Review Article

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The effect of antenatal magnesium sulfate on intraventricular hemorrhage in premature infants: a systematic review and meta-analysis

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Objective

The aim of this systematic review and meta-analysis study was to determine the pooled estimate of the effect of antenatal magnesium sulfate ($MgSO_4$) on intraventricular hemorrhage (IVH) in premature infants.

Methods

Two review authors independently searched all randomized clinical trials from international databases, including Medline (PubMed), Web of Sciences, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Research Registers of ongoing trials (ClinicalTrials.gov), from January 1989 to August 2017. Two independent review authors were responsible for data collection. After extracting the necessary information from the evaluated articles, meta-analysis of the data was performed using Stata version 14. Also, sources of heterogeneity among studies were determined by Meta regression.

Results

In this study, among 126 articles that were extracted from primary studies, 7 papers that evaluated the effect of $MgSO_4$ on IVH were eligible for inclusion in the meta-analysis. The results of the meta-analysis showed that pooled relative risk (95% confidence interval [CI]) was 0.80 (95% CI, 0.63 to 1.03) for the effect of $MgSO_4$ on IVH.

Conclusion

Results of this study showed that although $MgSO_4$ had a protective effect on IVH in premature infants, this effect was not statistically significant. Further studies are needed to determine the best dosage, timing, and gestational age to achieve the optimum effect of $MgSO_4$ on IVH.

Systematic Review Registration

International Prospective Register of Systematic Reviews (PROSPERO) Identifier: CRD42019119610

Keywords: Magnesium Sulfate; IVH; Premature infants; Systematic review; Meta-analysis

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Introduction

Intraventricular hemorrhage (IVH) consists of bleeding inside or around the ventricles, which are the areas in the brain that contain the cerebral spinal fluid. IVH is a common problem in premature infants, especially in very low birth weight infants (<1,500 g) [1]. Ancel et al. [2] reported that 56 children with normal ultrasound findings accounted for 35% of children with cerebral palsy. In the same study, children with isolated IVH, and those with white matter disease, accounted for 14% and 52% of cerebral palsy cases, respectively [2].

Many factors are involved in the incidence of IVH, the most important of which include respiratory distress, hypoxia-induced damage, ischemia, high or low blood pressure, increased venous blood pressure, pneumothorax, and hypovolemia [3]. Symptoms of IVH are nonspecific and differ according to the severity of the disease [4]. In severe and acute IVH cases, symptoms such as pale skin, acute anemia, respiratory dysfunction, and fontanel bulge can occur. Currently, cerebral ultrasound or magnetic resonance imaging is performed in the first 3 days of life and is repeated two or three times in suspected cases of IVH to assess its severity [5,6]. Bleeding from the germinal matrix around the brain ventricle based on IVH extension in brain ultrasonography is divided into four categories: grade 1 for limited bleeding to germinal matrix; grade 2 for IVH; grade 3 for bleeding with ventricular extension; and grade 4 for extension of bleeding to brain parenchyma. Grades 1 and 2 are automatically removed without any consequence; however, grades 3 and 4 are associated with severe consequences [7]. Given that preterm birth is a major cause of IVH, various methods have been proposed for its prevention [8]. Tocolytic treatments are among the conventional methods; however, there is disagreement about the best treatment method [9]. Magnesium sulfate, prostaglandin inhibitors, calcium channel blockers, and nitric oxide releasing drugs are some of the therapeutic methods in which positive effects have been reported [10,11]. Currently, magnesium sulfate is one of the most common methods used to prevent preterm delivery. Various studies have suggested that magnesium sulfate reduces the risk of brain injury in preterm infants [12-14]. In contrast, there are some studies that do not confirm the effect of magnesium sulphate on risk reduction of IVH, cerebral palsy, and perinatal mortality [15-17]. Therefore, given the controversy in the results of various studies in this field, the aim of this systematic review and meta-analysis study was to determine the effect of antenatal magnesium sulfate ($MgSO_4$) on IVH in premature infants.

Materials and methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. The protocol of this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019119610).

1. Search strategy

Two review authors (YM and KM) independently searched all randomized clinical trials from international databases, including Medline (PubMed), Web of Sciences, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Research Registers of ongoing trials (ClinicalTrials.gov), from January 1989 to August 2017. The search was performed based on 11 English phrases and keywords, including "Magnesium Sulfate ($MgSO_4$)", "Heptahydrate Magnesium Sulfate", "Tocolysis Preterm", "Newborn", "Newborn Infant", "Newborn Infants", "Fetal", "Neonatal", "Preterm Prelabor Rupture of Membranes (PPROM)", "Prelabor Rupture of Membranes (PROM)", "Preterm Birth", "Premature Births", "Intraventricular hemorrhage (IVH)", "Cerebral Intraventricular Hemorrhages", "Neuroprotection", "Neuronal Protection", "Dystonic-Rigid Cerebral Palsy", "Mixed Cerebral Palsy", "Rolandic Type Cerebral Palsy", "Congenital Cerebral Palsy", "Spastic Diplegia", "Monoplegic Cerebral Palsy", "Athetoid Cerebral Palsy", "Dyskinetic Cerebral Palsy", "Atonic Cerebral Palsy", "Hypotonic Cerebral Palsy", "Diplegic Infantile Cerebral Palsy", "Spastic Cerebral Palsy", and "Cerebral Palsy (CP)". We exported the search results to the End-Note software version 9. The duplicated primary studies were deleted. The primary search results were reviewed based on the inclusion and exclusion criteria, and some of the articles were eliminated after reviewing their title and abstract. Subsequently, we investigated the search results and excluded some studies after full text review (Fig. 1).

2. Inclusion and exclusion criteria

We included all randomized controlled trials (RCTs) which assessed or reported the effect of antenatal magnesium sulfate

on IVH in premature infants. Therefore, only articles in which the primary outcome was IVH in premature infants, and gestational age between 24 to 37 weeks, were included in this review. Also, we considered primary studies in which IVH was diagnosed after birth by cranial ultrasound. We excluded duplicate citations, non- peer reviewed, cross-sectional studies, case control studies, review papers, book chapters, conference proceedings, and studies with other primary outcomes.

3. Data extraction and quality assessment

After assessment of the titles, abstracts, and texts, the full text of each selected article was retrieved for detailed analysis. Data were extracted using a data collection form with the name of the first author, date of publication, study title, study design, geographical setting, sample size, type of comorbidities (IVH-related), and main outcome. The entire process, from systematic search to final data extraction, was performed independently by two research experts (Kappa statistic for agreement for quality assessment; 0.75). Two reviewers (KM and ZN) independently evaluated the articles. Any disagreement was assessed by both reviewers, and if a consensus was not reached, a third author (YM) would evaluate the study. Moreover, quality assessment (using CONSORT) was determined by the same data extractor for each study. Risk of bias in the included studies was assessed using the Cochrane Risk of Bias Tool [19]. The bias domains that were assessed included sequence generation, allocation concealment, blinding, outcome data, and outcome reporting. Trials were rated as high risk of bias when the methodological flaw was likely to have affected the true outcome, low risk of bias if the flaw was deemed inconsequential to the true outcome, and unclear risk of bias when insufficient information was provided to permit judgment.

4. Statistical analysis

In this meta-analysis, we used two measures of association measurement: odds ratio (OR) and relative risk (RR). When the frequency of outcome (IVH in premature infants) is relatively low, OR and risk ratio provide similar estimates of RR [20]. We used logarithm and standard error logarithm RR for meta-analysis. The pooled RR with 95% confidence interval (CI) was derived through the DerSimonian and Laird method using random and fixed models [21]. Finally, for the estimated RR, we used the random effects model, since the test for heterogeneity was statistically significant in some analyses. In the present study, we used Cochran's Q test and I^2 statistic, with a significance level set at *P*-value <0.10 for evaluating statistical heterogeneity between the studies [22].

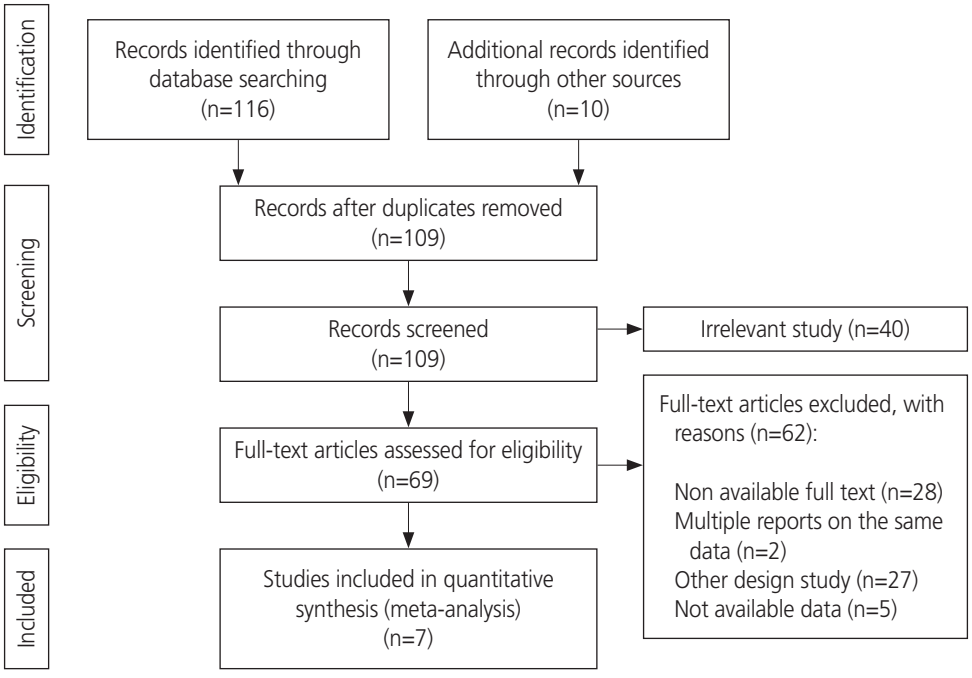

Fig. 1. Flow diagram of the literature search and study selection.

Table 1. Characteristics of studies included by principal outcome evaluated

Authors	Date of publication	Study name	Study design	Geographical setting	Sample size	Comorbidities (IVH)	Age of pregnancy (weeks)	Cases	Doses of intervention	RR (95% CI)	OR (95% CI)
Hirtz et al. [24]	2015	Antenatal magnesium and cerebral palsy in preterm infants	RCT	US	Intervention group: 953 Placebo group: 1,026	Cranial ultrasounds	24–37	PPROM/PTL	6 g loading and 2 g/hr infusion	-	0.57 (0.37–0.87)
Mirzamoradi et al. [27]	2014	Does magnesium sulfate delay the active phase of labor in women with premature rupture of membranes	RCT	Iran	Intervention group: 46 Placebo group: 46	Cranial ultrasounds	<34	PPROM	4 g loading and 2 g/hr infusion	-	3.2 (0.4–4.8)
Crowther et al. [10]	2003	Effect of magnesium sulfate given for neuroprotection before preterm birth	RCT	Australia	Intervention group: 535 Placebo group: 527	Cranial ultrasounds	<30	Planned and expected within 24 hr	4 g loading and 2 g/hr infusion	1.10 (0.90–1.33)	-
Mittendorf et al. [30]	2002	Association between maternal serum ionized magnesium levels at delivery and neonatal intraventricular hemorrhage	RCT	US	Intervention group: 72 Placebo group: 72	Cranial ultrasounds	<34	PTL	Before active phase (4 g loading and 2 g/hr infusion) After active phase (4 g single dose)	1.11 (0.53–2.34)	-
Horton et al. [25]	2015	The effect of magnesium sulfate administration for neuroprotection on latency in women with preterm premature rupture of membranes	RCT	US	Intervention group: 621 Placebo group: 638	Cranial ultrasounds	24–32	PPROM	6 g loading and 2 g/hr infusion	-	0.31 (0.10–0.96)
Rouse et al. [29]	2008	Magnesium sulfate for the prevention of cerebral palsy	RCT	US	Intervention group: 1,096 Placebo group: 1,145	Cranial ultrasounds	24–31	PPROM/PTL	6 g loading and 2 g/hr infusion	0.91 (0.78–1.08)	-
Marret et al. [26]	2006	Effect of magnesium sulphate on mortality and neurologic morbidity of the very-preterm newborn (of less than 33 weeks) with two-year neurological outcome: results of the prospective PREMAG trial	RCT	French	Intervention group: 286 Placebo group: 278	Cranial ultrasounds	<33	Planned and expected under 30 hr	4 g single dose	0.83 (0.62–1.09)	-

IVH, intraventricular hemorrhage; RR, relative risk; CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; PPROM, Preterm Prelabor Rupture of Membranes; PTL, preterm labor.

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Table 2. Quality assessment of included studies according to the CONSORT checklist

Item No.	Hirtz et al. [24]	Mirzamoradi et al. [27]	Crowther et al. [10]	Mittendorf et al. [30]	Horton et al. [25]	Rouse et al. [29]	Marret et al. [26]
1a	No	Yes	Yes	No	No	Yes	Yes
1b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2a	Yes	Yes	Yes	No	Yes	Yes	No
2b	Yes	Yes	No	No	Yes	No	Yes
3a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3b	Yes	Yes	Yes	No	Yes	Yes	Yes
4a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4b	Yes	Yes	No	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a	Yes	Yes	Yes	Yes	Yes	No	Yes
6b	No	No	No	No	No	No	No
7a	No	Yes	No	Yes	No	Yes	Yes
7b	No	No	Yes	No	No	Yes	Yes
8a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8b	No	No	Yes	No	No	No	Yes
9	No	No	Yes	No	No	No	Yes
10	No	No	Yes	No	No	No	Yes
11a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11b	No	No	No	No	No	Yes	Yes
12a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12b	No	No	No	No	No	Yes	No
13a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13b	Yes	Yes	No	No	No	No	No
14a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15	No	Yes	Yes	Yes	Yes	Yes	Yes
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17b	No	No	No	No	No	No	No
18	Yes	Yes	No	Yes	No	No	No
19	No	No	Yes	No	No	No	No
20	Yes	No	Yes	Yes	Yes	Yes	No
21	No	No	No	No	No	No	No
22	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23	Yes	No	No	No	No	No	Yes
24	No	No	No	No	No	Yes	No
25	No	No	No	No	No	No	No
Total	22	23	24	19	20	24	26

An I^2 <50%, I^2 ≥50%, and I^2 ≥75% were considered to be evidence of "moderate", "substantial", and "considerable" heterogeneity, respectively [19]. In addition, to assess the source of heterogeneity between the studies, the authors conducted a meta regression and subgroup analysis. Publication bias was assessed by funnel plot, Egger and Begg's test, with a significance level set at *P*-value<0.10 [23]. The statistical analysis was performed using Stata 14.0 (Stata Corp, College Station, TX, USA) and Review Manager (RevMan), version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

At the end of the database search, we obtained 126 articles. Among these articles, 17 were removed due to duplication. After reviewing the titles and abstracts of the articles, 40 were excluded due to non-relevance, resulting in 69 articles. After reviewing the full text of these 69 articles, only 7 were eligible for entry in the meta-analysis (Fig. 1).

The total sample size of the included studies in meta-analysis was 8,578 cases [10,24-29], in which 4 studies reported RR with a total sample size of 4,135 [10,26,28,29], and 3 studies reported OR with a total sample size of 4,443 [24,25,27] (Table 1). Table 1 shows the characteristics and results of the studies included in the meta-analysis.

As previously described in the methodology section, when the frequency of outcome (IVH in premature infants) is relatively low, OR and risk ratio provide similar estimates of RR [20]. Therefore, the OR and RR were combined, and the pooled RR was extracted with 95% CI.

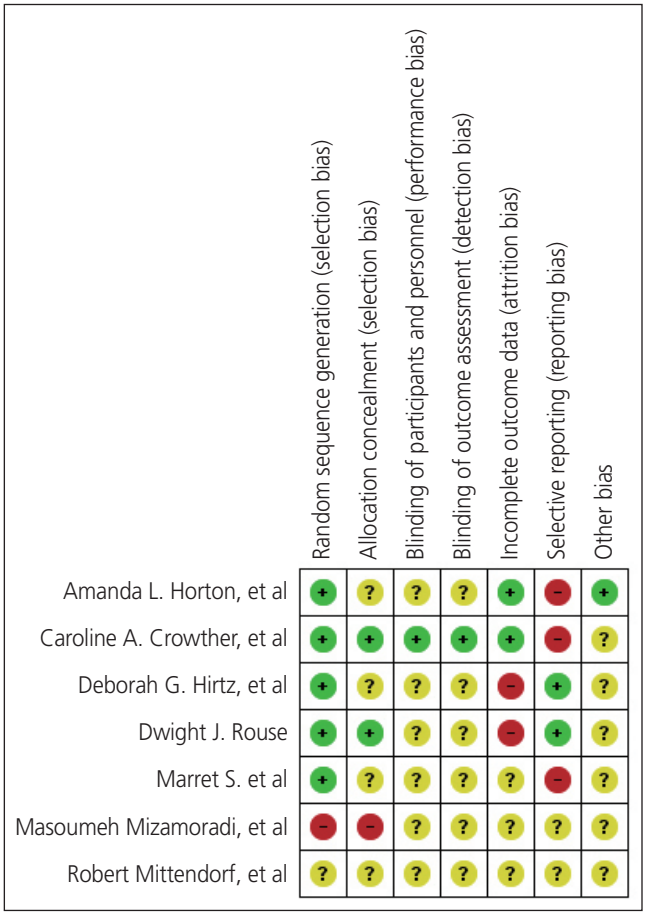

Fig. 3. Risk of bias summary (review authors' judgments about each risk of bias item for each included study).

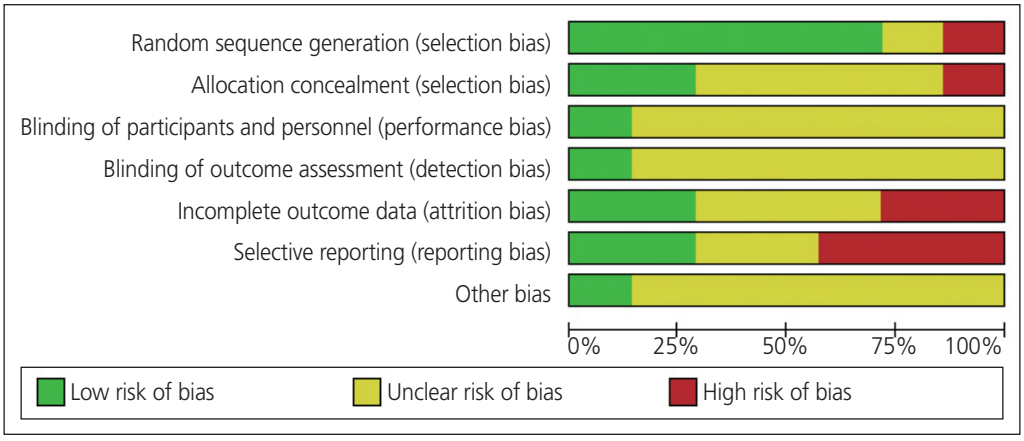

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

1. Quality assessment and risk of bias

The quality assessment of the studies was performed by CONSORT checklist. Table 2 shows quality assessment of included studies according to the CONSORT checklist. As can be seen, the quality of all studies was high based on this checklist, except the study by Mittendorf et al. [30] (Table 2). The risk of bias was also performed for the articles included in the analysis. We considered the probability of the risk of bias according to sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The results showed that most studies were low risk in terms of random sequence generation (selection bias) and allocation sequence concealment (selection bias). Additional information is provided in Fig. 2. Also, the study by Crowther et al. [10] presented the lowest risk among the studies Fig. 3. The studies did not provide adequate description of their methods, including randomization and blinding, which made it difficult for the researchers to make judgments about the risk of bias among the included studies. Also, outcome data was incomplete in all the included studies, so the risk of selective reporting was high or unclear (Fig. 2).

2. Meta-analysis

The results showed that pooled RR was 0.80 (95% CI, 0.63 to 1.03; I^2=63.0%; *P*=0.013), although $MgSO_4$ had a protective effect on IVH; however, this effect was not statistically significant (Fig. 4). The results also indicated the heterogeneity of the studies; however, bias in the publication of the results was not statistically significant (χ^2=3.25; *P*=0.352; I^2=8.2%); however, the CI of the test includes zero (Begg's test: Z=0.34; *P*=0.978) (Egger's test: t=0.10; *P*=0.930 95% CI, –0.743 to 0.779).

3. Subgroup analysis

Table 3 shows subgroup analysis by gestational age and $MgSO_4$. The RR for 6 g loading and 2 g/hr regimen of $MgSO_4$ on IVH in premature infants was 0.84 (95% CI, 0.72 to 0.98; I^2=42.5%; *P*=0.345). Also, RR for 4 g loading and 2 g/hr infusion $MgSO_4$ was 1.13 (95% CI, 0.94 to 1.36; I^2=27.8%; *P*=0.250); however, 4-g single dose $MgSO_4$ had a protective effect on IVH in premature infants (RR, 0.86; 95% CI, 0.66 to 1.12; I^2=0.0%; *P*=0.473) (Table 3).

The results of the subgroup analysis based on gestational age showed that the effect of $MgSO_4$ on IVH in premature infants between 24–37 weeks and <34 weeks were 0.93

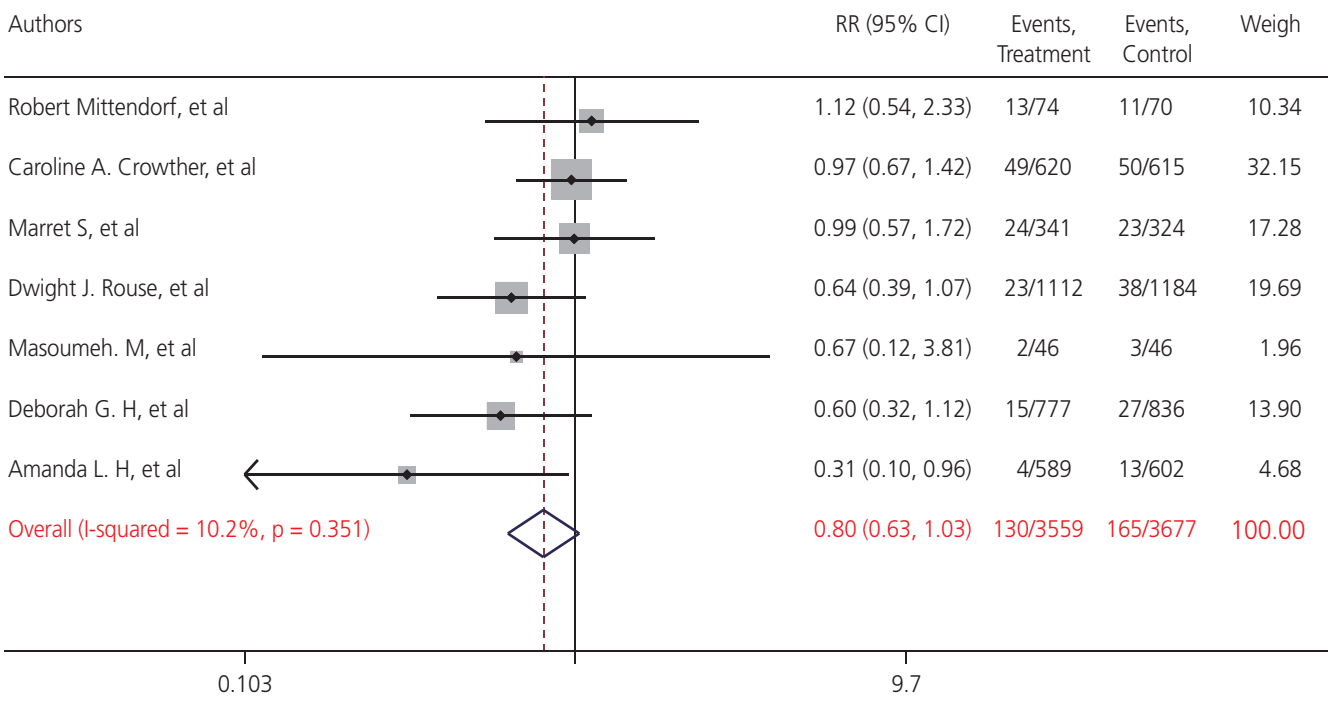

Fig. 4. Frost plot for relative risk (RR) and 95% confidence interval (CI) of magnesium sulfate ($MgSO_4$) on intraventricular hemorrhage (IVH).

Table 3. Summary relative risk (RR) Estimates (95% confidence intervals [CIs]) for randomized controlled trial studies conducted on the effect of antenatal magnesium sulfate ($MgSO_4$) on intraventricular hemorrhage in premature infants by gestational age, and $MgSO_4$ regimen

Subgroup	Number of studies (Sample size)	Summery RR (95% CI)	Between studies			Between subgroups	
			I^2	$P_{heterogeneity}$	Q	Q	$P_{heterogeneity}$
$MgSO_4$ regimen							
6 g loading and 2 g/h infusion	3 (6,592)[a]	0.84 (0.72–0.98)	42.5%	0.345	7.07	6.07	0.048
4 g loading and 2 g/h infusion	3 (1,298)[b]	1.13 (0.94–1.36)	27.8%	0.250	2.77		
4 g single dose	2 (832)[c]	0.86 (0.66–1.12)	0.0%	0.473	0.51		
Gestational age (wk)							
24 to 37	4 (7,654)	0.93 (0.83–1.05)	74.1%	0.009	11.57	16.21	0.013
<34	3 (1,842)	0.91 (0.70–1.18)	56.7%	0.099	4.62		

[a]Hirtz et al. [24], Horton et al. [25], and Rouse et al. [29]; [b]Mirzamoradi et al. [27], Crowther et al. [10], and Mittendorf et al. [30]; [c]Marret et al. [26] and Mittendorf et al. [30].

(95% CI, 0.83 to 1.05; I^2=74.1%; *P*=0.009) and 0.92 (95% CI, 0.70 to 1.18; I^2=56.7%; *P*=0.099), respectively (Table 3).

4. Meta regression

The results of the meta regression analysis, used to explore the sources of interstudy heterogeneity according to gestational age, indicated that the effect of $MgSO_4$ on risk of IVH is unrelated to gestational age (Q test=2.43, df=2, *P*-value=0.467).

Discussion

IVH is one of the most common complications in premature infants, and can cause long-term disability, cerebral palsy, mental retardation, seizures, behavioral and cognitive impairment, and death [31,32]. Studies have shown that the immature antioxidant system of the preterm infant can cause damage to the endothelial cells and alter brain hemostasis, can increase the susceptibility to reactive oxygen species, and, finally, increase the risk for IVH [33-35], Furthermore, studies have shown that approximately one third of cerebral palsy cases and IVH occur in premature infants [36]. Therefore, the present systematic review and meta-analysis study was designed to investigate the effect of antenatal $MgSO_4$ on IVH in premature infants.

The results of our study indicate that although $MgSO_4$ had a protective effect on IVH, this effect is not statistically significant (pooled RR, 0.80; 95% CI, 0.63 to 1.03). Although studies have shown $MgSO_4$ being used for the first time in obstetric practice, there is a controversy about its effect on the outcomes of premature infants [37,38]. Indeed, some studies have concluded that $MgSO_4$ is harmful due to increased risk of death and neurological problems for neonates [39-41]. In contrast, other studies have shown that $MgSO_4$ has a protective and beneficial effect on low birth weight infants [42-44]. For example, a study by Nelson et al. showed that the use of $MgSO_4$ can reduce the IVH incidence (OR, 0.14; 95% CI, 0.05 to 0.51) [42]. In a systematic review study conducted by Doyle et al. [45] with the aim of studying the effect of antenatal $MgSO_4$ on neurologic outcomes in preterm infants, the results showed that use of $MgSO_4$ dramatically reduced the risk of cerebral palsy in the children of women at risk of preterm birth (RR, 0.69; 95% CI, 0.54 to 0.87); also, a significant decrease was observed in the rate of substantial gross motor dysfunction (RR, 0.61; 95% CI, 0.44 to 0.85) [45]. In general, there are many reports that show that $MgSO_4$ increases the antioxidant properties of the brain, protects the brain cells against hypoxia and apoptosis, and normalizes platelet aggregation [46-50]. In other words, the $MgSO_4$ is a tocolytic method for preventing preterm labor. Epidemiological studies have shown that $MgSO_4$ in mothers leads to myocardial stability and blood supply in placenta and fetal brain, as well as reduction of the ischemic region and antioxidant effects, with decreased platelet adhesion in the fetus [51-53].

In contrast, some studies concluded that use of $MgSO_4$ had no effect, or had a minor and insignificant effect, on premature infants [16,17].The large RCTs that were conducted using different doses of $MgSO_4$ have shown an insignificant

reduction in the combined death, cerebral palsy, or gross motor dysfunction among premature infants [10,26,29]. For example, the results of a clinical trial study by Marret et al. [26] showed that although $MgSO_4$ has a protective effect on IVH, this effect was not statistically significant (OR, 0.83; 95% CI, 0.55 to 1.32). Meanwhile, the study by Crowther et al. [10] showed that magnesium sulfate had a protective effect on the risk of IVH; however, this effect was not statistically significant (OR, 0.83; 95% CI, 0.64 to 1.32). Also, a systematic review by Doyle et al. [45] that studied the effect of antenatal magnesium sulfate on neurologic outcome in preterm infants indicated that antenatal magnesium sulfate therapy has no statistically significant effect on pediatric mortality, or on other neurologic impairments or disabilities, in the early years of life of children (RR, 1.01; 95% CI, 0.82 to 1.23). A study by Petrova and Mehta [54] in 2012 revealed that there was no significant association between the use of magnesium sulfate, IVH, and parenchyma injury. Evidently, the results of these studies are consistent with our results. However, the results among various studies in this field are inconsistent, which may be due to differences in study design, study population or sample size, gestational age, follow-up patterns, and/or different doses of the $MgSO_4$.

There several limitations of this study that should be considered when interpreting the results. First, potential publication bias may exist in the observed results, since only some established electronic literature databases were searched. Second, language bias may threaten the results, given that only published articles in English were reviewed. Third, due to lack of detailed information, the quality assessment of the eligible studies may have been influenced by personal judgment. Finally, the last limitation is heterogeneity among the studies. Indeed, the included studies were not directly comparable with each other due to different methods for outcome assessment and experimental variation.

In conclusion, the results of this review showed that although $MgSO_4$ had a protective effect on IVH in neonates, this effect is not statistically significant. However, based on the heterogeneity in study population, sample sizes, gestational age, magnesium sulfate dosage, and follow-up patterns among the included studies, further investigation is needed to evaluate the best dosage, timing and gestational age for the optimum effect of magnesium sulfate on IVH.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Ethical approval

The study is applicable to Institutional Review Board (IRB: IR.IUMS.REC.1397.830).

Patient consent

There is no need for patient consent in this review article.

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