Magnesium sulphate for newborns with HIE; synopsis of evidence from a systematic review

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CONTEXT

Perinatal asphyxia remains a major cause of long-term sensorineural impairments and disabilities; with an incidence of 1-2 per 1,000 births in developed countries and up to 5 per 1,000 births in developing countries. Despite the improvement in clinical outcomes with therapeutic hypothermia, 50% of newborns with moderate-to-severe hypoxic-ischemic encephalopathy (HIE) will die or survive with major disabilities. Therefore, the search is ongoing for adjuvant treatment to therapeutic hypothermia. Magnesium was proposed for clinical use to combat glutamate excitotoxicity associated with birth asphyxia.

The objective of this review was to systematically review the efficacy and safety of postnatal magnesium therapy in newborns with HIE.

MATERIALS AND METHODS

Study selection

Randomized controlled trials that compared magnesium to placebo or no therapy to treat newborns ≥35 weeks gestation with HIE were included.

Type of intervention

Magnesium given within the first 24 h after birth as a neuroprotective agent in any dose and by any route.

Data sources

MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials were searched for eligible studies till December 2012. A combination of both text word fields and database subject heading fields were searched. No language restrictions were applied.

Study identification, quality assessment, and data extraction

All titles and abstracts identified as potentially relevant by the literature search were assessed independently by two reviewers for eligibility. Any disagreement on the studies to be selected was resolved by the third reviewer. Subsequently, the full texts for potentially eligible studies were reviewed against the predefined criteria for risk of bias. The methodological quality of the studies was assessed using the risk of bias assessment tool as recommended by the Cochrane Neonatal Review Group. Studies that had a high risk of bias were considered to have significant limitations and were excluded. Data were extracted by two reviewers on a predefined data extraction form.

Outcomes measures

The primary outcome

A composite of death or long-term (≥18 months) major neurodevelopmental disability (cerebral palsy) or developmental delay (<2 SD below the mean in: Mental Developmental Index score in Bayley Scales for Infant Development II (BSID-II), a cognitive scale score or a language composite scale score on the BSID-III, Griffith assessment, Brunet-Lezine quotient, Gesell Child Development Age Scale, or Denver II, or intellectual impairment (IQ < 2 SD below mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification).

Secondary outcomes

A composite of short-term (<18 months) unfavorable outcomes (survival with abnormalities in any of the following: Neurodevelopmental exam, neuroimaging, or neurophysiologic studies), death before discharge, seizures, hypotension requiring inotropic support after enrolment, and length of mechanical ventilation.

Data analysis

Meta-analyses were performed using the Review Manager software 5.0 utilizing the Mantel-Haenzel method and a random effects model. Risk ratios (RRs) with 95% confidence intervals (CIs), were calculated.

RESULTS

Six studies fulfilled the inclusion criteria and only five[1-5] studies with acceptable quality were included in this review comprising a total of 182 participants. The included trials had similar enrollment criteria. The dose of magnesium varied between studies.

Outcomes

The primary outcome was assessed in one study. The other four included studies had variable short-term primary outcomes. All the studies reported data on mortality before discharge from the hospital.

There was no difference in the composite primary outcome of death or moderate-to-severe neurodevelopmental disability at age 18 months (one study, 22 participants, RR 0.81, 95% CI 0.36-1.84) between the magnesium and the control groups. Magnesium reduced the risk of unfavorable short-term composite outcome (three studies, 98 participants, RR 0.48, 95% CI 0.30-0.77) when compared to the control group.

There was no difference between newborns treated with magnesium and controls in mortality (five studies, 182 participants, RR 1.39, 95% CI 0.85-2.27), hypotension (two studies, 92 participants, RR 1.28, 95% CI 0.69-2.38), or seizures (five studies, 182 participants, RR 0.84, 95% CI 0.59-1.19).

COMMENTARY

This systematic review of the randomized controlled trials in newborns with HIE who received magnesium therapy compared to controls shortly after birth did not yield sufficient data to allow analysis of the primary outcome of mortality or long-term neurodevelopment as it was only evaluated in one study with a small sample size.

The results from this review indicate an improvement in the short-term composite outcome of survival with abnormalities in any of the following: Neurodevelopmental exam, neuroimaging, or neurophysiologic studies.

Side-effects were not consistently evaluated in included studies. In the two studies that evaluated hypotension requiring inotropic support, there was no difference between the magnesium and the control groups. One trial reported no difference between the magnesium and the control groups in newborns that required mechanical ventilation at 72 h of age despite the observation that there were tendency toward the use of more mechanical ventilation in the magnesium group (34.8 versus 16.7%). It is important to note that the sample sizes in the included studies were small and there was insufficient power to detect a potentially clinically important differences.

The therapeutic window for magnesium to act as a neuroprotective agent is unknown. In the included studies, magnesium was used in the first 24 h of life, but seems prudent to initiate magnesium therapy as soon as possible after the hypoxic insult.

We could not evaluate whether magnesium modified the severity of encephalopathy but such evaluation deserves further investigation.

CONCLUSION

There is insufficient evidence to determine if magnesium therapy given shortly after birth to newborns with HIE reduces death or moderate-to-severe disability. The improvement in short-term outcomes without significant increase in adverse effects supports the need for further adequately powered trials to determine if there are long-term benefits of magnesium and to confirm its safety. Mortality should be monitored closely in all future trials involving magnesium therapy for newborns with HIE. Further opportunity for research exists for magnesium to act as an adjuvant treatment to therapeutic hypothermia.

Abstracted from

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REFERENCES

1. Bhat MA, Charoo BA, Bhat JI, Ahmad SM, Ali SW, Mufti MU. Magnesium sulfate in severe perinatal asphyxia: A randomized, placebo-controlled trial. Pediatrics 2009;123:e764-9.
2. Ichiba H, Tamai H, Negishi H, Ueda T, Kim TJ, Sumida Y, *et al*. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. Pediatr Int 2002;44:505-9.
3. Gathwala G, Khera A, Singh J, Balhara B. Magnesium for neuroprotection in birth asphyxia. J Pediatr Neurosci 2010;5:102-4.
4. Groenendaal F, Rademaker CM, Toet MC, de Vries LS. Effects of magnesium sulphate on amplitude-integrated continuous EEG in asphyxiated term neonates. Acta Paediatr 2002;91:1073-7.
5. Khashaba MT, Shouman BO, Shaltout AA, Al-Marsafawy HM, Abdel-Aziz MM, Patel K, *et al*. Excitatory amino acids and magnesium sulfate in neonatal asphyxia. Brain Dev 2006;28:375-9.