Effect of Magnesium Sulfate Given for Neuroprotection Before Preterm Birth

A Randomized Controlled Trial

Caroline A. Crowther, MD, FRANZCOG
Janet E. Hiller, PhD
Lex W. Doyle, MD, FRACP
Ross R. Haslam, FRACP
for the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO4) Collaborative Group

Context Prenatal magnesium sulfate may reduce the risk of cerebral palsy or death in very preterm infants.

Objective To determine the effectiveness of magnesium sulfate given for neuroprotection to women at risk of preterm birth before 30 weeks' gestation in preventing pediatric mortality and cerebral palsy.

Design, Setting, and Patients Randomized controlled trial at 16 tertiary hospitals in Australia and New Zealand with stratification by center and multiple pregnancy. A total of 1062 women with fetuses younger than 30 weeks' gestation for whom birth was planned or expected within 24 hours were enrolled from February 1996 to September 2000 with follow-up of surviving children at a corrected age of 2 years.

Interventions Women were randomly assigned to receive a loading infusion of 8 mL (4 g [16 mmol] of 0.5 g/mL of magnesium sulfate solution or isotonic sodium chloride solution [0.9%]) for 20 minutes followed by a maintenance infusion of 2 mL/h for up to 24 hours.

Main Outcome Measures Rates of total pediatric mortality, cerebral palsy, and the combined outcome of death or cerebral palsy at a corrected age of 2 years.

Results Data were analyzed for 1047 (99%) 2-year survivors. Total pediatric mortality (13.8% vs 17.1%; relative risk [RR], 0.83; 95% confidence interval [CI], 0.64-1.09), cerebral palsy in survivors (6.8% vs 8.2%; RR, 0.83; 95% CI, 0.54-1.27), and combined death or cerebral palsy (19.8% vs 24.0%; RR, 0.83; 95% CI, 0.66-1.03) were less frequent for infants exposed to magnesium sulfate, but none of the differences were statistically significant. Substantial gross motor dysfunction (3.4% vs 6.6%; RR, 0.51; 95% CI, 0.29-0.91) and combined death or substantial gross motor dysfunction (17.0% vs 22.7%; RR, 0.75; 95% CI, 0.59-0.96) were significantly reduced in the magnesium group.

Conclusions Magnesium sulfate given to women immediately before very preterm birth may improve important pediatric outcomes. No serious harmful effects were seen.

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Infants born very preterm have increased risks of mortality or of surviving with cerebral palsy or other neurosensory impairments and disabilities. Very preterm birth and very low birth weight are principal risk factors for cerebral palsy.[1-5] Intraventricular hemorrhage (IVH) is a known risk factor for cerebral palsy,[6,7] with the risk of IVH increasing the lower the gestational age at birth.[8]

In observational studies, maternal administration of magnesium sulfate has been associated with a subsequent reduction in the risk of IVH,[9-12] cerebral palsy,[11,13-15] and pediatric mortality.[16] However, not all observational studies that examined risk factors for IVH,[17-20] cerebral palsy,[17,21-23] or pediatric mortality[19] have shown protective effects for magnesium sulfate, and neither has a small randomized controlled trial.[24-26]

Although observational studies suggest a role for prenatal magnesium sulfate as a neuroprotective agent, there have been no large randomized controlled trials in which magnesium sulfate was given solely for neuroprotection. The Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO4) was designed to determine the efficacy of magnesium sulfate given solely for neuroprotection to women at risk of preterm birth before

See also p 2677 and 2730.

Author Affiliations: Departments of Obstetrics and Gynaecology (Dr Crowther) and Public Health (Dr Hiller), The University of Adelaide, and Department of Neonatal Medicine, Women's and Children's Hospital (Dr Haslam), Adelaide, South Australia; and Departments of Obstetrics and Gynaecology and Paediatrics, The University of Melbourne, The Royal Women's Hospital, Melbourne, Victoria, Australia (Dr Doyle).

A Complete list of the members of the ACTOMgSO4 Collaborative Group appears at the end of the article.

Corresponding Author and Reprints: Caroline A. Crowther, MD, FRANZCOG, Department of Obstetrics and Gynaecology, The University of Adelaide, Women's and Children's Hospital, King William Road, North Adelaide, South Australia, 5006 Australia (e-mail: caroline.crowther@adelaide.edu.au).

30 weeks' gestation in preventing pediatric mortality and/or cerebral palsy.

METHODS

Participants

Women pregnant with single, twin, triplet, or quadruplet fetuses younger than 30 weeks' gestational age were eligible for the trial if birth was planned or expected within 24 hours. There was no lower limit on gestational age at enrollment; such limits were determined by individual hospital policies about viability. A best estimate of gestational age was made at trial entry derived from the menstrual history and early ultrasound. Women were excluded if they were in the second stage of labor, if they had received magnesium sulfate therapy in this pregnancy, or if there were contraindications to magnesium sulfate (respiratory rate <16/min, absent patellar reflexes, urine output <100 mL during the previous 4 hours, renal failure, or hypocalcemia). Recruitment started in February 1996 and stopped in September 2000.

Randomization

The study protocol was approved by the research and ethics committee at each of the 16 collaborating tertiary hospitals, all with a neonatal intensive care unit (13 in Australia and 3 in New Zealand). Stratification was by center and multiple pregnancy (3 groups—singleton, twin, and higher-order multiple). The study randomization numbers were generated by computer with variable block sizes of 4, 6, or 8 and managed by nonclinical staff at the University of Adelaide's Maternal Perinatal Clinical Trials Unit. Each study number was placed on a masked treatment pack. Packs were sent to participating centers ready for use.

Eligible women who gave written informed consent were enrolled by taking the next treatment pack, corresponding to the number of fetuses, from the drug supplies held at the center. If eligible, the treatment pack was opened, which was the point of randomization, regardless of whether the infusion was commenced or completed.

Interventions

Each treatment pack looked identical and contained an infusion bag of 60 mL of either a 0.5-g/mL solution of magnesium sulfate or isotonic sodium chloride solution (0.9%). Women were given a loading infusion of 8 mL (4 g [16 mmol] of magnesium sulfate or isotonic sodium chloride solution) for 20 minutes followed by a maintenance infusion of 2 mL/h until birth (if occurred within 24 hours) or up to 24 hours. Magnesium sulfate was given as a neuroprotective agent only and not for tocolysis.

Women's pulse rate, blood pressure, and respiratory rate were monitored throughout the infusion and any maternal adverse effects recorded. The loading or maintenance infusions were stopped if the respiratory rate decreased more than 4/min or the diastolic blood pressure decreased more than 15 mm Hg below the baseline level. The infusion could be resumed when the respiratory rate or blood pressure returned to baseline levels. Clinicians were asked not to measure magnesium levels to maintain blinding.

The care women and infants received was otherwise according to standard practice at each collaborating center. All perinatal staff were blinded to treatment group allocation. All surviving infants had a cranial ultrasound performed within the first 7 days of life to detect IVH and a later ultrasound (beyond 4 weeks of age and as close to discharge as possible) to identify periventricular leukomalacia. Women and their children were followed up until the child was 2 years of age, corrected for prematurity. All pediatric deaths were reviewed by an independent committee, blinded to therapy, to determine the principal cause of death.

Surviving children were assessed at a corrected age of 2 years by developmental pediatricians and psychologists blinded to treatment group allocation. The criteria for cerebral palsy included abnormalities of tone and loss of motor function as previously reported.[27] Apart from providing criteria for the diagnosis of cerebral palsy, we did not attempt to train assessors at all 16 centers in its diagnosis. Instead we relied on the judgment of individual developmental pediatricians. In addition, gross motor function in all children was assessed by criteria derived from Palisano et al[28]; children were classified as walking normally, walking with minimal limitations such as toe walking or asymmetrical gait, or not walking independently, the last group being considered to have substantial gross motor dysfunction. Vision was assessed and children were considered blind if vision in both eyes was worse than 6/60. Hearing was assessed and children were considered deaf if they required hearing aids. The psychological assessment included the Psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI) of the Bayley Scales of Infant Development.[29] Children unable to complete the PDI or MDI because of severe psychomotor or developmental delay were assigned scores of 49, a score that automatically implies severe disability.

Outcomes

The primary outcomes were total pediatric mortality up to a corrected age of 2 years (including stillbirths, neonatal deaths, and mortality after hospital discharge), cerebral palsy at a corrected age of 2 years, and the combined adverse outcome of death or cerebral palsy at 2-year follow-up.

For infants, secondary outcomes were rates of major IVH (grade III or IV), cystic periventricular leukomalacia, and neurosensory disability. Severe neurosensory disability comprised any of severe cerebral palsy (considered permanently nonambulant), severe developmental delay (MDI, <3 SDs), or blindness. Moderate disability comprised any of moderate cerebral palsy (nonambulant at 2 years but likely to walk), moderate developmental delay (MDI, –3 SDs to <–2 SDs), or deafness. Mild disability comprised either mild cerebral palsy (walking at 2 years) or mild developmental delay (MDI, –2 SDs to <–1 SD). Children without any neuro-

sensory impairment were considered to have no disability.

For the mother, secondary outcomes were adverse cardiovascular and respiratory effects of the infusion (defined as a respiratory rate of <16/min, decrease in diastolic blood pressure of >15 mm Hg, cardiac arrest, respiratory arrest), primary postpartum hemorrhage (defined as estimated blood loss of >600 mL), and major postpartum hemorrhage (defined as blood loss of >1000 mL). Subsidiary outcomes included other adverse effects of the infusion, pregnancy outcome, and other neonatal outcomes.

Statistical Methods

All statistical analyses were undertaken on an intention-to-treat basis, including outcome data from women who did not give birth preterm. Baseline variables were included as confounders if there was imbalance between the treatment groups and an association with the primary outcome under analysis. The variables with imbalance—race, hospital, public patient status, and either antepartum hemorrhage or preterm prelabor rupture of the membranes as reasons for preterm birth—were only associated with mortality, not with cerebral palsy, so an adjusted analysis was only performed for mortality. Analysis of all available data was performed for each outcome. Binary outcomes are presented as relative risks (RRs) with 95% confidence intervals (CIs). The RRs were calculated using log binomial regression,[30] since the resulting metric is an RR that is more easily interpreted by clinicians than an odds ratio.[31] Robust variance estimation was used to account for clustering of infants within mothers. The statistical software used was SAS version 8.2 (SAS Institute Inc, Cary, NC), and the significance level was .05.

Sample Size

Sample size was calculated to detect a 50% reduction in the risk of cerebral palsy at 2 years in survivors from 10% to 5%, with 80% probability at an α level of .05. This was considered a conservative estimation given the 86% reduction in the odds of cerebral palsy in a case-control study.[13] This sample size of 848 children was adjusted upward to 1250 infants to account for a predicted mortality rate of 20% and a small design effect due to nonindependence of observations from multiple births.

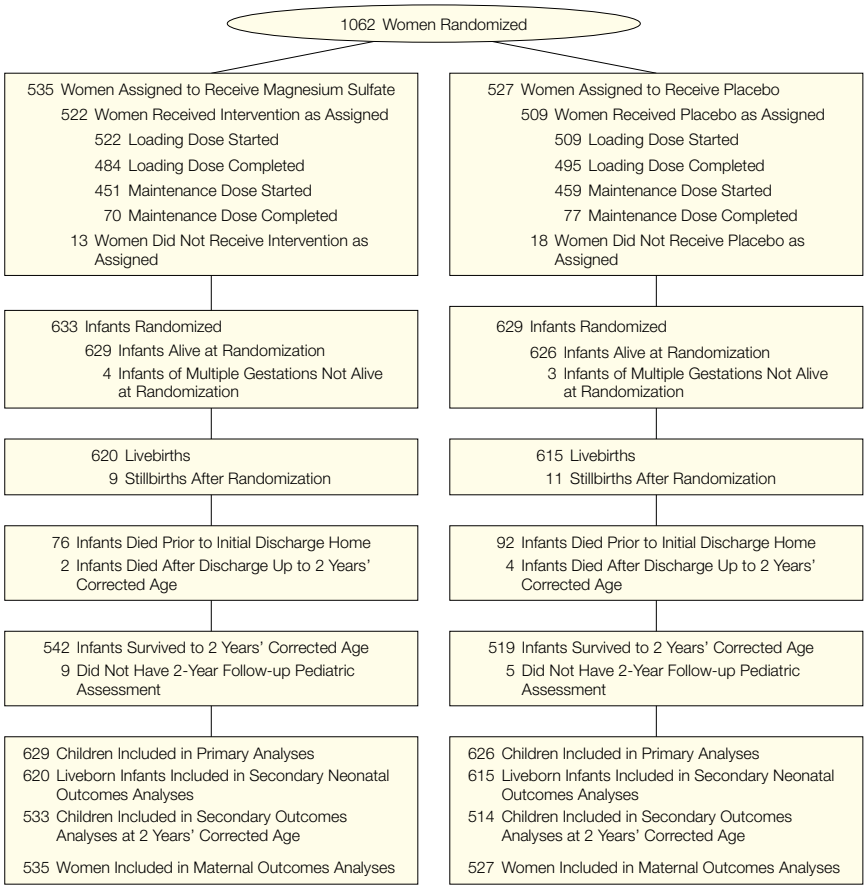
Interim Analyses

Data were reviewed twice by an independent data monitoring committee. These reviews were undertaken in June 1997 for safety reasons following the recruitment of 219 women and in November 1999 to look at the overall cerebral palsy rates in the 230 infants with assessments at a corrected age of 2 years.

RESULTS

A total of 1062 women entered the study; 535 were allocated to the magnesium sulfate group and 527 to placebo (FIGURE). Approximately 65% of all women who gave birth before 30 weeks' gestation in participating centers were enrolled. A similar number of women in each group with a multiple pregnancy had infants who were dead at the time of randomization (4 in the magnesium sulfate group and 3 in the placebo group). Outcome data were obtained, up to the time of hospital discharge, on all 1062 women and their 1255 infants alive at the time of randomization, and 2-year corrected age outcomes were available for 1047 children (99% of 2-year survivors). Fourteen children (9 in the magnesium sulfate group and 5 in the placebo group) without 2-year corrected age cerebral palsy assessments were treated as missing data and excluded from the cerebral palsy analysis.

Figure. Randomization, Treatment, and Follow-up of Participants in the Australasian Collaborative Trial of Magnesium Sulphate Study



Baseline maternal characteristics and reasons for preterm birth were similar in both groups (TABLE 1) and reflect the eligible high-risk population. The median gestational age at entry was 27 weeks. Almost half the women were in their first pregnancy, 17% had a multiple pregnancy, 27% had experienced a previous very preterm birth (<32 weeks) and 19% had experienced a perinatal death. The primary reason for preterm birth was preterm labor (63%), followed by preeclampsia (15%), antepartum hemorrhage (14%), chorioamnionitis (14%), severe intrauterine growth restriction (9%), preterm prelabor rupture of the membranes (9%), and fetal distress (3%). Of the infants who were alive at randomization, there were 343 male infants (55%) in the magnesium sulfate group and 357 male infants (57%) in the placebo group.

Treatment

Most women (522 [98%] in the magnesium sulfate group and 509 [97%] in the placebo group) received some of the loading infusion, with the full loading dose given to 484 women (90%) who were allocated magnesium sulfate and 495 (94%) who were allocated placebo. Somewhat fewer women (451 [84%] in the magnesium sulfate group and 459 [87%] in the placebo group) received some of the maintenance infusion (Figure). The total dose of infusion administered was similar in both groups, with median volumes of medication received of 13 mL (interquartile range [IQR], 9-28 mL) in the magnesium sulfate group and 13 mL (IQR, 10-29 mL) in the placebo group. Few women received magnesium for clinical reasons after enrollment (4 [0.7%] in the magnesium sulfate group and 11 [2.1%] in the placebo group).

Table 1. Characteristics of Women in the Magnesium Sulfate and Placebo Groups at Trial Entry*

	No. (%)	
	Magnesium Sulfate (n = 535)	Placebo (n = 527)
Maternal age, mean (SD), y	28.4 (5.8)	28.7 (5.8)
Parity		
0	279 (52.1)	239 (45.4)
1-3	225 (42.1)	256 (48.6)
≥4	31 (5.8)	32 (6.1)
Race*		
Nonindigenous	502 (93.8)	488 (92.6)
Indigenous	33 (6.2)	39 (7.4)
Gestational age at entry, median (IQR)	27 wk 3 d (25 wk 5 d to 28 wk 5 d)	27 wk 2 d (25 wk 5 d to 28 wk 5 d)
Blood pressure, median (IQR), mm Hg		
Systolic	114 (110-124)	115 (110-120)
Diastolic	70 (60-75)	70 (60-75)
Multiple pregnancy	88 (16.4)	89 (16.9)
Previous obstetric history		
Very preterm birth <32 wk	71 (27.7)	75 (26.0)
Preterm birth 32-36 wk	57 (22.3)	58 (20.1)
Perinatal death ≥20 wk	47 (18.4)	58 (20.1)
Reason for preterm birth		
Preterm labor	335 (62.6)	330 (62.6)
Preeclampsia/eclampsia	86 (16.1)	75 (14.2)
Chorioamnionitis	73 (13.6)	72 (13.7)
Antepartum hemorrhage	70 (13.1)	81 (15.4)
Severe IUGR	50 (9.3)	43 (8.2)
PROM	43 (8.0)	54 (10.2)
Fetal distress	20 (3.7)	13 (2.5)
Other	29 (5.4)	30 (5.7)

Abbreviations: IQR, interquartile range; IUGR, intrauterine growth retardation; PROM, premature rupture of membranes.
*Indigenous race included Aboriginal and Maori women.

Pregnancy Outcomes

There were no important differences between the treatment groups for outcomes related to pregnancy, labor and delivery, or measures of neonatal morbidity. The time from randomization to birth was similar in the magnesium sulfate group (median, 3.7 hours; IQR, 1.4-13.8 hours) and the placebo group (median, 3.1 hours; IQR, 1.3-12.9 hours). Gestational age at birth was also similar in the magnesium sulfate group (median, 27 weeks 5 days; IQR, 26 to 29 weeks) and the placebo group (median, 27 weeks 3 days; IQR, 25 weeks 6 days to 29 weeks). Just more than half of all women gave birth by cesarean delivery (magnesium sulfate group, 289 [54%]; placebo group, 290 [55%]). There were no substantial differences between the groups in the mean (SD) birth weight of the infants (magnesium sulfate group, 1027 [370] g; placebo group, 1026 [370] g) or in the proportion with Apgar scores less than 7 at 5 minutes of age (magnesium sulfate group, 94 [15%] of 620; placebo group, 91 [15%] of 615).

Primary Outcomes

The primary outcomes of total pediatric mortality, cerebral palsy in survivors, and combined death or cerebral palsy were all lower in the magnesium sulfate group, but no differences were statistically significant (TABLE 2). Among infants alive at randomization, there were 194 deaths (15.5%), 87 (13.8%) in the magnesium sulfate group and 107 (17.1%) in the placebo group, although this was not a statistically significant difference (adjusted RR, 0.83; 95% CI, 0.64-1.09). The mortality rate difference between the groups was similar for singleton (RR, 0.82; 95% CI, 0.60-1.12) and multiple pregnancies (RR, 0.80; 95% CI, 0.46-1.39). The principal causes of death were similar between the 2 groups. The cerebral palsy rate at a corrected age of 2 years was lower for children in the magnesium sulfate group (36 [6.8%] vs 42 [8.2%]), al-

though this was not a statistically significant difference (RR, 0.83; 95% CI, 0.54-1.27) (Table 2). The combined outcome of death or cerebral palsy was also lower for children in the magnesium sulfate group (123 [19.8%] vs 149 [24.0%]), although this was not a statistically significant difference (RR, 0.83; 95% CI, 0.66-1.03) (Table 2). A sensitivity analysis that included participants who had received a complete loading dose gave similar results for each of these primary analyses.

Secondary Outcomes

There were no major maternal adverse effects (death, cardiac arrest, respiratory arrest) seen in either treatment group. There were no differences in the rate of respiratory depression of less than 16/min, but significantly more women in the magnesium sulfate group had a decrease in diastolic blood pressure of more than 15 mm Hg from baseline (77 [14.4%] vs 52 [9.9%]; RR, 1.46; 95% CI, 1.05-2.03). There were no substantial differences between treatment groups in the rates of postpartum hemorrhage (TABLE 3).

Minor maternal adverse effects were more common in the magnesium sulfate group compared with the placebo group (89.0% vs 37.8%; RR, 2.36; 95% CI, 2.10-2.64), including tachycardia (>160/min or pulse >20/min from baseline), respiratory depression (decrease of >4/min from baseline), a feeling of warmth over the body, discomfort in the arm receiving the infusion, dryness of the mouth, nausea, sleepiness, sweating, dizziness, and blurred vision (Table 3). The adverse effects led to the infusion being stopped only in a small percentage of women but more often in the magnesium sulfate group (78 [14.6%] vs 28 [5.3%]; RR, 2.74; 95% CI, 1.81-4.15).

For the infant secondary outcomes of major IVH and cystic periventricular leukomalacia, no substantial differences were seen between the treatment groups (TABLE 4). There were also no major differences in the rates of chronic lung disease, necrotizing enterocolitis, or mechanical ventilation or in the duration of hospitalization between the treatment groups (Table 4).

There was no significant difference between the groups in the distribution of neurosensory disability (TABLE 5), although a significant reduction was seen in the proportion of children at the corrected age of 2 years with substantial motor dysfunction in the magnesium group compared with the placebo group (3.4% vs 6.6%; RR, 0.51; 95% CI, 0.29-0.91) (Table 5). Of the 52 children with substantial gross motor dysfunction, 39 had cerebral palsy (3 mild, 27 moderate, and 9 severe). The combined rate of death or substantial motor dysfunction at a corrected age of 2 years was significantly lower in the magnesium group compared with the placebo group (105 [17.0%] vs 141 [22.7%]; RR, 0.75; 95% CI, 0.59-0.96) (Table 5). There were no

Table 2. Total Mortality and Cerebral Palsy at a Corrected Age of 2 Years Among Infants*

	No. (%) of Infants			
	Magnesium Sulfate (n = 629)	Placebo (n = 626)	RR (95% CI)	*P* Value
Stillbirths after trial entry	9 (1.4)	11 (1.8)	0.81 (0.34-1.95)	.64
Deaths of infants born live before initial discharge home	76 (12.3)	92 (15.0)	0.82 (0.60-1.11)	.20
Deaths at ≤28 days	61 (9.8)	75 (12.2)		
Deaths at >28 days	15 (2.4)	17 (2.8)		
Postdischarge deaths (up to a corrected age of 2 years)	2 (0.3)	4 (0.6)		
Total deaths	87 (13.8)	107 (17.1)	0.83 (0.64-1.09)	.19
Cerebral palsy	36 (6.8)	42 (8.2)	0.83 (0.54-1.27)	.38
Death or cerebral palsy	123 (19.8)	149 (24.0)	0.83 (0.66-1.03)	.09

Abbreviations: CI, confidence interval; RR, relative risk.
*Analyses are adjusted for clustering within mother. Samples sizes are infants alive at randomization.

Table 3. Secondary Maternal Outcomes for Women Assessed During Treatment Infusion and Delivery

	No. (%) of Women			
Outcomes	Magnesium Sulfate (n = 535)	Placebo (n = 527)	RR (95% CI)	*P* Value
Respiratory rate of <16/min	34 (6.4)	28 (5.3)	1.20 (0.74-1.94)	.47
Diastolic blood pressure decrease of >15 mm Hg	77 (14.4)	52 (9.9)	1.46 (1.05-2.03)	.02
Primary postpartum hemorrhage	86 (16.1)	99 (18.8)	0.86 (0.66-1.11)	.24
Major postpartum hemorrhage	26 (4.9)	25 (4.7)	1.02 (0.60-1.75)	.93
Clinical and self-assessed maternal adverse effects of the infusion				
Infusion stopped due to adverse effects	78 (14.6)	28 (5.3)	2.74 (1.81-4.15)	<.001
Any adverse effects	476 (89.0)	199 (37.8)	2.36 (2.10-2.64)	<.001
Warmth over body	393 (73.5)	88 (16.7)	4.40 (3.61-5.36)	<.001
Arm discomfort with infusion	355 (66.4)	39 (7.4)	8.97 (6.59-12.2)	<.001
Mouth dryness	212 (39.6)	99 (18.8)	2.11 (1.72-2.59)	<.001
Nausea	137 (25.6)	55 (10.4)	2.45 (1.84-3.28)	<.001
Sleepiness	119 (22.2)	47 (8.9)	2.49 (1.82-3.42)	<.001
Sweating	104 (19.4)	29 (5.5)	3.53 (2.38-5.24)	<.001
Dizziness	83 (15.5)	37 (7.0)	2.21 (1.53-3.19)	<.001
Blurred vision	38 (7.1)	16 (3.0)	2.34 (1.32-4.14)	.003
Tachycardia (pulse rate of >160/min or >20/min from baseline)	56 (10.5)	36 (6.8)	1.53 (1.03-2.29)	.04
Respiratory depression (decrease of >4/min from baseline)	54 (10.1)	51 (9.7)	1.04 (0.73-1.50)	.82

Abbreviations: CI, confidence interval; RR, relative risk.

Table 4. Secondary Infant Outcomes Assessed Before Hospital Discharge*

Outcomes	Magnesium Sulfate (n = 620)	Placebo (n = 615)	RR (95% CI)	*P* Value
Cranial ultrasound, No.	596	586		
IVH	165 (27.7)	148 (25.3)	1.10 (0.90-1.33)	.36
Grade III or IV IVH	49 (8.2)	50 (8.5)	0.96 (0.65-1.43)	.85
Periventricular leukomalacia	22 (3.7)	21 (3.6)	1.03 (0.57-1.87)	.92
Secondary neonatal outcomes Chronic lung disease (receiving oxygen at 28 days)	280 (45.2)	260 (42.3)	1.07 (0.93-1.22)	.34
Necrotizing enterocolitis	30 (4.8)	31 (5.0)	0.96 (0.59-1.57)	.87
Mechanical ventilation	577 (93.1)	562 (91.4)	1.02 (0.98-1.05)	.31
Length of stay, median (range), d	76 (61-94)	74 (59-95)		.66

Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; RR, relative risk.
*Data are number (percent) of infants unless otherwise indicated. Infant analyses are adjusted for clustering within mother.

Table 5. Secondary Neurosensory Outcomes for Children Assessed at a Corrected Age of 2 Years*

Outcomes	No. (%) of Children		RR (95% CI)	*P* Value
	Magnesium Sulfate (n = 533)	Placebo (n = 514)		
Neurosensory disability assessed† No. of children with data	504	483		
None	311 (61.7)	296 (61.3)	1.01 (0.91 to 1.12)	.90
Mild	104 (20.6)	109 (22.6)	0.91 (0.72 to 1.16)	.47
Moderate	54 (10.7)	44 (9.1)	1.18 (0.79 to 1.76)	.43
Severe	35 (6.9)	34 (7.0)	0.99 (0.61 to 1.61)	.96
Severity of cerebral palsy No. of children with data	533	513		
Mild	21 (3.9)	21 (4.1)	0.96 (0.53 to 1.74)	.90
Moderate	12 (2.3)	15 (2.9)	0.77 (0.36 to 1.62)	.49
Severe	3 (0.6)	6 (1.2)	0.48 (0.12 to 1.92)	.30
Bayley PDI No. of children with data	482	461		
Mean (SD)	88.9 (18.0)	90.2 (19.0)	−1.3 (−3.9 to 1.3)	.32
Bayley MDI No. of children with data	483	466		
Mean (SD)	89.0 (18.7)	90.4 (18.6)	−1.3 (−3.9 to 1.2)	.31
Delayed development† No. of children with data	494	478		
None	318 (64.4)	308 (64.4)	1.00 (0.90 to 1.10)	.98
Mild	97 (19.6)	103 (21.5)	0.91 (0.71 to 1.18)	.47
Moderate	47 (9.5)	34 (7.1)	1.34 (0.85 to 2.12)	.21
Severe	32 (6.5)	33 (6.9)	0.94 (0.57 to 1.55)	.80
Blind	1 (0.2)	1 (0.2)	0.96 (0.06 to 15.3)	.98
Deaf	8 (1.5)	7 (1.4)	1.10 (0.40 to 3.02)	.85
Gross motor dysfunction assessed No. of children with data	529	513		
None	427 (80.7)	406 (79.1)	1.02 (0.96 to 1.09)	.55
Minimal	84 (15.9)	73 (14.2)	1.12 (0.82 to 1.51)	.48
Substantial	18 (3.4)	34 (6.6)	0.51 (0.29 to 0.91)	.02
Death or substantial gross motor dysfunction No. of children with data	616	620		
No. of children affected	105 (17.0)	141 (22.7)	0.75 (0.59 to 0.96)	.02

Abbreviations: CI, confidence interval; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; RR, relative risk.
*Child analyses are adjusted for clustering within mother.
†Includes a few children assessed with alternative psychometric tests.

major differences in the rates of blindness, deafness, or delayed development or in the mean scores for the PDI or MDI between the treatment groups (Table 5).

COMMENT

In our randomized controlled trial of magnesium sulfate as a neuroprotective agent before very preterm birth, total mortality, cerebral palsy, and the combined outcome of mortality or cerebral palsy were all lower in the magnesium sulfate group, but differences were not statistically significant. Despite the lack of statistical significance, the average sizes of the reductions in these adverse outcomes are potentially clinically important. There was a statistically significant reduction in substantial motor dysfunction among survivors in the magnesium sulfate group and in the combined outcome of death or substantial motor dysfunction, both of which are considered to be clinically important.

Since most preterm children with cerebral palsy are not severely disabled,[25] we considered it essential to find out if the overall rates of neurosensory disability or motor dysfunction were lowered with maternal magnesium therapy rather than solely determining the presence or absence of cerebral palsy at a corrected age of 2 years. Moreover, the diagnosis of cerebral palsy is not 100% accurate in early childhood,[32] especially in preterm children, even when only a few well-trained experts are involved in the diagnosis.[33] A limitation of our study is that we did not have the resources to train individual assessors or to ensure that every child suspected of having cerebral palsy was evaluated by several well-trained independent experts, which would have improved the diagnostic accuracy. However, the way that cerebral palsy was diagnosed in this study was reflective of usual clinical practice. We did not find any substantial differences between the groups when neurosensory disability was determined solely by the presence and severity of specific neurosensory impairments (cerebral palsy, blindness, deafness, and developmental delay).

However, when we used the Gross Motor Classification System developed by Palisano et al,[28] we found a reduction in substantial gross motor dysfunction in the group treated with magnesium sulfate. Follow-up into school age will be important to determine if magnesium sulfate has any long-term beneficial cognitive or other neurological effects.

The only other trial of which we are aware that has reported on the use of magnesium sulfate for prophylactic neuroprotection, in the preventive groups of the trial, randomly allocated 57 women in active labor who were more than 4 cm dilated to either a 4-g loading dose of magnesium sulfate or isotonic sodium chloride solution.[24] The trial was stopped early because of concerns of a higher total pediatric mortality rate in the magnesium sulfate group. Pediatric mortality was lower in our trial. Childhood neurological outcome from the trial by Mittendorf et al[25,26] showed that of the 43 survivors assessed at 18 months of age, 3 (15%) of 20 exposed to magnesium sulfate had cerebral palsy compared with 0 of 23 exposed to saline. The small size of the study, the follow-up rate of survivors to 18 months of age (77%; 43/56), and lack of reported methodological details make it difficult to compare the results with our findings.

Our study is the largest randomized trial of magnesium sulfate used solely as a neuroprotective agent before very preterm birth, but the benefit observed was smaller than anticipated from the nonrandomized human studies, and the event rates for total mortality and cerebral palsy were lower than originally predicted. Hence, our study was relatively underpowered to detect smaller but still clinically important differences than we originally hypothesized.

Although the results of our trial suggest that prenatal magnesium sulfate given specifically for neuroprotection has beneficial effects for the fetus expected to be born before 30 weeks' gestation, we do not consider the evidence currently strong enough to recommend widespread use of magnesium sulfate unless confirmed by other randomized controlled trials in humans. We are aware of 2 such studies currently in progress in the United States and France.

Maternal adverse effects from magnesium sulfate therapy in obstetrics are well known. It was no surprise to find higher rates of minor adverse effects in women receiving magnesium sulfate infusion in our study, although in only a few women were they severe enough for the infusion to be stopped. We did not detect any obvious harmful effects of magnesium sulfate for either the fetus or infant.

Although there have been several reports that maternal administration of magnesium sulfate was associated with a reduced risk of IVH in infants,[9-12] there was little evidence in our study of any effect of magnesium sulfate on the rate of IVH, including the more severe grades, or on the rate of cystic periventricular leukomalacia. Any neuroprotective effect of magnesium sulfate on motor dysfunction might work through other mechanisms, such as stabilization of blood flow or ameliorating the effects of hypoxic ischemic episodes, free radicals, and infection, rather than by reducing IVH or cystic periventricular leukomalacia.

In conclusion, the potential clinically important improvement in pediatric outcomes from magnesium sulfate given to women immediately before very preterm birth for neuroprotection urgently needs confirmation in further trials. Widespread use of prenatal magnesium sulfate as a neuroprotective agent cannot be recommended solely on the basis of the current study. Although minor adverse effects are common in women receiving magnesium sulfate, there do not appear to be any serious harmful effects for the women or their children.

Author Contributions: Dr Crowther had full access to the data and takes responsibility for the integrity of the data and the accuracy of the analyses.
Study concept and design: Crowther, Hiller, Doyle.
Acquisition of data: Crowther, Doyle, Haslam.
Analysis and interpretation of data: Crowther, Hiller, Doyle, Haslam.
Drafting of the manuscript: Crowther, Hiller, Doyle.
Critical revision of the manuscript for important intellectual content: Crowther, Hiller, Doyle, Haslam.
Statistical expertise: Hiller, Doyle.
Obtained funding: Crowther, Hiller, Doyle, Haslam.
Administrative, technical, or material support: Crowther, Hiller, Haslam.
Study supervision: Crowther, Hiller, Haslam.
ACTOMgSO4 Collaborative Group: *Coordinating committee*: C.A. Crowther, FRANZCOG, J.E. Hiller, PhD, L.W. Doyle, FRACP, R.R. Haslam, FRACP, A. Thomas, DipEd, J. Marker, GradDipPH, E. Griffith, BA, S. Russell, GradDip CompSc & IS, J. Paynter, S. Gibbons, K. Willson, BSc(Hons), T.Y. Khong, FRCPath, J.S. Robinson, FRANZCOG.
Data monitoring committee: J. Lumley (Chair) FAFPHM, J. Carlin, PhD.
Collaboration by hospital; associate investigator on the NHMRC project grant,* (total number of women recruited):
Christchurch Women's Hospital, New Zealand (15): R. Reid, FRANZCOG, B. Darlow, FRACP, H. Liley, FRACP, N. Mogridge, RN, D. Poad, FRANZCOG.
King Edward Memorial Hospital for Women, Western Australia (65): J. Dickinson, FRANZCOG, N. French, FRACP, M. Capitti, RN, J. Newnham, FRANZCOG.
King George V Hospital, New South Wales (113): D. Henderson-Smart,* FRACP, A. Child, FRANZCOG, B. Peat, FRANZCOG, H. Phipps, MPH, N. Evans, MRCP, D. Osborn, FRACP, G. Malcolm, PhD, P. Beeby, FRACP, H. Jeffrey, FRACP, I. Rieger, FRACP, C. Wocadlo, PhD, S. Reid, RN.
Kirwan Hospital, Queensland (50): D. Watson, FRANZCOG, A. Blair, FRACP, D. Gandini, FRACP, K. Roberts, RN.
Monash Medical Centre, Victoria (51): C. Bessell, FRANZCOG, V. Yu, FRACP, E. Carse, FRACP, M. Hayes, GradDip MCH.
National Women's Hospital, New Zealand (62): D. Souter, FRANZCOG, L. McCowan, FRANZCOG, J. Harding, FRACP, S. Aftimos, MD, D. Knight, MRCP, P. Nobbs, FRACP, S. Rowley, FRACP, C. West, MBChB, P. Stone, FRANZCOG, R. Taylor, MHSc, G. Turner, FRANZCOG, M. Battin, FRACP, C. Karschel, FRACP.
Royal Darwin Hospital, Northern Territory (3): J. Mitchell, FRANZCOG, I. Bucens, FRACP.
Royal Hobart Hospital, Tasmania (17): G. Bury, FRACP, G. Standen, FRANZCOG, S. Bacic, RM.
Royal Hospital for Women, New South Wales (42): C. Fisher, FRANZCOG, D. Challis, FRANZCOG, K. Lui, FRACP, L. Sutton, FRACP, K. Askill, MClinPsych, D. Cameron, K. Dyer, RN, P. Garvey, FRACP, S. Milner, DipPhysio.
Royal Women's Hospital, Queensland (123): P. Colditz,* FRACP, M. Pritchard, BA, J. Wilson, FRANZCOG, J. Horn, RN, G. Hindmarsh, BA(Psych), W. Katterns, MNursg.
The Canberra Hospital, Australian Capital Territory (78): D. Ellwood, FRANZCOG, G. Reynolds, FRACP, P. Hand, RM, C. Barreda-Hanson, PhD, R. Blake, RM.
The Mater Hospital, Queensland (95): P. Devenish-Mears, FRANZCOG, F.-Y. Chan, FRANZCOG, D. Tudehope, FRACP, P. Gray, FRACPI, V. Flenady, MMedSc, J. Hegarty, RN, Y. Rogers.
Mercy Hospital for Women, Victoria (85): A. Watkins,* FRACP, P. Wein, FRANZCOG, J. Keng, MHSc, S. Fraser, FRACP, E. Kelly, MA(Hons), H. Woods, RN, L. Horton, BSN, S. Walker, MD.
The Royal Women's Hospital, Victoria (88): L. Kornman, FRANZCOG, L.W. Doyle, FRACP, S. Brennecke, FRANZCOG, K. Callanan, RN, D. Rushford, SRM.
Waikato Hospital, New Zealand (22): N. Meher-Homji, FRANZCOG, D. Bourchier, FRACP, P. Weston, FRACP, D. Bruce, RM, S. Cole, RM, L. Hasan-Stein, MSc.
Women's and Children's Hospital, South Australia (159): C. Crowther, FRANZCOG, J. Robinson,* FRANZCOG, R. Haslam,* FRACP, A. McPhee, FRACP,* J. Marker, GradDipPH, C. Smith, PhD, A. Thomas, DipEd, J. Ramsay, GradDip CAFHN, M. Santich, MPsychol, J. Coffey, BNursg.
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