Original Investigation

School-age Outcomes of Very Preterm Infants After Antenatal Treatment With Magnesium Sulfate vs Placebo

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IMPORTANCE Antenatal magnesium sulfate given to pregnant women at imminent risk of very preterm delivery reduces the risk of cerebral palsy in early childhood, although its effects into school age have not been reported from randomized trials.

OBJECTIVE To determine the association between exposure to antenatal magnesium sulfate and neurological, cognitive, academic, and behavioral outcomes at school age.

DESIGN, SETTING, AND PARTICIPANTS The ACTOMgSO4 was a randomized clinical trial conducted in 16 centers in Australia and New Zealand, comparing magnesium sulfate with placebo given to pregnant women (n = 535 magnesium; n = 527 placebo) for whom imminent birth was planned or expected before 30 weeks' gestation. Children who survived from the 14 centers who participated in the school-age follow-up (n = 443 magnesium; n = 424 placebo) were invited for an assessment at 6 to 11 years of age between 2005 and 2011.

MAIN OUTCOMES AND MEASURES Mortality, cerebral palsy, motor function, IQ, basic academic skills, attention and executive function, behavior, growth, and functional outcomes. Main analyses were imputed for missing data.

RESULTS There were 1255 fetuses known to be alive at randomization. Of 867 survivors available for follow-up, outcomes at school age (corrected age 6-11 years) were determined for 669 (77%). There was little difference between groups on any of the cognitive, behavioral, growth, or functional outcomes.

Outcomes at School Age	No./Total No. (%)		Comparison (95% CI)	*P* Value
	Magnesium Sulfate Group	Placebo Group		
Mortality	88/629 (14)	110/626 (18)	RR, 0.80 (0.62-1.03)	.08
Cerebral palsy	23/295 (8)	21/314 (7)	OR, 1.26 (0.84-1.91)	.27
Abnormal motor function	80/297 (27)	80/300 (27)	OR, 1.16 (0.88-1.52)	.28

CONCLUSIONS AND RELEVANCE Magnesium sulfate given to pregnant women at imminent risk of birth before 30 weeks' gestation was not associated with neurological, cognitive, behavioral, growth, or functional outcomes in their children at school age, although a mortality advantage cannot be excluded. The lack of long-term benefit requires confirmation in additional studies.

TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12606000252516

JAMA. 2014;312(11):1105-1113. doi:10.1001/jama.2014.11189

Supplemental content at jama.com

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Survival rates for infants born at less than 28 weeks' gestation at birth have increased with the advent of modern perinatal and neonatal intensive care, but rates of adverse long-term neurodevelopmental outcomes remain high relative to the outcomes for term infants.[1]

The major use for magnesium sulfate in obstetrics is to prevent eclampsia in women with severe preeclampsia.[2] It is also used as a tocolytic, although evidence for this indication is lacking,[3] and as a neuroprotectant for preterm fetuses.[4-6] Experimental studies[7] and observational data from humans[8] are consistent with a possible neuroprotective effect. Five completed randomized clinical trials (RCTs) of magnesium sulfate and a meta-analysis support that magnesium sulfate is neuroprotective, reducing the prevalence of cerebral palsy in early childhood compared with no magnesium sulfate (risk ratio [RR], 0.69; 95% CI, 0.54-0.87).[4] Magnesium sulfate also lowered the prevalence of substantial motor dysfunction in early childhood (RR, 0.61; 95% CI, 0.44-0.85).

The Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO4),[9] 1 of the 5 trials included in the Cochrane review, was designed to assess whether antenatal magnesium sulfate given to women at risk of preterm birth before 30 weeks' gestation was related to mortality and neurosensory morbidity, particularly cerebral palsy, in early childhood.[9] The prevalence of cerebral palsy at age 2 years was similar in the 2 groups—6.8% (36/533) in the magnesium sulfate group and 8.2% (42/514) in the placebo group (RR, 0.83; 95% CI, 0.54-1.27)—but the prevalence of substantial motor dysfunction was reduced to 3.4% from 6.6% (RR, 0.51; 95% CI, 0.29-0.91).

Outcomes beyond early childhood have not been reported from any of the RCTs to date. As antenatal magnesium sulfate has been introduced into routine clinical practice to reduce the prevalence of cerebral palsy in very preterm infants in many parts of the world,[5,6] any delayed adverse outcomes and benefits of this treatment should be identified. The aim of this study was to determine outcomes into school age from antenatal magnesium sulfate compared with placebo from the ACTOMgSO4.[9]

Methods

Full details of the study design and outcomes to age 2 years have been reported previously (see trial protocol in Supplement 1).[9] Briefly, a total of 1062 women with a pregnancy less than 30 weeks' gestational age for whom birth was planned or expected within 24 hours were randomized at 16 centers in Australia and New Zealand to receive either intravenous magnesium sulfate (n = 535; 4-g loading dose; 1 g/h maintenance, for up to a maximum of 24 hours) or normal saline placebo (n = 527). These women had a total of 1255 fetuses alive at randomization, and there were 1066 survivors to hospital discharge (n = 544 exposed to magnesium sulfate; n = 522 placebo). Participants were recruited between February 1996 and September 2000. Of the 16 study centers from the original trial, 14 agreed to participate in a follow-up protocol at school age. This follow-up of participating children at school age was not part of the original protocol developed in 1994. Ethical approval for further follow-up was obtained from each site, and parents gave written informed consent for their child to participate.

Outcomes

The outcomes for the school-age follow-up were cerebral palsy, motor function, general intellectual ability, academic skills, attention, executive function, behavior, growth, and functional and other neurosensory outcomes, all areas in which very preterm children have worse performance compared with children born at term.[10] Broad outcomes were selected because there is no experimental evidence to suggest selective neurological effects, either beneficial or harmful, for magnesium sulfate, as well as to ensure there were no unexpected consequences of treatment. Mortality was also recorded because it is a competing risk for long-term outcomes.

It was planned to assess the majority of children between the ages of 7 and 8 years, but to maximize the follow-up rate, we accepted data outside this range if they were the only assessments available. Assessments started in 2005 and finished in 2011. Children were assessed without reference to any previous results by members of the study team who were blinded to treatment group allocation. Age was corrected for prematurity because even at school age, correction for prematurity results in elimination of a small but potentially clinically important bias in cognitive test scores.[11,12]

Motor Function

A developmental pediatrician examined the children to detect the presence of cerebral palsy, the diagnosis of which comprised nonprogressive loss of motor function with disordered tone or tendon reflexes. The severity of gross motor function in children with cerebral palsy was classified according to the Gross Motor Function Classification System (GMFCS).[13] The severity of the disability imposed by cerebral palsy was graded into severe (GMFCS level 5 [has limited voluntary control of movement] or level 4 [uses a wheelchair]), moderate (GMFCS level 3 [walks on a level surface with an assistive mobility device] or level 2 [walks on uneven surfaces, climbs stairs holding a railing]), or mild (GMFCS level 1 [walks without restrictions, limitations in more advanced gross motor skills]). Some children without cerebral palsy also had gross motor dysfunction assigned according to the GMFCS. Motor function was also assessed by the Movement Assessment Battery for Children (MABC), the first edition for most children.[14] The MABC is a standardized test of motor function. Those who scored below the 15th centile according to the test norms were considered to have borderline motor function, and those who scored below the 5th centile were considered to have a definite motor problem. Some children (n = 32) were assessed with the second edition of the MABC,[15] and their centiles were classified as for the first edition.

Psychological Outcomes

General cognitive ability was assessed using the Wechsler Intelligence Scale for Children-Fourth Edition.[16] The full-scale IQ measured general intellectual ability, while the 4 index scores (verbal comprehension, perceptual reasoning, working memory, processing speed) were used to examine specific elements of cognitive functioning. Each scale/index is age standardized with a mean (SD) of 100 (15). A score less than 85 indicates intellectual impairment; moderate intellectual impairment is indicated by a score less than 70.

Academic skills were assessed using the Wide Range Achievement Test (WRAT3).[17] The WRAT3 includes 3 subtests that assess reading (word recognition and decoding), spelling, and arithmetic. Each scale is age standardized with a mean (SD) of 100 (15).

Attention and executive function are multidimensional constructs that are considered areas of concern for very preterm children.[18,19] The psychological assessment included a battery of tests sensitive to specific attentional and executive processes.

Attention | Sky Search, a subtest from the Test of Everyday Attention for Children (TEACh),[20] assesses selective visual attention. Children search for all the "target" spaceships as quickly as possible on a sheet filled with similar distractor spaceships. Performance was determined by the age-sex standardized score for the number of targets identified (mean [SD], 10 [3]).

Sustained attention was assessed by Score!, a subtest from the TEACh. For each of 10 trials, children count the number of beeps presented at random intervals on an audiotape. Performance was judged by the standardized score for the number of correct trials (mean [SD], 10 [3]).

Divided attention was assessed by Sky Search Dual Task, which involves children completing a visual search task (similar to Sky Search) and an auditory counting task (similar to Score!). Performance was determined by the average of the following: (proportion of visual targets correctly identified + proportion of correct auditory counting games) × 100.[19] Although there are no published norms for this scoring procedure, the range of possible values is 0 to 100, and in a recent study of 173 control children at age 8 years, the mean (SD) score was 80.3 (16.5).[19]

Shifting attention was assessed by Creature Counting, a subtest from the TEACh. Children are required to count the number of creatures with random arrows instructing them to count upwards or downwards (ie, to shift between counting upwards and downwards). Performance was judged by a standardized score of accuracy (mean [SD], 10 [3]).

Executive Function | The Rey Complex Figure[21,22] assesses spatial organization and strategic decision making. Children are required to copy, as accurately as possible, a complex geometrical figure. After an interval of at least 20 minutes, they are asked to draw the figure again from memory. Accuracy was assessed using the scoring procedure developed by Osterrieth (maximum score, 36)[23,24] for both the initial attempt (copy score) and from memory (recall score).

The Behavior Rating Inventory of Executive Function[25] is a questionnaire that assesses behavioral manifestations of inattention and executive dysfunction. Both parent and teacher versions were administered. Summary scores of interest were the General Executive Composite and the Metacognition and Behavioral Regulation Indices (mean [SD], 50 [10]; higher scores indicate more problems). Clinical validity has been supported with a variety of diagnostic groups.[25]

Behavioral Problems

Attention-deficit/hyperactivity disorder (ADHD) symptoms were evaluated with parent and teacher versions of the Conners ADHD/*DSM-IV* Scales (Psychological Corporation), which have age/sex T scores (mean [SD], 50 [10]; higher scores indicate more problems).[26] General behavior problems were also assessed using the total difficulties score from parent and teacher reports of the Strengths and Difficulties Questionnaire, with possible scores ranging from 0 to 40: normal is 0 to 13; borderline, 14 to 16; and abnormal, greater than 17.[27]

Other Health and Functional Outcomes

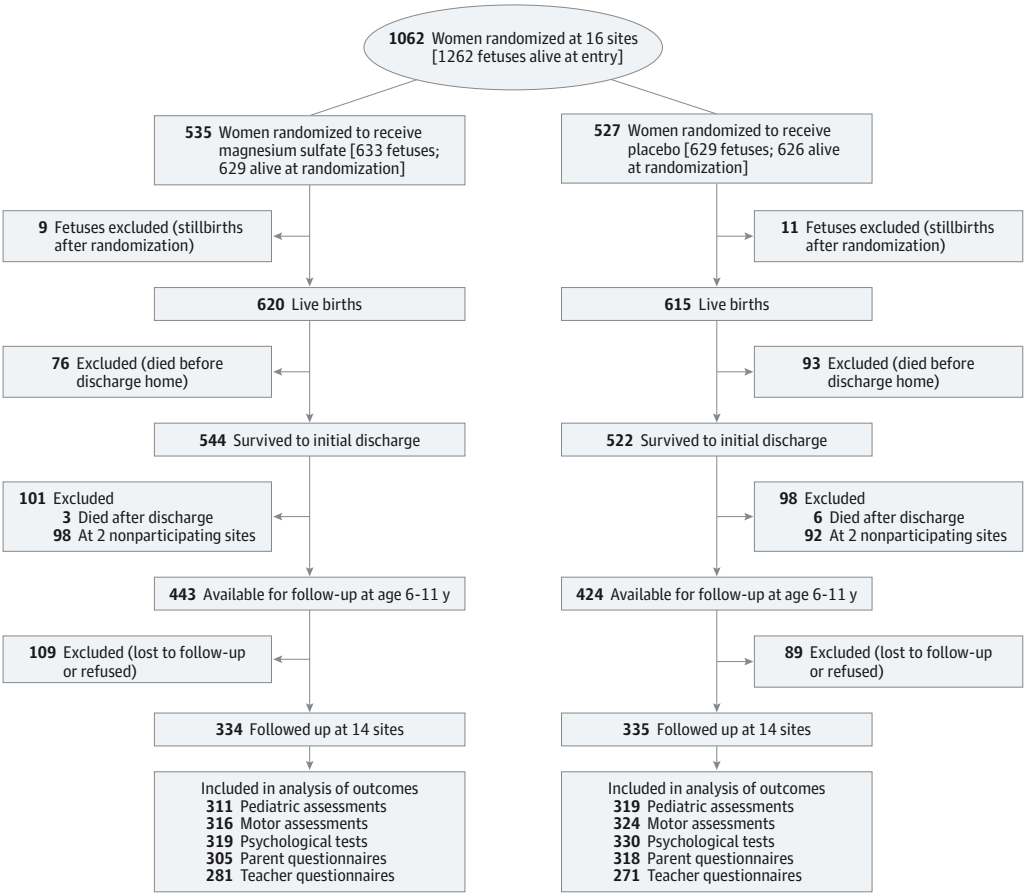
Weight and height were measured with the child wearing minimal clothing and either bare feet or light socks and values for SD scores computed from the British Growth Reference data.[28] Health-related quality of life was measured by the parent-completed Multiattribute Health Status classification system, which has been adapted for children.[29] A Health Utility Index is obtained, which ranges from 1 for perfect health to 0 for death. Children were also assessed with the parent-completed Australian Authorised Adaptation of the Child Health Questionnaire (CHQ).[30] The CHQ has been normed with more than 5000 Australian children aged 5 to 18 years and provides assessments of the child's psychosocial health (score, 0-600) and physical health (score, 0-400), with higher scores being better. Visual acuity was assessed with a standard eye chart. Children were considered blind if vision in both eyes was worse than 20/200. Children with suspect hearing problems, either from a history of hearing difficulties or delayed language development or on examination by the pediatrician, including a whispered hearing test, were referred for audiological evaluation; children were considered deaf if they required hearing aids or worse.

Neurosensory disability was classified as previously described.[31,32] Severe disability comprised any of severe cerebral palsy, an IQ less than 55, or blindness. Moderate disability comprised any of moderate cerebral palsy, deafness, or an IQ from 55 to 69. Mild disability comprised any of mild cerebral palsy or an IQ from 70 to 85. The children who did not meet these criteria were considered to have no neurosensory disability.

Statistical Analysis

Data were analyzed by a statistician independent of the clinical investigators using Stata version 13 (StataCorp). Dichotomous outcomes were compared between the groups using logistic regression and continuous outcomes by linear regression, both fitted using generalized estimating equa-

Figure. Randomization, Treatment, and School-age Follow-up of Participants in the ACTOMgSO4



tions to allow for the correlation between multiple births from the same pregnancy, and including a fixed effect for study centers (combining study centers with <50 participants into a single site). In a secondary analysis, treatment group differences were adjusted for potential confounders of race (white vs other), language spoken at home (English-only vs other), social class assessed by the occupation of the main income earner in the family (higher = professional, skilled, or semiskilled vs lower = unskilled, unemployed), and mother's education (≤11 vs >11 years of schooling), as well as sex of the child. We included race identified on self-report from the parents with options of white, indigenous, or other defined by the investigators because children of nonwhite race perform less well than children of white race on some cognitive tests.

Multiple imputation was carried out to impute the missing outcomes in the sites participating in the follow-up (including all 867 participants eligible for follow-up) (**Figure**). All outcomes were imputed simultaneously using a joint imputation model, including gestational age, birth weight, sex, multiple pregnancy, grade 3 or 4 intraventricular hemorrhage, cystic periventricular leukomalacia, postnatal corticosteroids, ethnicity, the Mental Developmental Index and the Psychomotor Developmental Index from the *Bayley Scales of Infant Development*, Second Edition,[33] at age 2 years, and maternal education and social class as predictors in the imputation model. Imputation was carried out separately in the 2 treatment groups using multivariate normal imputation in Stata version 13. Twenty imputed data sets were generated in each treatment group and the resulting data sets from the 2 groups from each imputation combined for analysis. Linear regression was used to compare all continuous outcomes between the groups after imputation combining the results across the 20 imputed data sets. Linear regression was used irrespective of the distribution of the outcome because it is not possible to combine the results from nonparametric tests following multiple imputation in Stata. Ordinal variables were compared between the groups using (unadjusted) Mann-Whitney tests using a complete case analysis as these tests were not available after multiple imputation. As a sensitivity analysis for the method used to handle the missing data, we repeated the analysis using a complete case analysis.

The significance threshold was set at $P < .05$. Given the large number of outcomes considered, results were interpreted with caution, and we considered the pattern and magnitude of events rather than focusing on individual P values. All tests were 2-sided.

Table 1. Perinatal, 2-Year, and Demographic Characteristics of Children Available for Follow-up at Corrected Age 6 to 11 Years[a]

	Magnesium Sulfate Group (n = 443)		Placebo Group (n = 424)		
	No. of Children	Summary	No. of Children	Summary	*P* Value
Perinatal					
Gestational age at birth, mean (SD), completed wk	443	27.3 (2.2)	424	27.4 (2.0)	.85
Birth weight, mean (SD), g	443	1053 (389)	424	1071 (365)	.48
Male sex	443	243 (55)	424	230 (54)	.86
Multiple pregnancy	443	124 (28)	424	128 (30)	.48
Grade 3 or 4 intraventricular hemorrhage	443	18 (4)	424	16 (4)	.83
Cystic periventricular leukomalacia	443	17 (4)	424	9 (2)	.14
Postnatal corticosteroids	443	144 (33)	424	121 (29)	.20
Follow-up at age 2 y					
Cerebral palsy	435	28 (6)	419	30 (7)	.67
Mental Developmental Index, mean (SD)[b]	394	89.2 (19.0)	386	90.7 (18.9)	.28
Psychomotor Developmental Index, mean (SD)[b]	395	89.5 (17.5)	380	91.8 (18.3)	.07
Blind	435	1 (<1)	420	0	>.99[c]
Deaf	435	6 (1)	420	7 (2)	.73
Not walking at age 2 y	432	14 (3)	419	25 (6)	.06
Follow-up at age 6-11 y					
Corrected age when assessed, mean (SD), y	328	8.4 (1.0)	330	8.4 (0.9)	.80
Maternal schooling >11 y	283	141 (50)	298	158 (53)	.44
Lower social class[d]	297	65 (22)	315	75 (24)	.57
Speaking only English at home	299	271 (91)	318	292 (92)	.60
White race	443	384 (87)	424	371 (88)	.72

[a] Data are No. (%), unless otherwise specified. *P* values are from a *t* test for continuous variables and a χ^2 test for binary variables.

[b] From the *Bayley Scales of Infant Development*, 2nd Ed.

[c] Fisher exact test was used for small cell sizes.

[d] Main income earner unskilled or unemployed.

With a sample size of 443 in the magnesium sulfate group and 424 in the placebo group, the study had 80% power to detect mean differences between groups as small as SD 0.19 or reductions in proportions observed in the placebo group from 27% to 18.9% for motor impairment or from 8% to 3.5% for cerebral palsy.

Results

Of the 1255 fetuses known to be alive at randomization, the known mortality rate to school age was lower in the magnesium sulfate group (14.0%; 88/629) compared with the placebo group (17.6%; 110/626) (Figure), although this difference did not reach statistical significance (RR, 0.80; 95% CI, 0.62-1.03; *P* = .08).

Of the 1060 known survivors at the 2-year follow-up, 3 children died before the school-age follow-up and 190 were from centers that did not participate in the school-age follow-up protocol, leaving 867 children (443 magnesium sulfate and 424 placebo) available for follow-up at school age (Figure). Of these 867 children, outcomes at school age were determined for 669 (77%), with the outcome data available for between 552 (64%) for the teacher-reported questionnaires and 649 (75%) for the psychological tests (Figure). Both groups were assessed at a mean (SD) age of 8.4 (1.0) years, corrected for prematurity. The magnesium sulfate and the placebo groups were well balanced for important perinatal, sociodemographic, and 2-year outcome variables among those assessed (**Table 1**). Children assessed at school age compared with available children who were not assessed were similar for most maternal, perinatal, and 2-year outcome variables, apart from being born at a lower gestational age and with a lower birth weight, being more likely to be from a multiple pregnancy, having more exposure to postnatal corticosteroids, and having a higher Mental Developmental Index score at 2 years (eTable 1 in Supplement 2).

Comparing the magnesium sulfate and placebo groups revealed no statistically significant differences with treatment in proportions with cerebral palsy or its severity (**Table 2**) (8% vs 7%; OR, 1.26; 95% CI, 0.84 to 1.91). There was 96% agreement between a diagnosis or not of cerebral palsy at age 6 to 11 years with that at age 2 years in children assessed at both ages, although 11 children with cerebral palsy at age 2 years no longer had the diagnosis at age 6 to 11 years, and 16 children with no cerebral palsy at age 2 years had the diagnosis at 8 years. Motor function on the GMFCS and distribution on the MABC centiles (29 vs 32 centile; mean difference, −2.8; 95% CI, −9.1 to 3.5) were similar between groups. The proportions with abnormal motor function based on the MABC and definite motor dysfunction were also similar in both groups (27% vs 27%; OR, 1.16; 95% CI, 0.88 to 1.52).

Table 2. Motor Outcomes at Corrected Age 6 to 11 Years

Outcomes	No./Total No. (%)		OR (95% CI)[a]	*P* Value[a]
	Magnesium Sulfate Group (n = 334)	Placebo Group (n = 335)		
Cerebral palsy	23/295 (8)	21/314 (7)	1.26 (0.84 to 1.91)	.27
Severity of cerebral palsy				
None	272/295 (92)	293/314 (93)		.60[b]
Mild	16/295 (5)	14/314 (4)		
Moderate	5/295 (2)	5/314 (2)		
Severe	2/295 (1)	2/314 (1)		
Gross motor function classification system[13]				
Level 0	264/304 (87)	277/314 (88)		.60[b]
Level 1	28/304 (9)	26/314 (8)		
Level 2	7/304 (2)	7/314 (2)		
Level 3	1/304 (<1)	2/314 (1)		
Level 4	3/304 (1)	1/314 (<1)		
Level 5	1/304 (<1)	1/314 (<1)		
MABC centile, median (IQR)[c]	29 (6-60)	32 (6-65)	−2.8 (−9.1 to 3.5)[d]	.38
Normal	187/297 (63)	191/301 (63)		.93[b]
Suspect	36/297 (12)	35/301 (12)		
Abnormal	74/297 (25)	75/301 (25)		
Definite motor dysfunction (<5th centile or cerebral palsy)	80/297 (27)	80/300 (27)	1.16 (0.88 to 1.52)	.28

Abbreviations: IQR, interquartile range; MABC, Movement Assessment Battery for Children; OR, odds ratio.

[a]Adjusted for study center and for clustering within mother. Analysis carried out using multiple imputation to handle missing data (n = 867) unless otherwise indicated.

[b]*P* values from Mann-Whitney U test, with no adjustment for study center or clustering, and no imputation for missing data.

[c]Available for 297 in the magnesium group and 301 in the placebo group.

[d]Mean difference (95% CI).

There were no substantial differences between groups on any of the cognitive, academic, attention, executive function, or behavioral outcomes as indicated by the limits of the 95% confidence intervals, which represented only small differences clinically, and none of the differences reached statistical significance (**Table 3**). There were no statistically significant differences between groups on any of the growth, functional, or other neurosensory outcomes (**Table 4**).

Adjusting for the potentially confounding social variables and sex of the child had little effect and altered no conclusions (eTable 2 in Supplement 2). No conclusions were altered in the complete case analysis (eTable 3 in Supplement 2).

Discussion

In this evaluation of neurological, cognitive, behavioral, growth, and functional outcomes at early school age of survivors from a large RCT, antenatal magnesium sulfate was not associated with any long-term benefits or harms compared with placebo. There was a nonsignificant reduction in mortality in the magnesium sulfate group, with the 95% confidence intervals consistent with a 38% reduction to a 3% increase in the risk of mortality compared with placebo. Importantly, only 3 of the 198 deaths overall occurred after age 2 years. Magnesium sulfate given to mothers just prior to preterm birth as neuroprotection for the fetus is one of the few therapies to offer any promise of improving neurologic outcome for preterm survivors. Given that this treatment is being introduced into clinical practice, it is important to know if there are any adverse long-term effects.

The follow-up rate of 77% of children available for follow-up was less than optimal. However, there were minimal differences between the treatment groups in perinatal or 2-year outcomes in those who were followed up at school age. The major exception was lower cognitive performance for those not assessed, which is consistent with worse cognitive function in children who are difficult to follow up.[34] Importantly, no conclusions were altered after complete case analysis, giving reassurance that the less than optimal follow-up rate is unlikely to have had a large effect on the results. We are unlikely to have missed important clinical differences between treatment groups because the confidence intervals for most outcomes were relatively narrow, given our large sample size. Ideally, more randomized trials will report on long-term outcomes after magnesium sulfate to be able to add to the pool of school-age data, as has been achieved for the early childhood data, from which clear evidence supports the use of magnesium sulfate to reduce cerebral palsy.[4]

The absence of benefit associated with antenatal magnesium sulfate into school age from the current trial does not negate the proven value of magnesium sulfate in reducing cerebral palsy, based on the collective evidence from all of the RCTs. Within the ACTOMgSO4, the risk of cerebral palsy at age 2 years was not substantially reduced by antenatal magnesium sulfate; the only notable benefit of magnesium sulfate at the 2-year follow-up was a reduction in the proportion of children with substantial gross motor dysfunction (GMFCS level 2 or worse). The reduction in gross motor dysfunction at age 2 years with magnesium sulfate did not appear to translate into improved motor outcome at school age in the current study. Although the confidence interval for the effect of magnesium sulfate on motor function at school age was relatively narrow, with the

Table 3. Cognitive, Academic, Attention, Executive Function, and Behavioral Outcomes at Corrected Age 6 to 11 Years

Outcome	Magnesium Sulfate Group		Placebo Group		Mean Difference (95% CI)[b]	*P* Value[b]
	No. of Children	Summary[a]	No. of Children	Summary[a]		
General cognitive function						
Full scale IQ	290	93.8 (15.8)	293	94.9 (15.0)	−1.4 (−4.2 to 1.4)	.32
Verbal comprehension index	298	94.2 (15.1)	303	94.9 (13.6)	−0.9 (−3.6 to 1.9)	.54
Perceptual reasoning index	298	96.1 (15.4)	303	97.6 (15.2)	−2.1 (−4.8 to 0.7)	.14
Working memory index	294	95.1 (14.9)	298	96.4 (14.7)	−1.2 (−4.0 to 1.6)	.38
Processing speed index	291	94.9 (15.1)	294	94.5 (14.1)	0.2 (−2.4 to 2.8)	.90
Academic skills						
Reading	287	99.4 (17.0)	301	98.9 (16.9)	1.0 (−2.4 to 4.4)	.58
Spelling	285	98.3 (15.7)	299	97.1 (15.2)	1.2 (−2.0 to 4.4)	.46
Arithmetic	288	89.8 (16.6)	299	89.5 (16.1)	0.5 (−2.6 to 3.7)	.74
Attention						
Selective-Sky Search	279	9.8 (3.3)	295	9.8 (3.4)	−0.3 (−0.9 to 0.4)	.39
Sustained-Score!	276	8.8 (3.6)	290	8.5 (3.8)	0.1 (−0.7 to 0.9)	.78
Divided-Sky Search Dual Task	278	79.1 (16.9)	290	77.6 (17.4)	0.3 (−3.1 to 3.7)	.85
Shifting-Creature Counting	267	9.1 (3.8)	285	8.7 (3.8)	0.2 (−0.6 to 1.0)	.65
Executive function						
Rey complex figure copy score	275	17.4 (7.1)	293	18.1 (7.4)	−1.1 (−2.4 to 0.3)	.12
Rey complex figure recall score	269	8.4 (5.4)	287	8.8 (5.6)	−0.6 (−1.8 to 0.6)	.34
BRIEF parent T scores						
Global executive composite	298	53.1 (12.5)	309	52.6 (12.1)	0.8 (−1.6 to 3.2)	.50
Metacognition index	298	53.4 (12.9)	309	52.8 (12.5)	1.2 (−1.2 to 3.6)	.35
Behavioral regulation index	298	51.7 (12.5)	310	51.7 (11.6)	−0.0 (−2.4 to 2.4)	.99
BRIEF teacher T scores						
Global executive composite	246	54.0 (12.4)	261	53.1 (10.9)	1.5 (−0.7 to 3.8)	.18
Metacognition index	243	54.5 (12.6)	252	54.0 (11.1)	1.4 (−0.8 to 3.7)	.21
Behavioral regulation index	265	52.0 (11.9)	272	51.5 (10.7)	1.3 (−0.9 to 3.5)	.26
Behavior						
CADS parent T scores						
ADHD index	305	57.3 (11.5)	318	56.3 (10.7)	1.3 (−0.7 to 3.3)	.19
DSM-IV inattentive	305	56.1 (11.6)	318	55.4 (10.7)	1.2 (−0.8 to 3.2)	.25
DSM-IV hyperactive-impulsive	305	56.1 (12.3)	318	55.9 (12.0)	0.3 (−2.0 to 2.6)	.81
DSM-IV	305	56.6 (11.7)	318	56.0 (11.2)	0.9 (−1.2 to 3.0)	.41
CADS teacher T scores						
ADHD index	271	54.3 (11.3)	281	53.8 (10.5)	1.4 (−0.8 to 3.5)	.22
DSM-IV inattentive	271	50.0 (8.6)	281	49.4 (8.4)	1.0 (−0.6 to 2.7)	.22
DSM-IV hyperactive-impulsive	271	51.9 (10.4)	281	51.2 (9.4)	1.5 (−0.3 to 3.3)	.09
DSM-IV	271	52.8 (10.2)	281	52.0 (9.1)	1.6 (−0.2 to 3.5)	.08
SDQ total difficulties						
Parent scores[c]	304	11 (6 to 17)	318	10 (6 to 15)	0.9 (−0.3 to 2.1)	.14
Teacher scores[c]	269	8 (4 to 14)	279	8 (4 to 13)	0.5 (−0.9 to 1.8)	.49

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BRIEF, Behavior Rating Inventory of Executive Function; CADS, Conners ADHD/*DSM-IV* Scales; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); SDQ, Strengths and Difficulties Questionnaire.

[a] Summary values are mean (SD) unless stated otherwise.

[b] Adjusted for study center and for clustering within mother. Analysis carried out using multiple imputation to handle missing data (n = 867).

[c] Summaries presented as median (interquartile range).

rate of GMFCS level 2 or worse decreasing to 3.5% in the placebo group, it was unlikely we would find evidence of a reduction in the magnesium group unless the rate decreased almost to zero. It is also possible that magnesium sulfate as used in our study has no effect on school-age motor outcomes.

Apart from investigating the effects of magnesium sulfate on the motor system, we have used an extensive battery of assessments designed to detect other beneficial or harmful neurological, psychological, or other effects that might exist from exposing infants to magnesium sulfate before birth.

Table 4. Growth, Functional, or Other Neurosensory Outcomes and Death or Moderate/Severe Disability at Corrected Age 6 to 11 Years

	Magnesium Sulfate Group		Placebo Group			
	No.	Mean (SD)	No.	Mean (SD)	Treatment Effect (95% CI)[a,b]	*P* Value[a]
Growth (SD scores)						
Height	302	−0.25 (1.24)	316	−0.09 (1.20)	−0.11 (−0.35 to 0.14)	.38
Weight	298	−0.18 (1.43)	316	0.05 (1.33)	−0.22 (−0.48 to 0.04)	.10
Body mass index	297	−0.04 (1.43)	315	0.15 (1.37)	−0.22 (−0.46 to 0.03)	.08
Head circumference	298	−1.07 (1.13)	311	−0.86 (1.26)	−0.18 (−0.39 to 0.03)	.10
Functional outcomes		Median (25th-75th Centile)		Median (25th-75th Centile)		
Health utility index	260	1 (1 to 1)	276	1 (1 to 1)	−0.00 (−0.03 to 0.02)	.82
Child health questionnaire summary scores						
Physical	265	361 (326 to 379)	288	355 (324 to 375)	−2.2 (−12.8 to 8.4)	.69
Psychosocial	265	501 (412 to 542)	283	489 (423 to 544)	−8.1 (−24.7 to 8.4)	.34
Other neurosensory outcomes	No./Total No. (%)		No./Total No. (%)			
Blindness	1/269 (0.4)		0/285			>.99[c]
Deafness	6/280 (2)		7/304 (2)		0.93 (0.31 to 2.81)	.55
Neurosensory disability						.92[d]
None	174/257 (68)		171/254 (67)			
Mild	50/257 (19)		56/254 (22)			
Moderate	24/257 (9)		20/254 (8)			
Severe	9/257 (4)		7/254 (3)			

[a]Adjusted for clustering within mother and study center unless otherwise indicated. Analysis carried out using multiple imputation to handle missing data.

[b]Treatment effects are mean difference (95% CI) or odds ratio (95% CI).

[c]Not possible to calculate a treatment effect because there was only 1 case in the magnesium sulfate group; *P* value from Fisher exact test.

[d]*P* value from a Mann-Whitney test with no adjustment for study center or clustering and no imputation for missing data.

Despite a reasonable power of finding true differences if any existed, none were found.

A limitation of the current study is that the results apply to only 1 of the known RCTs of antenatal magnesium sulfate therapy. The existing RCTs differ in patient characteristics and dosing regimens.[4] It is possible that other RCTs may have different conclusions than the current study if they report school-age outcomes using similar assessment techniques. It is also possible that other RCTs might report no important long-term benefits or harms. Other strategies to determine long-term effects of magnesium sulfate include studies linking efforts to improve its uptake as a fetal neuroprotectant with long-term outcomes of the children in Australia and New Zealand.[35] If the collective pooled evidence indicates no long-term gain, those who are currently using magnesium sulfate to reduce cerebral palsy might reconsider doing so. Strengths of the current study include the randomization, blinded follow-up assessments, and extensive outcome battery designed to not miss clinically important neurological effects of treatment if they existed.

Conclusions

Magnesium sulfate given to pregnant women at imminent risk of birth before 30 weeks' gestation was not associated with neurological, cognitive, behavioral, growth, or functional outcomes in their children at school age, although a mortality advantage cannot be excluded. The lack of long-term benefit requires confirmation in additional studies.

ARTICLE INFORMATION

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Obtained funding: Doyle, Anderson, Crowther.
Administrative, technical, or material support: Doyle, Anderson, Haslam, Crowther.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Funding/Support: This study was funded by a project grant (350326) from the National Health and Medical Research Council Australia and the Victorian Government's Operational Infrastructure Support Program.

Role of the Funder/Sponsor: The funding bodies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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