Tocolytic Magnesium Sulfate Exposure and Risk of Cerebral Palsy among Children with Birth Weights Less Than 1,750 Grams

C. A. Boyle, M. Yeargin-Allsopp, D. E. Schendel, P. Holmgreen, and G. P. Oakley

The authors examined the relation between intrapartum magnesium sulfate exposure and risk of cerebral palsy in a case-control study of low birth weight children designed to control for confounding by the clinical indications for magnesium in pregnancy. Case children (n = 97) included all singleton children with cerebral palsy who were born in 1985–1989 in Atlanta, Georgia with a birth weight less than 1,750 g and whose mothers had not had a hypertension-related disease during pregnancy. Control children (n = 110) were randomly selected from the infant survivors using identical selection criteria. Data on magnesium sulfate exposure, labor and delivery, and infant characteristics were abstracted from hospital records. The authors found no association between exposure to magnesium sulfate and cerebral palsy risk (odds ratio = 0.9; 95% confidence interval: 0.3, 2.6) either in all children or in subgroups with varying likelihoods for exposure to magnesium. However, the association did vary by birth weight, with a protective effect being seen in children born weighing less than 1,500 g and an elevated risk in children with birth weights of 1,500 g or more; all confidence intervals included 1.0 except for the combined <1,500 g group. Several ongoing randomized clinical trials of magnesium and cerebral palsy may shed more definitive light on this relation.


cerebral palsy; infant, low birth weight; magnesium

While several recent epidemiologic studies have suggested that magnesium sulfate used in the treatment of preeclampsia or preterm labor may dramatically reduce risk for cerebral palsy among children born weighing less than 1,500 g (1, 2), several other studies have reported a less dramatic effect or no association (3–5). Confounding by indication has been suggested as an explanation for the protective effect observed in some studies (6, 7). Specifically, magnesium sulfate is used in the treatment of preeclampsia to prevent convulsions (8) and to delay or stop preterm labor (9). In both of these instances, the exposed populations may have lower risks for cerebral palsy, independent of magnesium sulfate exposure, than unexposed populations. Studies have shown that preeclampsia is an independent protective factor for cerebral palsy in very low birth weight children (6, 10). Women in preterm labor who are eligible for tocolysis lack clinical indications for immediate delivery, such as prolonged rupture of membranes and advanced stage of labor, and the absence of such indications is associated with a lower risk of cerebral palsy (10, 11). However, previous studies have not been able to adequately address issues of confounding by indication.

The purpose of our study was to further investigate the association between magnesium sulfate exposure and cerebral palsy in children with birth weights less than 1,500 g by using a larger sample size than those of previous studies, collecting detailed clinical information with which to address the role of clinical decision-making for magnesium treatment, and examining the dose and timing of magnesium sulfate exposure. In addition, we extended the birth weight distribution to 1,750 g to determine whether a protective effect is found in children with birth weights between 1,500 g and 1,750 g.

MATERIALS AND METHODS

Data collection

We used a case-control study design in which children with cerebral palsy were identified from the records of an ongoing population-based developmental disabilities surveillance program in Atlanta, Georgia. Control children were selected at random from the same cohort of infant survivors. Magnesium sulfate exposure was determined by review of maternal hospital labor and delivery records.

Case children were children with cerebral palsy identified in 1991–1992 by the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP), among
1981–1989 singleton births to residents of five metropolitan Atlanta counties with birth weights less than 1,750 g (from birth certificate data). Details on case-finding methods used in the MADDSP are provided elsewhere (12). Children are included in the MADDSP if, at age 2 years or later, 1) they have been diagnosed with cerebral palsy by a physician specialist (e.g., a developmental pediatrician or neurologist) or 2) they have been diagnosed by a nonphysician specialist whose diagnosis is corroborated by physical findings (e.g., from a physical therapy report) consistent with the diagnosis of cerebral palsy. The diagnosis and type of cerebral palsy are confirmed by a developmental pediatrician (M. Y.-A.) upon review of all of the diagnostic information for each child. Disabling cerebral palsy was defined using the criteria of Pinto-Martin et al. (13). We excluded children who acquired cerebral palsy from an event (e.g., infection, injury) that occurred more than 28 days after birth.

We randomly selected control children from automated Georgia vital records files of infant survivors using the same birth year, maternal residence, and birth weight criteria as those used for the case children. A sampling ratio of 1:1 was used for case children with birth weights greater than or equal to 1,000 g, and a ratio of 1:1.5 was used for case children with birth weights less than 1,000 g.

All maternal labor and delivery records, records from previous hospital admissions for the index pregnancy, and any prenatal records in the mother’s labor and delivery record were reviewed for information on the receipt of magnesium sulfate and other tocolytic agents and selected maternal and infant factors. The study conducted by Schendel et al. (2) and the present investigation are not independent observations: Two of the five calendar years included in this study for children with birth weights less than 1,500 g (during which 27 of the 98 children with cerebral palsy were born) were included in that study. We included these children in the present study to obtain more detailed information on potentially confounding factors that was not available previously.

Analytical approach

We controlled for potential confounding due to indication in both the design and the analysis. In the design, we excluded women with hypertension-related disorders, including preexisting hypertension (based on a physician’s diagnosis) and preeclampsia, following the criteria of Paneth et al. (3). In one subanalysis, we addressed possible confounding due to the clinical indication for magnesium in preterm labor by excluding children whose mothers were admitted to a facility for labor and delivery with indications of immediate delivery, including: spontaneous rupture of membranes plus indications of maternal infection (clinical diagnosis of chorioamnionitis, placental histologic diagnosis of chorioamnionitis, maternal fever of >99.4°F, or foul-smelling amniotic fluid); placenta previa or placental abruption and bleeding upon admission; or dilation of >4 cm at the time of labor-and-delivery admission (9). In a second subanalysis, we included only pregnancies in which all case and control children had been exposed to a tocolytic agent, and therefore not only had an indication for tocolysis but were actually treated with a tocolytic agent (primarily magnesium sulfate, ritodrine, and terbutaline).

The percentage of control children was weighted to reflect oversampling in the <1,000 g birth weight category. We calculated odds ratios and 95 percent confidence intervals using SUDAAN logistic regression (14). When sample sizes allowed, odds ratios and 95 percent confidence intervals were adjusted for differences in birth weight, gestational age, and maternal receipt of corticosteroids—a factor that was strongly associated with both use of magnesium and risk for cerebral palsy. Other factors that we considered as possible confounders in the logistic regression models but found to have no appreciable effect on the odds ratios included gender, race, maternal age, hospital payment status (public/private), mode of delivery (cesarean/vaginal), infant position at delivery (breech/vertex), physician or pathologic diagnosis of chorioamnionitis, placenta previa or placental abruption, and advanced stage of labor at admission (dilation of <4 cm vs. ≥4 cm).

RESULTS

As table 1 shows, 183 case children and 252 control children met eligibility criteria for the study. Of these, 18.6 percent and 26.2 percent of case and control children, respectively, were excluded, chiefly because the maternal records could not be found or the mother had a hypertension-related disease. Our initial analysis of the use of magnesium as a tocolytic agent over the period of this study (1981–1989) indicated that only three control children and two case children born before 1985 had been exposed to magnesium sulfate. Consequently, we limited our analyses to the birth years 1985–1989, which resulted in a final sample size of 97 case children and 110 control children.

Table 2 presents the demographic, pregnancy, and infant characteristics of the case and control children. Children with cerebral palsy were less likely to be African-American, more likely to have been delivered by cesarean section, and more likely to have a maternal history of placenta previa or placental abruption and were less likely to have been exposed in utero to antenatal corticosteroids in comparison with control children.

### Table 1. Sample sizes in a study of intrapartum magnesium sulfate exposure and cerebral palsy, Atlanta, Georgia, 1991–1992

<table>
<thead>
<tr>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial sample</td>
<td>183</td>
<td>100.0</td>
<td>252</td>
</tr>
<tr>
<td>Exclusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s labor and delivery record not found</td>
<td>13</td>
<td>7.6</td>
<td>12</td>
</tr>
<tr>
<td>Death before age 3 years</td>
<td>1</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Birth weight ≥1,750 g</td>
<td>20</td>
<td>10.9</td>
<td>45</td>
</tr>
<tr>
<td>Hypertensive disease during pregnancy</td>
<td>52</td>
<td>28.4</td>
<td>76</td>
</tr>
<tr>
<td>Final sample</td>
<td>97</td>
<td>53.0</td>
<td>110</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of children with cerebral palsy and control children in a study of intrapartum magnesium sulfate exposure and cerebral palsy, Atlanta, Georgia, 1991–1992

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 97)</th>
<th>Controls (n = 110)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Demographic factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American race</td>
<td>59</td>
<td>61</td>
<td>83</td>
</tr>
<tr>
<td>Male sex</td>
<td>59</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td>Maternal age &gt;35 years</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Public hospital</td>
<td>43</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Pregnancy-related factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>38</td>
<td>39</td>
<td>30</td>
</tr>
<tr>
<td>Rupture of membranes &gt;24 hours before birth</td>
<td>24</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Breech delivery</td>
<td>18</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Clinical chorioamnionitis</td>
<td>22</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Placental abruption or placenta previa</td>
<td>25</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Dilation &gt;4 cm</td>
<td>31</td>
<td>36</td>
<td>41</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>8</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Infant-related factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age ≤28 weeks</td>
<td>38</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Birth weight &lt;1,000 g</td>
<td>38</td>
<td>39</td>
<td>48</td>
</tr>
</tbody>
</table>

* Numbers are lower than total numbers because of missing values.
† Percentages are weighted to account for oversampling of control children with birth weights less than 1,000 g.
‡ Unweighted data.

Table 3 shows the associations between any exposure to magnesium sulfate during labor and delivery and risk of cerebral palsy for all case and control children and for two analytical subgroups: 1) children from pregnancies without clinical indications for immediate delivery and 2) children from pregnancies in which the mother was treated with a tocolytic drug. Among all case and control children, there was no association between receipt of magnesium and risk for cerebral palsy. The analysis of the two subgroups of children—those from pregnancies without clinical indications for immediate delivery and those who were exposed in utero to a tocolytic drug during labor and delivery—produced similar results.

Previous reports of the association between intrapartum exposure to magnesium sulfate and cerebral palsy risk were focused on children with birth weights less than 1,500 g. Consequently, we examined the association between magnesium sulfate exposure and cerebral palsy by birth weight using standard cutpoints: <1,000 g, 1,000–1,499 g, and ≥1,500 g (Table 4). The magnesium sulfate-cerebral palsy association varied by birth weight, with a protective effect being seen among children with birth weights less than 1,500 g and an increase in risk among higher birth weight children; only confidence intervals for the <1,500 g group combined excluded 1.0.

Table 3. Tocolytic magnesium sulfate exposure among children with cerebral palsy and control children, by analytical subgroup, Atlanta, Georgia, 1991–1992

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio†</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% exposed</td>
<td>No.</td>
<td>% exposed</td>
</tr>
<tr>
<td>All children</td>
<td>97</td>
<td>10</td>
<td>110</td>
<td>13</td>
</tr>
<tr>
<td>Children from pregnancies without indications for immediate delivery</td>
<td>33</td>
<td>18</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Children from pregnancies with tocolytic drug use only</td>
<td>25</td>
<td>40</td>
<td>39</td>
<td>38</td>
</tr>
</tbody>
</table>

* Control percentages, odds ratios, and 95% confidence intervals are weighted to account for oversampling of control children with birth weights less than 1,000 g.
† Adjusted for birth weight, gestational age, and antenatal use of corticosteroids.
Similar birth weight-specific odds ratios were found for the two analytical subgroups.

Several investigators (1, 3) have found that the protective effect of magnesium may be more pronounced among or perhaps limited to subgroups of children with specific types or severity of cerebral palsy. We found no association between magnesium and cerebral palsy either for children with disabling cerebral palsy (odds ratio (OR) = 1.2; 95 percent confidence interval (CI): 0.3, 4.0) or for children with nondisabling cerebral palsy (OR = 0.7; 95 percent CI: 0.2, 2.7). Magnesium use did appear to be associated with a lower risk in children with cerebral palsy who had a coexisting developmental disability (primarily mental retardation) (OR = 0.2; 95 percent CI: 0.02, 2.0), while the odds ratio associated with magnesium exposure for children with isolated cerebral palsy was 1.4 (95 percent CI: 0.5, 4.0). There was also some indication of a reduction in risk for spastic diplegia as compared with other types of cerebral palsy. Of the 39 children with spastic diplegia, only 5 percent had been exposed intrapartum to magnesium sulfate (OR = 0.2; 95 percent CI: 0.02, 1.1), as opposed to 12–15 percent of children with other types of spastic cerebral palsy and 12 percent of control children.

Maternal doses of magnesium sulfate ranged from 4 g to 159 g for children with cerebral palsy and from 14 g to 197 g for control children, with mean doses of 57.3 g and 55.3 g, respectively. Given the considerable variation in exposure to magnesium sulfate, we examined whether higher doses or timing of exposure in relation to the birth of the child modified the risk of cerebral palsy. There were no remarkable differences in the odds ratios according to dose level (<20 g vs. ≥20 g) or according to whether the magnesium was received well in advance of the birth or shortly before birth.

DISCUSSION

The intent of this study was to further test the association between magnesium sulfate exposure and cerebral palsy risk among children with birth weights less than 1,500 g, after controlling for the effects of confounding by clinical indications for use of magnesium sulfate during pregnancy. In addition, we attempted to extend the findings of previous investigators by including children with higher birth weights (up to 1,750 g).

To control for confounding by indication (7, 8), in the design of the study we excluded women who had had hypertensive disease during pregnancy, because there would have been little variation in exposure among these women; in addition, children born to preeclamptic women tend to have a lower risk for cerebral palsy (10). In the analysis, we had adequate sample sizes for examination of subgroups of women with varying eligibilities for tocolysis. The results of these subgroup analyses were remarkably similar to the overall results, suggesting little confounding by indication. As with any observational study, however, the identification of clinical signs for immediate delivery based on historical information in records is not without error, and the possibility of residual confounding remains.

Over all birth weights, we found no association between intrapartum exposure to magnesium sulfate and risk for cerebral palsy. However, among children with birth weights less than 1,500 g, we did see a reduction in cerebral palsy risk that was of comparable magnitude to that found in previous investigations (1, 2), although it was statistically significant only in the combined <1,500 g group. This was in contrast to an elevated risk found among children with higher birth weights which was statistically unstable because of the small sample size but was of sufficient magnitude to warrant further investigation. Only the study by Paneth et al. included children in this higher birth weight range (3). Although their results were not reported separately for the ≥1,500 g category, we can infer from the lower odds ratio for all birth weights combined, relative to the odds ratio for the <1,500 g group, that the risk for higher-birth-weight children would not be elevated. The increased risk among heavier children that we observed in our study may be an artifact of small sample sizes, may reflect residual confounding, or may indicate that the causal mechanism for cerebral palsy among children of higher


<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio†‡</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% exposed</td>
<td>No.</td>
<td>% exposed</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>38</td>
<td>11</td>
<td>48</td>
<td>19</td>
</tr>
<tr>
<td>1,000–1,499</td>
<td>45</td>
<td>7</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>&lt;1,500</td>
<td>83</td>
<td>8</td>
<td>76</td>
<td>18</td>
</tr>
<tr>
<td>1,500–1,749</td>
<td>14</td>
<td>21</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>10</td>
<td>110</td>
<td>13</td>
</tr>
</tbody>
</table>

* Control percentages, odds ratios, and 95% confidence intervals are weighted to account for oversampling of control children with birth weights less than 1,000 g.
† Total group data were adjusted for birth weight, gestational age, and antenatal use of corticosteroids.
‡ Birth weight-specific odds ratios were adjusted for gestational age only.
birth weights may not involve a pathway in which magne-
sium sulfate is a factor.

Our cases and controls differed in terms of some impor-
tant factors, some of which are consistent with the findings
of other studies (i.e., placental abnormalities, corticosteroid
use) (11, 15) and some of which are not (cesarean delivery,
clinical chorioamnionitis) (4, 11). However, our overall
results did not change appreciably when we accounted for
these factors. In the birth weight-specific analyses, small
numbers of subjects precluded our carrying out multivari-
ate adjustment for some confounders, particularly ante-
natal corticosteroid exposure. In a stratified analysis con-
ducted among children with and without antenatal corticos-
teroid exposure, the protective effect of magnesium among
children with birth weights under 1,500 g was still evident,
although it was somewhat attenuated among children who
had also been exposed to corticosteroids.

Unlike the study by Paneth et al. (3), in this study we did
not find a more pronounced protective effect among chil-
dren with disabling cerebral palsy. We did find a suggestion
of a protective effect among children with spastic diplegia
and those who also had mental retardation. Similar findings
were noted by Schendel et al. (2) for children with co-occur-
ing mental retardation and by Nelson and Grether (1) for
spastic diplegia. There was little variation in risk by dose or
 timing of magnesium administration in relation to the birth
of the child, although the sample sizes were small.

The principal strength of this study was its use of a
population-based series of children with cerebral palsy
drawn from a base population of 171,304 3-year-old chil-
dren who were born in 1985–1989. The study was originally
designed to include nine birth years, which we estimated
would provide sufficient statistical power to detect an 80
percent reduction in risk. However, from our record review,
we found that prior to 1985 in Atlanta, magnesium sulfate
was infrequently used as a tocolytic agent, which reduced
the sample size and consequently the study’s power by
nearly one half. Even with these limitations, the sample size
was larger than those of most previous investigations. The
study was also strengthened by the successful recovery of
all but 6 percent of maternal labor and delivery records.
Since magnesium sulfate is primarily administered intra-
vaneously in hospitals, its use should be well documented in
medical records.

In conclusion, for children born weighing less than 1,500
 g, our findings extend those of previous investigations by
suggesting that confounding by clinical indications for mag-
nesium use in pregnancy does not appear to explain the
apparent protective effect of magnesium. The elevated risk
that we found among children with birth weights of 1,500 g
or more should be investigated further. The possible neuro-
protective role of magnesium sulfate should be further eluci-
dated by the findings of several ongoing randomized clinical
trials.

ACKNOWLEDGMENTS

The authors acknowledge the hard work of the study field
staff: Sheryl Epps, Patricia Mersereau, Teri Hirschfield, and
Elizabeth Tracy.

REFERENCES

1. Nelson KB, Grether JK. Can magnesium sulfate reduce the
risk of cerebral palsy in very low birth weight infants? Pedi-

exposure to magnesium sulfate and the risk of cerebral palsy
or mental retardation among very low birth weight children aged

labor and risk of neonatal brain lesions and cerebral palsy in low
birth weight infants. The Neonatal Brain Hemorrhage Study
pediatrics.org/cgi/content/full/99/5/e1).

4. O’Shea TM, Klimentek KL, Dillard RG. Prenatal events and
the risk of cerebral palsy in very low birth weight infants. Am

5. Wilson-Costello D, Borawski E, Friedman H, et al. Perinatal
 correlates of cerebral palsy and other neurologic impairment
among very low birth weight children. Pediatrics 1998;102:
115–22.

6. Blair E, Palmer L. Cerebral palsy in very low birth weight
infants, pre-eclampsia and magnesium sulfate. (Letter). Ped-

7. Allred EN, Dammann O, Kuban KK, et al. Prenatal magne-
sium sulfate exposure and risk of cerebral palsy. (Letter).
JAMA 1997;277:1003.

of preeclampsia. (ACOG technical bulletin no. 91). Wash-
ington, DC: American College of Obstetrics and
Gynecology, 1986.

labor. (ACOG technical bulletin no. 133). Washington, DC:

10. Murphy DJ, Sellers S, Mackenzie IZ, et al. Case-control study
of antenatal and intrapartum risk factors for cerebral palsy in

infection and the risk of cerebral palsy in very low-birth weight

of selected developmental disabilities in children
3–10 years of age: The Metropolitan Atlanta Developmental
Disabilities Surveillance Program, 1991. MMWR CDC

prediction of disabling and nondisabling cerebral palsy at age
two in a low birth weight population. Pediatrics 1995;95:
249–54.

14. Shah BV, Barnwell BG, Bieler GS. SUDAAN: software for the
statistical analysis of correlated data. User’s manual, release
7.0. Research Triangle Park, NC: Research Triangle Institute,
1996.

15. Cooke RW. Trends in incidence of cranial ultrasound lesions
and cerebral palsy in very low birthweight infants 1982–93.
Arch Dis Child Fetal Neonatal Ed 1999;80:115F–17F.