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SYSTEMATIC REVIEW AND META-ANALYSIS

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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 ($MgSO_4$) with placebo or other treatments in patients at high risk of preterm labor and reporting effects and safety of $MgSO_4$ 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, $MgSO_4$ 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, $MgSO_4$ exhibited obvious side-effects, such as respiratory depression, nausea and so forth, but there exited great heterogeneity.

$MgSO_4$ 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 exit many unfavorable effects on mothers, yet they may be lessened through reduction of the dose of $MgSO_4$ and could be tolerable for mothers. So $MgSO_4$ is both beneficial and safety to be used as a neuroprotective agent for premature infants before a valid alternative was discovered.

(*Medicine* 95(1):e2451)

Abbreviations: 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, $MgSO_4$ = magnesium sulfate, NEC = necrotizing enterocolitis, OR = odds ratio, PVL = periventricular leukomalacia, RCTs = randomized controlled trials, wk = gestational weeks, WMI = white matter injury.

Editor: Undurti Das.
Received: September 18, 2015; revised: December 9, 2015; accepted: December 10, 2015.
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The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002451

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 al[2] 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.[4,5] So the therapy which can have a substantial effect on reducing the risk of neurological impairments is eagerly needed.

Luckily, magnesium sulfate ($MgSO_4$) shunts light upon such a head-scratching problem. In 1992, Kuban et al[6] found $MgSO_4$ to be associated with a reduction in risk of intraventricular hemorrhage (IVH). A few years later, a case–control study demonstrated $MgSO_4$ had an effect in decreasing the risk of subsequent development of CP among preterm infants.[7] However, 2 observational studies reported that prenatal use of $MgSO_4$ had no effects in reducing risk of IVH or CP.[8,9] Subsequently, researches regarding the association between $MgSO_4$ and CP mushroomed. To date, there have been 2 randomized control trials (RCTs) supporting that antenatal exposure to $MgSO_4$ could significantly decrease the risk of CP for preterm infants.[10,11] However, a meta-analysis suggested there were no significant effects of antenatal $MgSO_4$ therapy on combined rates of mortality with CP, and there were higher rates of minor maternal side effects in the $MgSO_4$ group.[12] Regardless of $MgSO_4$'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-

threatening conditions, that restricted its use in clinics. As you witnessed, the issue concerning the effects and safety of $MgSO_4$ used in clinics still remained controversial. Considering this, we sought to probe the correlation between $MgSO_4$ 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 $MgSO_4$ 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 RCTs[13–15] were did at 18 months of corrected age, 2 RCTs[16,17] were did at 24 months of corrected age, the 2 cohort studies[18,19] 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 I^2 statistic. If substantial heterogeneity was found ($I^2 > 25\%$), 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 Mittendorf et al[13] 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 RCTs[13] 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 $MgSO_4$ 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 study[23] 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 study[23] exploited tocolytic, the remaining RCT[24] and one retrospective study[25] 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 $MgSO_4$ in uteri and those did not. For the rate of CP, $MgSO_4$ 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

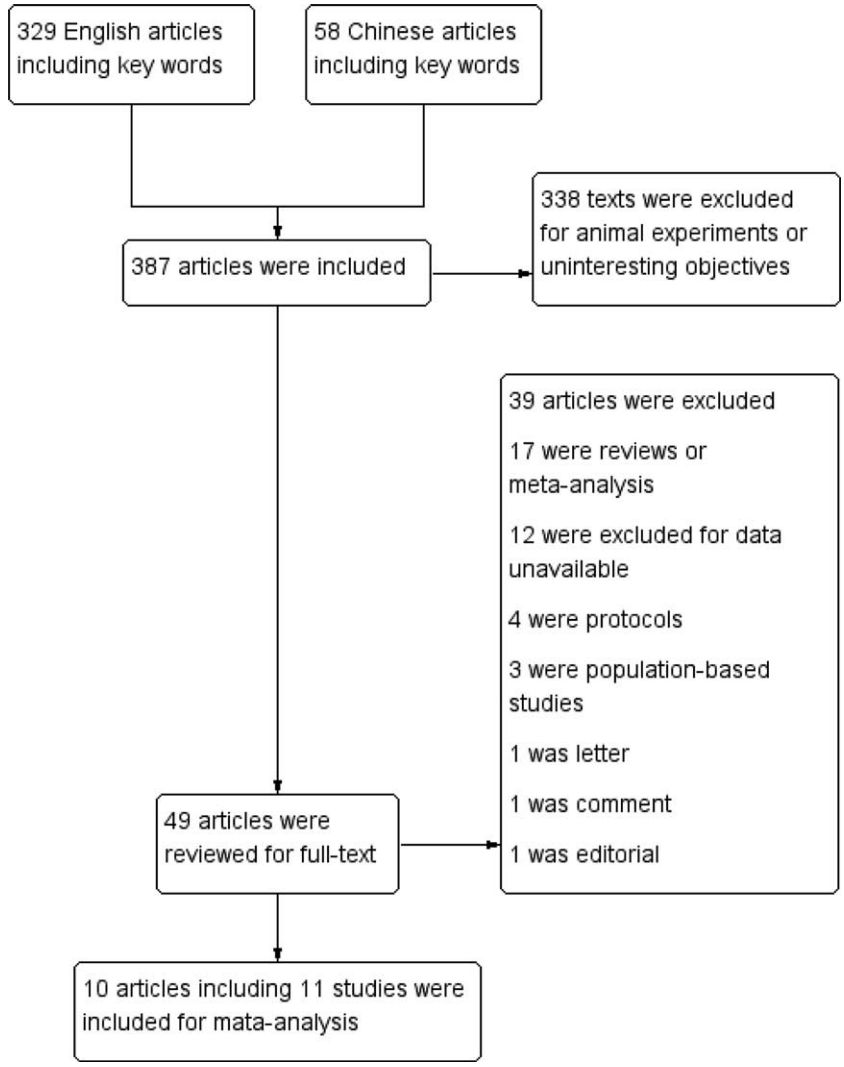

FIGURE 1. Search algorithm.

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

TABLE 1. Characteristics of Included Studies

Study	Period	Location	Inclusion Criteria	Exclusion Criteria	Gestational Week	No. of Magnesium Sulfate (n)	No. of Control Group (n)
Mittendorf et al[13]	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, indomethaci, nifedipine (51)
Mittendorf et al[13]	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[16]	ACTO $MgSO_4$ 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 al[17]	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[10,24]	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 (1188)	Not reported (1256)
Altman et al[15]	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 (5055)	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[14]	Magpie Trial Follow Up (1998/7–2001/11)	125 centers in 19 countries across 5 continents	–	–	at 18 mo of age	– (1635)	– (1648)
Doyle et al[18]	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[19]	PREMAG follow-up (2009/12–2012/4)	18 tertiary hospitals in French	–	–	7–14 y of age	– (266)	– (257)
Rantonen et al[23]	1995–1998	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[25]	2007/10–2011/2	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.

TABLE 2. Description of Quality Assessment of Included Studies

		Modified Jadad Score for Assessment of Methodologic Quality of Included Studies						
Study	Study Style	Method to Generate Randomization Appropriate	Double Blind	Methods for Blinding Appropriate	Method of Concealment of Allocation	Description of Withdrawal or Dropout	Completeness of Follow-Up of Fetuses, %	Total Score
Mittendorf et al[13]	RCT	Y*	Y	Y	U	N*	U	4
Mittendorf et al[13]	RCT	Y	Y	Y	U	N	U	4
Crowther et al[16]	RCT	Y	Y	Y	Adequate	Y	98.9	8
Marret et al[17]	RCT	Y	N	Y	Adequate	Y	98.43	7
Rouse et al[10,24]	RCT	Y	Y	Y	Adequate	Y	95.6	8
Altman et al[15]	RCT	Y	Y	Y	Adequate	Y	83.91	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); 0 points, no concealment of allocation or inadequate method or not described. Thus, the total score ranged from 0 (lowest quality) to 8 (highest quality). *Yes 1 point, *No 0 point; follow-up ≥95% 1 point, follow-up <95% or unreported 0 point. RCT = randomized controlled trials.

consistent with a previous study.[24] And the number needed to treat to prevent one case of disabling CP estimated by one study varied from 30 to 60.[26] 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,[24] 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,[23,24] 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 $MgSO_4$.[27]

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, hypotension, postpartum hemorrhage, and infant development, including infant Bayley mental development (BMD) and Bayley psychomotor development (BPD)[28] which were routinely used as the quantitative assessment of infant later development. One study[24] 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.[18] Adverse effects may occur in women who become hypermagnesemic during $MgSO_4$ treatment, such as 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.[29] 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.[30] 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.[12] To verify whether there exited long-term effects, a follow-up study reported there were no serious maternal or perinatal complications ascribed to $MgSO_4$.[25]

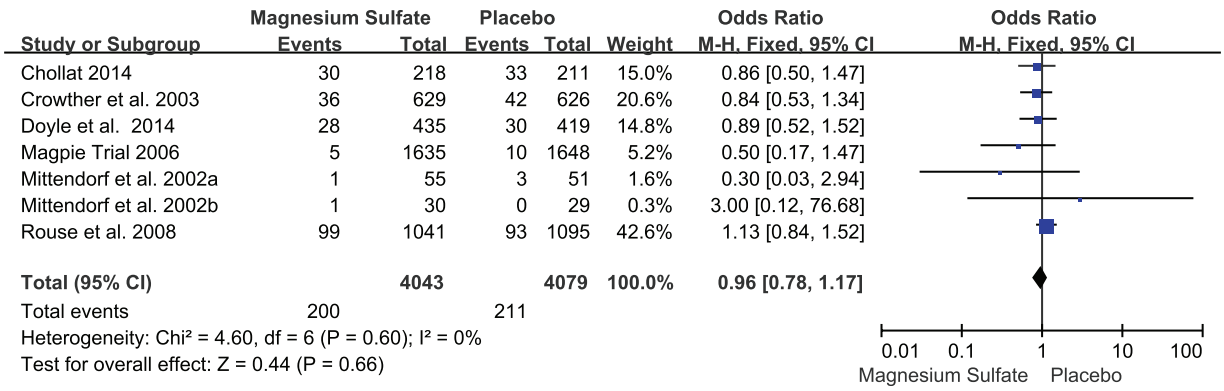

FIGURE 2. Meta-analysis of data about cerebral palsy from 7 studies using a fixed-effect model. CI = confidence interval, OR = odds ratio.

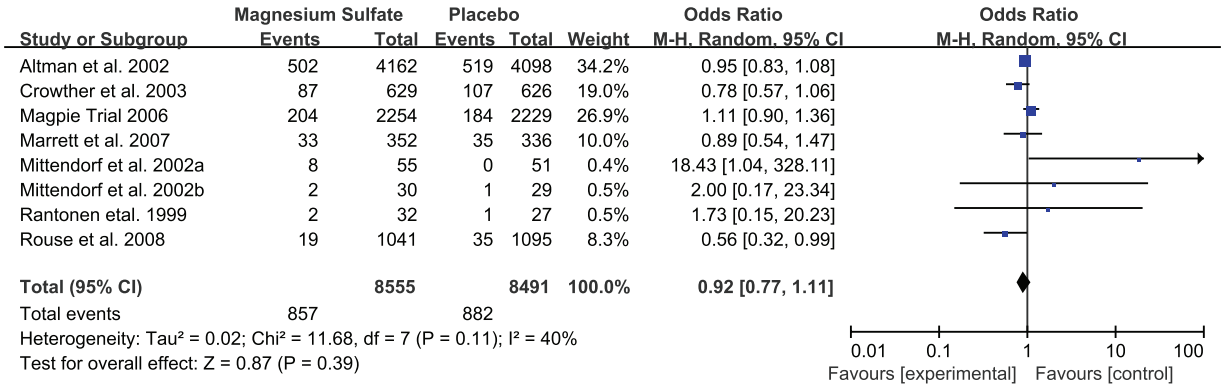

FIGURE 3. Meta-analysis of data about death from 8 studies using a random-effect model. CI = confidence interval, OR = odds ratio.

TABLE 3. Primary Outcomes

Outcome	No. of Studies	No. of Infants Exposing to $MgSO_4$		OR	95% CI	*P*	I^2, %
		Yes	No				
Overall CP	7	2200/4043	211/4079	0.96	0.78–1.17	0.66	0
Mild CP	4	50/3504	67/3588	0.76	0.53–1.11	0.16	6
Moderate to severe CP	4	45/3504	75/3588	0.61	0.42–0.89	0.01	0
Death	8	857/8555	882/8491	0.92	0.77–1.11	0.39	40
<28 d	2	92/970	107/950	0.83	0.62–1.11	0.21	0
>28 d	2	46/970	49/950	0.9	0.59–1.37	0.62	0
Before discharge	2	93/858	69/1738	1.26	0.91–1.73	0.16	17
After discharge	2	24/2264	26/2274	0.93	0.53–1.62	0.79	0
Fatal death	2	107/970	74/950	1.35	0.65–2.78	0.42	80
Still birth	3	124/6514	125/6548	1.00	0.77–1.29	0.99	0
IVH	4	249/1022	233/990	1.05	0.86–1.29	0.64	0
IVH (III–IV)	5	62/1156	73/1117	0.81	0.57–1.15	0.25	8
PVL	3	40/1069	30/1039	1.30	0.81–2.10	0.28	0
WMI	2	55/373	62/351	0.81	0.54–1.21	0.30	0

$P < 0.05$ was considered to be of statistical significance; if substantial heterogeneity was found $I^2 > 50\%$ was considered to be of substantial heterogeneity, a random-effects model was used. CI = interval confidence, CP = cerebral palsy, IVH = intraventricular hemorrhage, $MgSO_4$ = magnesium sulfate, OR = odds ratio, PVL = periventricular leukomalacia, WMI = white matter injury.

TABLE 4. Neonatal Outcomes

Outcome	No. of Studies	No. of Infants Exposing to $MgSO_4$		OR	95% CI	*P*	I^2, %
		Yes	No				
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 $I^2 > 50\%$ was considered to be of substantial heterogeneity, a random-effects model was used. CI = interval confidence, ISCU = in special care baby unit, $MgSO_4$ = magnesium sulfate, NEC = necrotizing enterocolitis, OR = odds ratio, RDS = respiratory distress syndrome.

TABLE 5. Long-Term Outcomes for Preterm Children

Outcome	No. of Studies	No. of Infants Exposing to $MgSO_4$		OR	95% CI	*P*	I^2, %
		Yes	No				
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 $I^2 > 50\%$ 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	No. of Infants Exposing to $MgSO_4$		OR	95% CI	*P*	I^2, %
		Yes	No				
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 $I^2 > 50\%$ was considered to be of substantial heterogeneity, a random-effects model was used. CI = interval confidence, OR = odds ratio.

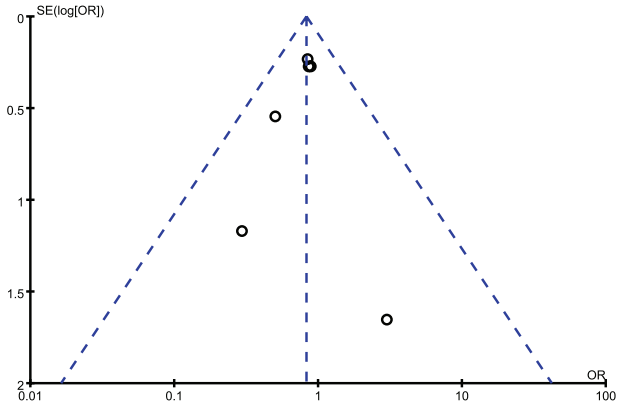

FIGURE 4. Publication bias is assessed by funnel plot, of which the asymmetry is exhibited by evidence of small studies with higher odds ratio and the paucity of small negative studies in the lower right of the funnel plot.

Nevertheless, several study limitations must be kept in mind when considering the generalizability of the data. Firstly, from the methodological aspect, the weakness was that the recruited studies included 5 cohort studies that were of low-to-medium quality. Although we searched all the literature worldwide, the 6 RCTs were done 10 years ago. So whether the data collected were suitable for the current requires more newly researches. Besides, there was a wide gap of the number of objects in recruited trails, ranging from 59 to 10,110.[13,15] But the analysis including or excluding the smallest or the largest number of study generated the same results. In addition, we failed to appraise the status of neurosensory outcomes in later development, such as cognitive and academic abilities on account of data unavailable. Moreover, the lack of adequate data about the related risks, such as CP or death and other neonate outcomes at different gestational ages, say 24 to 28 wk or 28 to 34 wk, leads to a pity that the analysis was contracted greatly. Further investigations may focus on such issues.

Despite of all the shortages above, the strength of this study is stronger than any single study since the included primary studies are quite homogeneous. This secondary analysis was derived from a large, prospectively collected cohort, providing a relatively large number of women exposed to $MgSO_4$ antenatally. What is more, precedent studies usually used the composition of CP and death as the primary outcomes expecting to obtain supportive result. Nevertheless, we insist on calculating the OR for CP and death separately, because CP and death are divergent endpoints. The accumulative data of CP and death lack scientific theory, because the 2 are rivals. To obtain the best evidence, a meta-analysis based on RCTs perhaps assists a lot. However, the data about the neuroprotective effects of $MgSO_4$ in fetus was collected few years ago and lacked results of long-term follow-up. So in our study, we incorporated 3 follow-up studies and 2 respective studies which provided data regarding outcomes later in life for children surviving the initial neonatal period. The results showed no conspicuous discrepancies. Certainly that lefts a pitiful flaw in view of the methodological aspect. So more large multicenter studies designed to explore the neuroprotective effects and safety of $MgSO_4$ used for preterm infants are in urgent need.

CONCLUSIONS

In conclusion, the effect of $MgSO_4$ 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, $MgSO_4$ is beneficial and safe to be used as a special neuroprotective agent for premature infants before discovering a valid alternative.

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