

Magnesium Sulfate in Labor and Risk of Neonatal Brain Lesions and Cerebral Palsy in Low Birth Weight Infants

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ABSTRACT. *Objectives.* We tested the hypothesis that administration of magnesium sulfate in labor protects against the development of neonatal brain lesions and cerebral palsy (CP) in low birth weight infants.

Methods. Magnesium exposure was ascertained in a population-based cohort of 1105 infants weighing 2000 g or less through review of medical records of maternal magnesium sulfate administration and, where available, elevated maternal serum magnesium levels. Neonatal germinal matrix/intraventricular hemorrhage and parenchymal brain lesions were ascertained by a prospective, timed ultrasound scanning protocol in the first week of life. CP was ascertained at 2 years of age by clinical examination in 80% of survivors and by interview and medical record review in another 6% and was classified as disabling or nondisabling.

Results. No significant reduction in risk of nondisabling CP (adjusted odds ratio [OR], 1.00; 95% confidence interval [CI], 0.53 to 1.88) or disabling CP [DCP] (adjusted OR, 0.63; 95% CI, 0.32 to 1.24) CP with magnesium exposure was found in a logistic regression model that controlled for gestational age, fetal growth, gender, multiple birth status, mode of delivery, amnionitis, and hypertensive disorders. In a small subset of infants, those with onset of parenchymal lesions at 7 days of age or later ($n = 29$), magnesium exposure was associated with a significantly reduced risk of DCP (OR, 0.10; 95% CI, 0.02 to 0.65). Magnesium sulfate exposure was not associated with germinal matrix/intraventricular hemorrhage (adjusted OR, 0.89; 95% CI, 0.64 to 1.25) or with parenchymal brain lesions (adjusted OR, 0.83; 95% CI, 0.53 to 1.30).

Conclusions. The hypothesis that magnesium sulfate use reduces the risk of neonatal brain lesions or CP in low birth weight infants was not statistically supported in this study, although a modest reduction in risk of DCP cannot be excluded. The data further suggest that magnesium exposure may be associated with reduction in risk of CP in low birth weight infants who have late-onset brain lesions, but this unpredicted observation requires confirmation in another data set. *Pediatrics* 1997; 99(5). URL: <http://www.pediatrics.org/cgi/content/full/99/5/e1>; cerebral palsy; magnesium sulfate; infant, low birth weight; preeclampsia; cerebral hemorrhage, infant.

ABBREVIATIONS. PE, preeclampsia; CP, cerebral palsy; NBH, Neonatal Brain Hemorrhage (cohort); DCP, disabling CP; GM/IVH, germinal matrix or intraventricular hemorrhage; PEL/VE, parenchymal lesion/ventricular enlargement; HYP, hypertension; OR, odds ratio; CI, confidence interval.

Magnesium sulfate is widely used in obstetric practice both to treat preeclampsia (PE) and to attempt to arrest the progress of premature labor. A recent case-control study in infants weighing less than 1500 g at birth demonstrated a substantial reduction in cerebral palsy (CP) in children whose mothers received magnesium sulfate in labor.¹

This observation is coherent with the multiple catalytic roles of magnesium in cellular enzyme systems and neuronal functioning² and particularly with evidence that magnesium can block the *N*-methyl-D-aspartate receptor and thus prevent excitatory amino acids, commonly released during episodes of hypoxia and ischemia, from producing neuronal damage.³

We set out to test the hypothesis suggested by this case-control study, namely, that magnesium exposure is associated with a decreased risk of CP in the Central New Jersey Neonatal Brain Hemorrhage (NBH) cohort. In the NBH cohort, low birth weight infants were assessed prospectively with cranial ultrasound scanning in the neonatal period and examined at 2 years of age for the presence or absence of CP. Included in this cohort of 1105 infants are 362 infants whose mothers received magnesium sulfate, 280 infants with ultrasonographically diagnosed neonatal brain lesions, and 113 children with the diagnosis of either disabling CP (DCP) or nondisabling CP. This study thus provides considerable power to assess the relationships of magnesium sulfate exposure to important neurologic outcomes in the neonatal and early childhood periods.

METHODS

Study Population

The NBH study is an investigation into the causes and consequences of ultrasonographically diagnosed brain lesions in low birth weight infants. The cohort is a geographically representative sample of 1105 infants weighing 2000 g or less born or cared for in three neonatal intensive care units in central New Jersey between 1984 and 1987.⁴ The ultrasound screening protocol called for scans at 4 hours, 24 hours, and 7 days of age. Such films were obtained in more than 95% of eligible infants. Additional later scans were obtained, usually just before discharge, in about half of the cohort. Study films were read by two or, if needed, three radiologists to obtain consensus on the diagnosis. In 94% of study infants, the

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ultrasound diagnosis was based on agreement by two independent readers. Information on CP status was available on 86% of surviving infants at 2 years of age, and in 80% this was based on a standardized motor examination by a trained nurse or nurse practitioner supplemented by medical record review and examination by study child neurologists in cases of suspected abnormality.

Outcomes of Interest

Five health outcomes were selected for study: neonatal outcomes included death in the first 28 days, sonographic diagnosis of germinal matrix or intraventricular hemorrhage (GM/IVH) and sonographic diagnosis of parenchymal lesion/ventricular enlargement (PEL/VE), a category that includes lesions commonly referred to as periventricular leukomalacia, porencephalic cyst, and grades III and IV IVH. Based on pathological and outcome studies, the above dichotomy of brain lesions distinguishes milder lesions (GM/IVH), which do not themselves damage cortex or white matter and are not usually associated with substantial elevation of handicap risk, from more severe lesions (PEL/VE), which reflect pathologic evidence of damage to white matter and predict subsequent neurologic impairment. These groupings are also more consistent with pathologic findings⁵ than is the widely used classification of Papile et al.⁶ When both brain lesions occurred, the infant was categorized as having PEL/VE.

The two outcomes assessed at 2 years of age were DCP and nondisabling CP. The term DCP was used when at least one of five markers of disability was present in addition to specific neurologic findings⁷:

1. Inability to walk ten steps unaided by 2 years of age;
2. Bayley motor score greater than 1 SD lower than performance score;
3. Receipt of physical therapy for motor disability;
4. Receipt of surgical intervention for motor disorder; and
5. Use of braces or physical assistance devices.

The majority of children with DCP had Bayley motor scores of less than 50. (Previous papers^{7,20} mistakenly cited five steps rather than ten steps as the walking criterion; no case of CP was classified as disabled based on this criterion).

Although the stimulus for this analysis was a finding about the relationship of magnesium sulfate to CP, we examined death before discharge, because a reduction in CP risk might be found if there were an increased risk of neonatal death associated with magnesium sulfate exposure. Neonatal brain lesions were examined because of their strong relationship to risk of CP.⁷ Changes in their incidence might therefore constitute a mechanism by which risk of CP is influenced by magnesium exposure.

Exposure Assessment

In the NBH data set, diagnoses made during pregnancy and delivery, medications used in the 72 hours before delivery, and blood tests obtained in the 24 hours before labor were systematically abstracted from prenatal and labor and delivery records. Mothers were also interviewed shortly after delivery about illnesses and medications taken during pregnancy. Because magnesium sulfate is used to treat PE, and because PE has been associated, in some studies, with reduced risk of CP,⁸ control for PE is essential for proper understanding of the relationship of magnesium sulfate to neurologic sequelae. Thus, we first categorized hypertensive mothers as having either preexisting hypertension (HYP) or PE. The presence of proteinuria during pregnancy was not required for the diagnosis of PE, but was recorded when noted. Figure 1 sets out the criteria for the above diagnoses and the data sources in the NBH study used to establish them. HYP was found in the mothers of 47 infants (4.3%), and PE was found in 212 (19.2%), which was associated with proteinuria in 136 (12.3%).

Magnesium sulfate use was ascertained in two ways: from the recording of magnesium sulfate administration in medical records and from the recording of elevated (>2.8 mEq/L) maternal serum levels of magnesium sulfate. In addition, infants were presumed exposed to magnesium sulfate if an elevated (>1.7 mEq/L) serum magnesium level was recorded in the neonatal period.

Data Analysis

The associations between magnesium exposure of infants (defined by magnesium sulfate administration, elevated serum mag-

Preexisting Hypertension (HYP)

1. Preexisting hypertension noted in prenatal records.
or
2. Diastolic blood pressure ≥ 90 mm Hg at first prenatal visit

Preeclampsia (PE)

1. No evidence of **preexisting hypertension**
and
2. Hypertension in pregnancy, based on one or more of the following three observations:
 - a. Diastolic BP ≥ 90 on two prenatal visits.
 - b. Diastolic BP ≥ 110 on one visit, or in labor and delivery.
 - c. Diagnosis of hypertension or preeclampsia or eclampsia recorded in prenatal or labor and delivery records.
 - d. Maternal recall of diagnosis of preeclampsia or eclampsia at postpartum interview.
3. **Proteinuria during pregnancy was noted, but was not required for the diagnosis of PE.**

Fig 1. Criteria for the diagnoses of preexisting hypertension and preeclampsia and the data sources in the Neonatal Brain Hemorrhage cohort used to establish them.

nesium level, or both) and the five health outcomes are shown both unadjusted and adjusted for several potentially confounding variables. The selection of the model for adjustment was based on known associations of the variables in the model with outcomes of interest as well as with receipt of magnesium therapy, either in our study or in the literature. The final model chosen included the following variables in the analysis: gestational age, fetal growth ratio (defined as the ratio of the infant's birth weight to the median birth weight for its week of gestation based on the standards of Arbuckle et al⁹), gender, mode of delivery (vaginal, cesarean with labor, or cesarean without labor), multiple birth status, diagnosis of amnionitis during labor, and maternal diagnoses of PE (with or without proteinuria) and preexisting HYP.

In addition, to replicate the findings of Nelson and Grether¹ more closely, we selected singleton infants in the NBH cohort who weighed less than 1500 g and repeated, as best we could in our data, the analytic model used by Nelson and Grether¹ to control for extraneous variables.

We calculated unadjusted odds ratios (ORs) using Cornfield 95% confidence intervals (CIs) and adjusted ORs by multiple logistic regression. Analyses included models containing all variables above and smaller models resulting from reverse-stepwise selection. Adequacy of fit was assessed by the grouped Hosmer-Lemeshow χ^2 test, and $\Delta\chi^2$ and $\Delta\beta$ diagnostic plots were used to examine potential outliers.¹⁹ All analyses were performed using Stata (Stata Corp, College Station TX).

RESULTS

Magnesium Sulfate Exposure and HYP-Related Diagnoses (Table 1)

A total of 362 infants were designated as exposed to magnesium. In 173, maternal serum magnesium was documented to be greater than 2.8 mEq/L in the 24 hours before delivery. Records of magnesium sulfate administration in the 72 hours before delivery were found in the mothers of 153 of these 173 infants. The mothers of an additional 176 infants had records

TABLE 1. Magnesium Sulfate Use by Maternal Diagnosis in 1105 Infants

Magnesium Use	Preeclampsia With Proteinuria	Preeclampsia Without Proteinuria	Preexisting Hypertension	Healthy	Total
Magnesium use based on medical record history only	45	14	10	107	176*
Magnesium use documented by serum Mg ⁺⁺ level >2.8 mEq/L	44	10	7	112	173
Infant serum Mg ⁺⁺ >1.7 mEq/L	0	1	0	12	13
Any magnesium use, n (%)	89 (65.4)	25 (33.8)	17 (37.8)	231 (29.5)	362 (34.9)
No magnesium use	47	49	28	551	675
Magnesium use uncertain	0	2	2	64	68
Total	136	76	47	846	1105

* In the mothers of 5 infants serum Mg⁺⁺ was not elevated, and in 171 no serum level was available.

of magnesium sulfate administration but had no records of serum magnesium measurement (n = 171) or had serum magnesium levels in the normal range (n = 5). Additionally, 13 infants were noted to have elevated serum magnesium levels (>1.7 mEq/L) without other evidence of maternal receipt of magnesium sulfate. These 13 infants were also categorized as magnesium sulfate exposed. An additional 91 newborns with elevated serum magnesium levels had additional evidence of maternal magnesium sulfate exposure and are included in the exposure categories above. In 68 infants (6.0%), insufficient information was available about details of labor and delivery to permit satisfactory classification of maternal exposure, and these infants were excluded from the analysis. Most had been transferred to study hospitals postnatally.

Magnesium sulfate use was substantially higher in mothers with the diagnosis of PE with proteinuria (65.4%) than in women with no HYP-related diagnosis (29.5%). Magnesium sulfate exposure was not significantly higher in infants whose mothers had HYP in pregnancy without proteinuria (33.8%) and in infants whose mothers had preexisting HYP (37.8%) than in women with no HYP-related diagnosis.

Despite the more frequent use of magnesium sulfate in mothers with PE, the bulk of exposure to magnesium sulfate in this cohort, 63.8%, occurred in infants whose mothers had no HYP-related diagnosis. We presume that mothers without HYP-related diagnoses who received magnesium sulfate received this treatment for tocolysis. The likelihood of the magnesium sulfate exposure having been determined by medication history or by

serum magnesium assessment did not differ by maternal diagnosis.

Relationship of Magnesium Sulfate Exposure to Neonatal Outcomes (Table 2)

No statistically significant relationship of magnesium sulfate exposure to either GM/IVH or PEL/VE was detected in these data. We assessed the ORs for this relationship in simple 2 × 2 tabulations (top row, unadjusted), and also in models that control for the potentially confounding variables listed in "Methods." In adjusted and unadjusted models, ORs for magnesium sulfate exposure and brain lesions ranged from 0.80 to 0.97. Mortality in the neonatal period was somewhat lower in magnesium sulfate-exposed infants, with ORs ranging from 0.64 to 0.93 depending on the mode of exposure determination and level of adjustment. The lack of any excess mortality in magnesium-exposed infants indicates that favorable effects of magnesium on later sequelae are unlikely to be attributable to selection bias produced by raised mortality in the neonatal period.

Relationship of Magnesium Sulfate Exposure to CP (Table 3)

Analyses in Table 3 are based on the 777 infants who were assessed at 2 years of age. Although there was a suggestion that magnesium sulfate might be protective against DCP, with all ORs less than 1, ranging from 0.57 to 0.65 depending on the level of adjustment and method of exposure determination, none of these relationships achieved statistical significance. Nondisabling CP bore no consistent relationship to magnesium sulfate exposure, with ORs varying from 0.84 to 1.11. Total CP, not surprisingly, was

TABLE 2. Odds Ratios (95% Confidence Intervals) for the Association of Magnesium Sulfate and Three Neonatal Outcomes: Unadjusted (Top Row) and Adjusted* (Second Row) Models

Magnesium Use	Germinal Matrix/ Intraventricular Hemorrhage (n = 238)	Parenchymal Lesions/ Ventricular Enlargement (n = 103)	Neonatal Death (n = 176)
Magnesium use based on medical record history only (n = 176)	0.80 (0.53–1.20) 0.85 (0.54–1.34)	0.89 (0.51–1.57) 0.87 (0.47–1.63)	0.93 (0.57–1.52) 0.90 (0.50–1.61)
Magnesium use documented by serum Mg ⁺⁺ level >2.8 mEq/L (n = 173)	0.97 (0.65–1.44) 0.91 (0.59–1.40)	0.91 (0.52–1.61) 0.84 (0.45–1.55)	0.75 (0.44–1.28) 0.64 (0.35–1.20)
Magnesium use by either definition or elevated infant serum Mg ⁺⁺ (n = 363)	0.89 (0.65–1.20) 0.89 (0.64–1.25)	0.96 (0.62–1.47) 0.94 (0.59–1.49)	0.77 (0.54–1.10) 0.83 (0.53–1.30)

* Adjusted for gestational age, fetal growth ratio, gender, multiple birth status, mode of delivery, labor status, amnionitis, preeclampsia, and preexisting hypertension.

TABLE 3. Odds Ratios (95% Confidence Intervals) for the Association of Magnesium Sulfate and Cerebral Palsy Unadjusted (Top Row) and Adjusted* (Second Row) Models

Magnesium Use	Disabling Cerebral Palsy (n = 61)	Nondisabling Cerebral Palsy (n = 52)	Any Cerebral Palsy (n = 113)
Magnesium use based on medical record history only (n = 134)	0.62 (0.28–1.40) 0.64 (0.26–1.58)	0.84 (0.38–1.85) 0.90 (0.38–2.11)	0.72 (0.40–1.30) 0.72 (0.38–1.38)
Magnesium use documented by serum Mg ⁺⁺ level >2.8 mEq/L (n = 135)	0.62 (0.28–1.40) 0.57 (0.23–1.40)	1.05 (0.51–2.18) 1.11 (0.51–2.41)	0.82 (0.47–1.44) 0.81 (0.44–1.50)
Magnesium use by either definition or elevated infant serum Mg ⁺⁺ (n = 276)	0.65 (0.35–1.19) 0.63 (0.32–1.24)	0.92 (0.51–1.67) 1.00 (0.53–1.88)	0.77 (0.50–1.20) 0.79 (0.49–1.27)

* Adjusted for gestational age, fetal growth ratio, gender, multiple birth status, mode of delivery, labor status, amnionitis, preeclampsia, and preexisting hypertension.

intermediate in its relationship to magnesium sulfate, with ORs slightly less than 1 in all analyses, none significant. Adjustment for covariates had only a marginal effect on the ORs.

ORs for DCP in Relation to Neonatal Brain Lesions

Figure 2 graphs adjusted ORs and their 95% CIs for DCP in study infants categorized by the presence or absence of neonatal brain lesions. ORs are adjusted for the same set of variables as used in the models presented in Tables 2 and 3. Among infants with neither GM/IVH nor PEL/VE, magnesium sulfate use was associated with reduced risk of DCP but not significantly so. Among infants with brain lesions, infants with PEL/VE without GM/IVH had the largest reduction in risk, bordering on significant. Thus, the presence of GM/IVH seems to identify infants with the least reduction in risk associated with magnesium sulfate exposure. Indeed in all infants without GM/IVH, the OR of 0.22 is nearly significant (upper CI boundary, 1.02). A Mantel-Haenzel test for heterogeneity indicates that the ORs in these two strata did not differ significantly from each other ($P = .12$). The reduced risk of CP in our cohort seem to be due entirely to an association found in the 29 infants

with late-onset (ie, after days 1 and 2) of PEL/VE. In these infants, magnesium sulfate use is associated with a large reduction in risk of CP, with an OR of 0.10 (95% CI, 0.02 to 0.64). This subset finding was not prehypoththesized and must therefore be treated with caution. The probability that the OR for DCP does not differ between infants with and without late PEL/VE is 0.07.

Replication of Analyses of Nelson and Grether¹

Nelson and Grether¹ reported a consistent pattern of reduction of risk with magnesium sulfate exposure in many subgroups of singleton infants weighing less than 1500 g. In Tables 4 and 5, we replicate, to the extent possible in our data, the categories they used to search for a possible protective effects of magnesium sulfate in subgroups of infants. The analyses in these tables are restricted to the 274 follow-up survivors in our data set who were singleton and weighed less than 1500 g at birth. Table 4 lists pregnancy and labor and delivery characteristics; Table 5 lists neonatal characteristics. Although we tabulate both of our CP categories, Nelson and Grether¹ restricted their attention to “moderate to severe” CP, which probably corresponds most closely to our category of DCP.

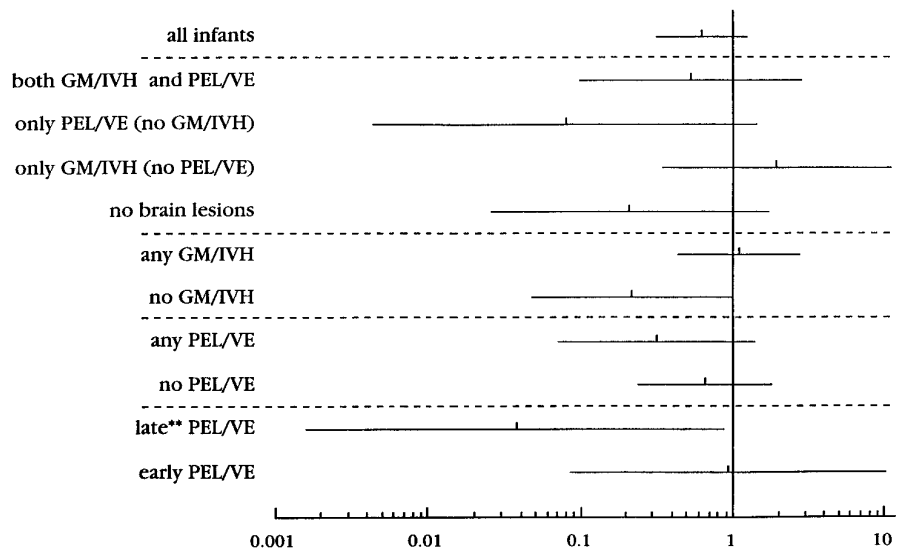


Fig 2. Adjusted odds ratios and 95% confidence limits for disabling cerebral palsy in study infants categorized by the presence or absence of neonatal brain lesions.

* Adjusted for gestational age, fetal growth ratio, gender, multiple birth status, mode of delivery, labor status, amnionitis, pre-eclampsia, and pre-existing hypertension

** No parenchymal lesion seen prior to 3rd protocol ultrasound (see text)

TABLE 4. Relation of Magnesium to Cerebral Palsy in Singleton Infants Weighing Less Than 1500 g by Several Pregnancy Conditions Studied by Nelson and Grether¹

Condition	Unadjusted Odds Ratios (95% confidence intervals) for Magnesium Use	
	Disabling Cerebral Palsy	Any Cerebral Palsy
All	0.71 (0.36–1.40)	0.92 (0.53–1.58)
Hypertension		
Preeclampsia	*	*
Preexisting hypertension	0 (0–4.6)	0 (0–4.6)
No hypertension	0.84 (0.40–1.70)	0.99 (0.54–1.81)
Bleeding at admission		
Yes	0.98 (0.26–3.8)	1.58 (0.53–4.7)
No	0.66 (0.30–1.45)	0.78 (0.41–1.47)
Abruptio or previa		
Yes	0.30 (0–2.5)	0.64 (0.14–3.1)
No	0.81 (0.39–1.65)	0.98 (0.55–1.76)
Rupture of membranes >24 h		
Yes	1.12 (0–8.3)	0.56 (0–3.8)
No	0.57 (0.26–1.25)	0.85 (0.45–1.61)
Breech presentation		
Yes	1.74 (0.61–4.9)	2.29 (0.93–5.6)
No	0.42 (0.16–1.07)	0.56 (0.27–1.15)
Cesarean section		
Yes	0.80 (0.35–1.85)	1.09 (0.55–2.1)
No	0.59 (0.19–1.89)	0.69 (0.27–1.78)
Gestational age, wk		
≤30	0.71 (0.34–1.46)	0.90 (0.49–1.63)
>30	0.70 (0–5.5)	1.04 (0.24–4.4)
Fetal bradycardia		
Yes	0 (0–0.85)†	0.23 (0–1.01)
No	0.97 (0.47–1.99)	1.25 (0.68–2.3)

* Insufficient number of cases to compute odds ratios.

† Statistically significant findings are boldface.

Just one association of statistical significance was found in these two tables. No magnesium sulfate-exposed infant had CP when fetal bradycardia was present (CI, 0 to 0.85) (Table 4). This subgroup analysis was not prespecified; therefore, this OR must be treated with caution. At the same time, there was no suggestion of a stronger reduction in risk in infants with low Apgar scores (Table 5).

DISCUSSION

In this cohort study, in which CP was prospectively ascertained and in which magnesium sulfate exposure was based not only on reported administration of the medication but also on documentation of elevated maternal serum magnesium levels in many women, we did not find the strong protective effect of magnesium sulfate for CP reported by Grether and Nelson¹ in their case-control study. However, our results are compatible with a more modest protective effect of magnesium sulfate for DCP, on the order of about a 35% reduction in risk, which although not statistically significant in these data, is sizable enough to encourage further investigation of the association. There is also a suggestion in these data that the presence of brain lesions may modify this risk reduction, accentuating it when late-onset lesions are present and reversing it when early hemorrhage occurs. It is important to note here that these interactions, although reasonable to examine, were not prespecified and may, therefore, have arisen by chance.

TABLE 5. Relation of Magnesium to Cerebral Palsy in Singleton Infants Weighing Less Than 1500 g by Several Neonatal Conditions Studied by Nelson and Grether¹

Condition*	Unadjusted Odds Ratios (95% confidence intervals) for Magnesium Use	
	Disabling Cerebral Palsy	Any Cerebral Palsy
Birth weight, g		
<1000	0.49 (0.15–1.64)	0.54 (0.19–1.54)
1000–1499	0.86 (0.38–1.95)	1.15 (0.60–2.2)
Gender		
M	0.74 (0.27–2.0)	1.05 (0.49–2.3)
F	0.70 (0.29–1.70)	0.80 (0.37–1.72)
5-min Apgar score		
<6	0.76 (0.14–4.2)	0.63 (0.12–3.4)
≥6	0.75 (0.36–1.56)	0.98 (0.55–1.75)
First pH		
<7.1	†	†
≥7.1	0.65 (0.32–1.30)	0.86 (0.50–1.50)
Respiratory distress syndrome		
Yes	0.76 (0.37–1.56)	0.98 (0.55–1.75)
No	0.56 (0–4.6)	0.75 (0.14–4.0)
Intubation		
Yes	0.80 (0.39–1.61)	0.90 (0.50–1.62)
No	0 (0–1.87)	1.05 (0.24–4.5)
GM/IVH		
Yes	1.21 (0.51–2.9)	1.43 (0.63–3.3)
No	0.31 (0–1.33)	0.72 (0.33–1.56)
PEL/VE		
Yes	0.33 (0.09–1.24)	0.43 (0.12–1.51)
No	0.78 (0.29–2.1)	0.98 (0.49–1.95)
Neonatal seizures		
Yes	1.50 (0.19–11)	1.07 (0.15–7.5)
No	0.56 (0.25–1.24)	0.90 (0.50–1.63)

* GM/IVH indicates germinal matrix/intraventricular hemorrhage; and PEL/VE, parenchymal lesion/ventricular enlargement.

† Insufficient number of cases to compute odds ratios.

The divergence in findings between these two studies cannot easily be attributed to the differences in populations. Although our study population included multiple births and extended to 2000 g birth weight, replication of the analyses for CP in the subset of our infants who, as in the population of Nelson and Grether,¹ were singleton and weighed less than 1500 g, did not produce evidence of magnesium sulfate protection against CP. We have no evidence that the low birth weight infants in the study by Nelson and Grether¹ differed in any important way from those in our study.

The use of magnesium sulfate in labor is not random. Mothers with PE (with proteinuria) were about twice as likely to receive magnesium sulfate as were other mothers in our study, and other investigators have shown that PE in the mother may itself be associated with a lower risk of CP and of neonatal brain lesions.^{10,11} One must also be concerned that women with magnesium sulfate use might be more likely to be delivered abdominally, a factor that has been shown in some studies to be associated with reduced risk of brain lesions.¹²

A third factor to consider is amniotic fluid infection. Mothers with amnionitis may not be candidates for tocolysis and will thus be less likely to receive magnesium sulfate. If amnionitis places them at higher risk for CP, as has also been suggested,^{13,14}

magnesium sulfate may artifactually seem protective. In our study, these three factors, as best we could ascertain them, were accounted for in the analysis.

The single most important predictor of CP in the low birth weight population is the finding of ultrasonographically imaged brain lesions in the neonatal period. Neither of the two major lesions, GM/IVH or PEL/VE, was reduced with magnesium sulfate exposure, and this might reasonably be viewed as diminishing support for the magnesium sulfate-CP association. However, half of the children with DCP did not have brain lesions diagnosed; therefore, a factor need not be associated with brain lesions to elevate risk of CP. Magnesium sulfate exposure was associated with a nonsignificant reduction of the neonatal death rate in analyses that controlled for several potential confounders.

Other recent studies, some only available in abstract form, have examined the relationship between magnesium sulfate use and either CP or neonatal brain lesions. Hauth et al¹⁵ found a substantial reduction in CP in magnesium sulfate-treated infants weighing less than 1 kg in Alabama, but a more recent report from some of the same authors found, in a different data set, no relationship of magnesium sulfate to neonatal brain lesions.¹⁶

Similarly, Lemons et al,¹⁷ examining data from the Neonatal Research Network, found no significant protective effect of magnesium sulfate exposure in very low birth weight infants on risk of neonatal brain lesions. Indeed, in an analysis restricted to singleton extremely low birth weight infants without maternal diabetes or PE, magnesium sulfate use was associated with a significant excess of brain lesions. Magnesium sulfate, was, however associated with lower mortality in that study. Leviton et al¹⁸ have now shown, in contrast to their findings from an earlier data set¹¹, that magnesium sulfate is not associated with reduced risk of neonatal brain lesions.

Thus, the results of studies examining the association of magnesium sulfate with either brain lesions or CP in low birth weight infants produce a mixed picture, and this inconsistency is mirrored in our own results. Although our findings are in general most consistent with the conclusion that magnesium sulfate does not protect low birth weight infants from CP, our results encourage further exploration of this possibility. In observational studies, magnesium sulfate exposure often co-occurs with other factors, some of which may themselves be protective against CP in as yet unknown ways. Thus, observational studies of magnesium sulfate and CP in low birth weight infants will require careful ascertainment and control of measures of infection, PE, other routes to preterm delivery, and modes of delivery among other factors. A randomized treatment trial would obviate these concerns and may, therefore, be the preferred way to test the hypothesis that magnesium sulfate can reduce the risk of CP in low birth weight infants.

Note Added in Proof. Schendel et al²¹ have recently reported a reduced risk of CP in relation to prenatal

magnesium sulfate exposure in very low birth weight children in Atlanta.

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REFERENCES

1. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birth weight infants? *Pediatrics*. 1995;95:263-269
2. Thordstein M, Bagenholm R, Thiringer K, et al. Scavengers of free oxygen radicals in combination with magnesium ameliorate perinatal hypoxic-ischemic brain damage in the rat. *Pediatr Res*. 1993;34:23-26
3. Marret S, Gressens P, Gadisseux JF, Evrard P. Prevention by magnesium of excitotoxic neuronal death in the developing brain: an animal model for clinical intervention studies. *Dev Med Child Neurol*. 1995;37:473-484
4. Pinto-Martin JA, Paneth N, Witomski T, et al. The Central New Jersey Neonatal Brain Hemorrhage Study. Design of the study and reliability of ultrasound diagnosis. *Paediatr Perinat Epidemiol*. 1992;6:273-284
5. Paneth N, Rudelli R, Kazam E, Monte W. *Brain Damage in the Preterm Infant*. London, England: Mac Keith Press; 1994. (Distributed in the US by Cambridge University Press)
6. Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhages: a study of infants with birth weights less than 1500 g. *J Pediatr*. 1978;92:529-534
7. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics*. 1995;95:249-254
8. Blair E. Pre-eclampsia, cerebral palsy, and magnesium sulfate. *Paediatr Perinat Epidemiol*. 1996;10:A16. Abstract
9. Arbuckle TE, Wilkins R, Sherman GJ. Birth weight percentiles by gestational age in Canada. *Obstet Gynecol*. 1993;81:39-48
10. Leviton A, Pagano M, Kuban KC, et al. The epidemiology of germinal matrix hemorrhage during the first half-day of life. *Dev Med Child Neurol*. 1991;33:138-145
11. Kuban KC, Leviton A, Pagano M, et al. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. *J Child Neurol*. 1992;7:70-76
12. Leviton A, Fenton T, Kuban KC, Pagano M. Labor and delivery characteristics and the risk of germinal matrix hemorrhage in low birth-weight infants. *J Child Neurol*. 1991;6:35-40
13. Grether JK, Nelson KB, Emery ES, Cummins SK. Prenatal and perinatal factors and cerebral palsy in very low birth weight infants. *Pediatrics*. 1996;128:407-414
14. Murphy DJ, Sellers S, Mackenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. *Lancet*. 1995;346:1449-1454
15. Hauth JC, Goldenberg RL, Nelson KG, Dubard MB, Peralta MA, Gaudier FL. Reduction of cerebral palsy with maternal MgSO₄ treatment in newborns weighing 500-1000 g. *Am J Obstet Gynecol*. 1995;172:419. Abstract
16. Kimberlin DF, Hauth JC, Goldenberg C, et al. The effect of maternal MgSO₄ treatment on neonatal morbidity in ≤1000 g neonates. *Am J Obstet Gynecol*. 1996;174:469. Abstract
17. Lemons J, Stevenson D, Verter J, et al. In utero magnesium exposure, risk of death and of intraventricular hemorrhage (IVH) in very low birthweight (VLBW) infants. *Pediatr Res*. 1996;39:225A. Abstract
18. Leviton A, Paneth N, Susser MW, et al. Maternal receipt of magnesium sulfate does not appear to reduce the risk of neonatal white matter damage. *Pediatrics*. 1997;99(4). URL: <http://www.pediatrics.org/cgi/content/full/99/4/e2>
19. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley and Sons; 1989
20. Reuss ML, Paneth N, Lorenz JM, Pinto-Martin J, Susser MW. The relation of transient hypothyroxinemia in preterm infants to neurodevelopment at two years of age. *N Engl J Med*. 1996;334:821-827
21. Schendel DE, Berg CJ, Yeargin-Allsop M, Boyle CA, Decoufle P. Prenatal magnesium sulfate exposure and the risk of cerebral palsy or mental retardation among very low birth weight children aged 3 to 5 years. *JAMA*. 1996;276:1805-1810

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