. *Am J Obstet Gynecol.* 2014;210:426.e1–426.e9.
3. Hutton JL, Cooke T, Pharaoh TOD. Life expectancy in children with cerebral palsy. *BMJ.* 1994;309:431–435.
4. Vincer MJ, Allen AC, Joseph KS, et al. Increasing prevalence of cerebral palsy among very preterm infants: a population-based study. *Pediatrics.* 2006;118:e1621–e1626.
5. Himmelmann K, Haggberg G, Beckung E, et al. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995–1998. *Acta Paediatr.* 2005;94:287–294.
6. Kuban KCK, Leviton A, Paganu M, et al. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. *J Child Neurol.* 1992;7:70–76.
7. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics.* 1995;95:263–269.
8. Canterino JC, Verma UL, Visintainer PF, et al. Maternal magnesium sulfate and the development of neonatal periventricular leucomalacia and intraventricular hemorrhage. *Obstet Gynecol.* 1999;93:396–402.
9. Weintrab Z, Solovechick M, Reichman B, et al. Effect of maternal tocolysis on the incidence of severe periventricular/intraventricular haemorrhage in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed.* 2001;85:F13–F17.
10. Rouse DJ, Hirtz DG, Thom E, et al. A randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med.* 2008;359:895–905.
11. Reeves S, Gibbo R, Clark S. Magnesium for fetal neuroprotection. *Am J Obstet Gynecol.* 2011;204:e1–e4.
12. Doyle LW, Crowther CA, Middleton P, et al. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev.* (1)2009CD004661.
13. Mittendorf R, Dambrosia J, Pyde PG, et al. Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants. *Am J Obstet Gynecol.* 2002;186:1111–1118.
14. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for children at 18 months. *BJOG.* 2007;114:289–299.
15. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet.* 2002;359:1877–1890.
16. Crowther CA, Hiller JE, Doyle LW, et al. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA.* 2003;290:2669–2666.
17. Marret S, Marpeau L, Zupan-Simunek V, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. BJOG. 2007;114:310–318.

18. Doyle LW, Anderson PJ, Haslam R, et al. School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo. JAMA. 2014;312:1105–1113.

19. Chollat C, Enser M, Houivet E, et al. School-age outcomes following a randomized controlled of magnesium sulfate for neuroprotecting of preterm infants. J Pediatr. 2014;165:398–400.

20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–188.

21. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.

22. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–634.

23. Rantonen T, Ekblad U, Grönlund J, et al. Influence of maternal magnesium sulphate and ritodrine treatment on the neonate: a study with six-month follow-up. Acta Paediatr. 1999;88:1142–1146.

24. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med. 2008;9:895–905.

25. Gibbins KJ, Browning KR, Lopes VV, et al. Evaluation of the clinical use of magnesium sulfate for cerebral palsy prevention. Obstet Gynecol. 2013;121((2 Pt 1)):235–240.

26. Rouse DJ. Magnesium sulfate for the prevention of cerebral palsy. Am J Obstet Gynecol. 2009;200:610–612.

27. McPherson JA, Rouse DJ, Grobman WA, et al. Association of duration of neuroprotective magnesium sulfate infusion with neonatal and maternal outcomes. Obstet Gynecol. 2014;124:749–755.

28. Bayley N. Bayley scales of infant development. 2nd ed. New York: Psychological Corporation; 1993.

29. Kattwinkel J, Boyle D, Bloom RS. Textbook of Neonatal Resuscitation. American Academy of Pediatrics. 5th ed. Elk Grove Village, IL: American Heart Association, American Academy of Pediatrics; 2006.

30. Johnson LH, Mapp DC, Rouse DJ, et al. Association of cord blood magnesium concentration and neonatal resuscitation. J Pediatr. 2012;160:573–577.