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Translating antenatal magnesium sulphate neuroprotection for infants born <28 weeks' gestation into practice – a geographical cohort study.

Short running title: Antenatal magnesium and cerebral palsy

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Abstract

Background: Magnesium sulphate was introduced for fetal neuroprotection in Australia in 2010. The aim of this study was to determine how often antenatal magnesium sulphate is used currently and its association with cerebral palsy in children born <28 weeks' gestation.

Materials and Methods: Participants comprised all survivors born <28 weeks' gestational age in the state of Victoria in 2016-17, and earlier, in 1991-92, 1997, 2005. Rates of cerebral palsy, diagnosed at 2 years for the 2016-17 cohort, and at 8 years in the earlier cohorts, were compared across eras. Within 2016-17, the proportions of children exposed to antenatal magnesium sulphate were determined, and rates of cerebral palsy were compared between those with and without exposure to magnesium sulphate.

Results: Overall, cerebral palsy was present in 6% (11/171) of survivors born in 2016-17, compared with 12% (62/499) of survivors born in the three earlier eras (odds ratio [OR]

0.48, 95% confidence interval [CI] 0.25, 0.94; p=0.032). Data were available for 213/215 (99%) survivors born in 2016-17, of whom 147 (69%) received magnesium sulphate. Data on cerebral palsy at 2 years were available for 171 (80%) survivors with magnesium data. Cerebral palsy was present in 5/125 (4%) of children exposed to magnesium sulphate and in 6/46 (13%) of those not exposed (OR 0.28, 95% CI 0.08, 0.96; p=0.043).

Conclusions: Antenatal magnesium sulphate is being translated into clinical practice for infants born <28 weeks' gestation, but there is room for improvement. It is associated with lower rates of cerebral palsy in survivors.

Introduction

Cerebral palsy occurs much more frequently in infants born <28 weeks' gestation than in infants born more mature at birth.[1] Despite advances in perinatal and neonatal intensive care that have improved survival rates substantially in infants born <28 weeks' gestation in the late 1990s and early 2000s,[2,3] rates of cerebral palsy remained consistently high: in the state of Victoria, rates of cerebral palsy at 8 years of age for survivors born <28 weeks' gestation were 13% [27/210] for children born in 1991-92, 11% [15/142] for children born in 1997, and 14% [20/147] for children born in 2005.[4] Although rates of cerebral palsy in children born <28 weeks' gestation have been reported to be falling in Victoria between 1995 and 2009,[5] there is a need to reduce these high rates of cerebral palsy in children born <28 weeks' gestation even further.

Approximately 20 years after it was first suggested that magnesium sulphate might reduce cerebral palsy in children born preterm, and after more than 6000 fetuses were recruited into randomised controlled trials (RCTs),[6] antenatal magnesium sulphate for fetal neuroprotection was introduced in 2010 in Australia for women likely to deliver <30 weeks' gestational age.[7] Surveys subsequently reported that magnesium sulphate neuroprotection in high-risk women had risen from 80%[8] in the early 2010s to 89%[9] in the late 2010s in Australia and New Zealand. Although surveys provide some insight, they do not measure precisely the translation of antenatal magnesium sulphate into clinical practice and its effects on rates of cerebral palsy in high-risk infants, which need to be determined.

The primary aim of this study was to document the translation of magnesium sulphate into clinical practice in Victoria by documenting how often magnesium sulphate neuroprotection is currently used in clinical care and its association with the rates of cerebral palsy in survivors born <28 weeks' gestation. It was hypothesised that most infants born extremely preterm recently would have been exposed to antenatal magnesium sulphate, and that its use would be associated with lower rates of cerebral palsy now than before antenatal magnesium sulphate neuroprotection was introduced into clinical practice in Australia in 2010, and also when compared between infants exposed and those not exposed to antenatal magnesium sulphate in the most recent cohort.

Materials and Methods

The Victorian Infant Collaborative Study Group has collated short- and long-term data on discrete cohorts of infants born <28 weeks' gestation over the last three decades.[3,4] The current study primarily reports data from the most recent cohort which comprised all livebirths 23-27 weeks' gestation free of lethal anomalies over 12 months from 1st April 2016 to 31st March 2017 in the state of Victoria, Australia. There were no survivors born <23 weeks' gestation. Extensive perinatal data were collected from medical records, including whether the mother received magnesium sulphate or not. Some mothers had severe pre-eclampsia and would have received magnesium sulphate for their own neuroprotection against eclampsia,[10] as well as for neuroprotection of their fetus, but the remainder of women who received magnesium sulphate did not have pre-eclampsia and so received it for fetal neuroprotection only.[6] Other details of the 2016-17 cohort have been reported elsewhere.[3] Results were compared with cohorts of consecutive survivors <28 weeks born in the calendar years 1991-92 (24 months), 1997 (12 months), and 2005 (12 months). Comparisons of some perinatal outcomes, including consumption of nursery resources and survival rates to hospital discharge between these cohorts have been reported previously.[3]

The studies were approved by the Human Research Ethics Committee at the Royal Women's Hospital, the Mercy Hospital for Women, Monash Medical Centre, and the Royal Children's Hospital, Melbourne (Approval no.: 16/05). Parents gave written informed consent for their child to participate.

Survivors from the 2016-17 cohort were assessed for the presence of cerebral palsy at 2 years of age, corrected for prematurity, whereas cerebral palsy was diagnosed at 8 years' corrected age for the earlier cohorts, as described previously.[4] Cerebral palsy was diagnosed in children with loss of motor function and abnormal tone or tendon reflexes by experienced and trained pediatricians with no knowledge of magnesium sulphate exposure. Since experts warn about making a diagnosis of cerebral palsy in children before the age of 5 years,[11,12] we focussed on rates of cerebral palsy at 8 years for the previous cohorts as the diagnosis would be more certain than a diagnosis of cerebral palsy at 2 years. For the 2016-17 cohort the children have only been assessed at 2 years, and have yet to reach the age of 5. Rates of cerebral palsy at 2 years and at 8 years for the earlier cohorts have been reported previously and are similar at both ages; 11% at 2 years[2] and 12% at 8 years.[4]

Data were analysed using Stata 16.1.[13] The rate of antenatal magnesium sulphate for the 2016-17 cohort was determined. Rates of cerebral palsy in the 2016-17 cohort were compared with the three earlier cohorts combined using logistic regression. Within the 2016-17 cohort, the association between magnesium sulphate use and cerebral palsy was assessed using logistic regression. Regression models were fitted using generalised estimating equations and reported with robust (sandwich) estimates of standard errors to account for clustering from multiple births within a family. In a sensitivity analysis for the association between magnesium sulphate use and cerebral palsy within the 2016-17 cohort, multiple imputation was conducted to handle missing data in survivors at 2 years using chained equations including perinatal events known at the time of birth (antenatal corticosteroids, being inborn [born in a tertiary maternity hospital with a neonatal intensive care unit], pre-eclampsia, multiple birth, cesarean delivery, sex, gestational age, birthweight and birthweight z-score) and cerebral palsy data at 2 years. Forty imputed datasets were created, and the result inference combined using Rubin's rules.[14] This analysis was repeated with adjustment for the above perinatal events, but not birthweight because of collinearity with gestational age.

Results

There were 274 livebirths at 23-27 weeks' gestation over the 12-month period from April 1, 2016, of whom 250 (91%) were offered active management. There were no data on magnesium sulphate administration for six infants. For those with data, 68% (165/244) of

those actively managed received magnesium sulphate antenatally. Overall, 215 (78%) livebirths survived to 2 years of age. Data on magnesium sulphate administration were available for 213 (99%) survivors, of whom 147 (69%) received magnesium sulphate. Survivors exposed to magnesium sulphate were more likely to have received antenatal corticosteroids and be inborn, and were less likely to be a multiple birth than survivors not exposed to magnesium sulphate (Table 1).

Data on cerebral palsy at 2 years were available for 172/215 (80%) survivors. Survivors for whom data on cerebral palsy were available were more likely to have received antenatal magnesium sulphate and be born in a tertiary maternity hospital with a neonatal intensive care unit (inborn), and they were less mature at birth than survivors for whom there were no data on cerebral palsy; other perinatal characteristics were similar between the two groups (Table 2).

Overall, cerebral palsy was present in 6% (11/172) of survivors born in 2016-17 at 2 years of age, compared with 12% (62/499) of survivors born in the three earlier eras at 8 years of age (odds ratio [OR] 0.48, 95% 95% confidence interval [CI] 0.25, 0.94; p=0.032).

Of the 172 survivors with data on cerebral palsy in the 2016-17 cohort, magnesium sulphate data were missing for one. In those with both magnesium sulphate and follow-up data, cerebral palsy was present in 5/125 (4%) of children exposed to magnesium sulphate and in 6/46 (13%) of those not exposed (OR 0.28, 95% CI 0.08, 0.96; p=0.043). Multiple imputation had little effect on the results (OR 0.26, 95% CI 0.08, 0.86; p=0.028), and neither did adjustment for perinatal variables (OR 0.25, 95% CI 0.06, 0.98; p=0.046).

Discussion

In this population-based study of livebirths <28 weeks' gestation in 2016-17, most infants had been exposed to antenatal magnesium sulphate, and its use was associated with a reduction in cerebral palsy in survivors both compared with previous cohorts born before the introduction of magnesium sulphate into clinical practice, and also within the 2016-17 cohort, as hypothesised. We are unaware of any similar reports of the rate of prescribing antenatal magnesium sulphate and of its effects on rates of cerebral palsy in geographical cohorts of high-risk infants born <28 weeks since magnesium sulphate was introduced into clinical practice for fetal neuroprotection.

The overall rate of cerebral palsy at 8 years of age for survivors born <28 weeks' gestation in the state of Victoria in the previous three eras of 12% is consistent with the 13% observed in the group not exposed to magnesium sulphate in the 2016-17 cohort, whereas the rate of 4% in those exposed to magnesium sulphate was considerably lower. The absolutes differences in rates of cerebral palsy between the unexposed and exposed groups of 9% in the 2016-17 cohort, and the 6% difference between the 2016-17 cohort overall and the earlier cohorts are larger than the difference of 2.4% observed in RCTs of the neuroprotective effects of magnesium sulphate.[6] This may be because the RCTs included many infants born ≥28 weeks' gestation, in whom rates of cerebral palsy are lower than in those born <28 weeks.[1] The differences in rates of cerebral palsy observed in the current study are also larger than the 3.2% observed in a subgroup from the RCTs with gestational ages <28 weeks when magnesium sulphate was first given to the mother, but again not all of those women would have delivered <28 weeks.[15] Some of the difference might also lie in the highly-selected nature of the infants who were enrolled in the RCTs of antenatal magnesium sulphate who might not truly represent all infants <28 weeks' gestation. In contrast, our cohorts comprise complete populations of infants <28 weeks' gestation, so they better represent that demographic than do infants born <28 weeks' gestation enrolled in RCTs.

Strengths of the current study include enrolling complete geographic cohorts of preterm livebirths, with survivors assessed by experienced, trained and blinded personnel. There are, however, several limitations. Only 80% of survivors in the 2016-17 cohort were assessed at 2 years, but multiple imputation to account for missing data had little effect on the odds ratio or its 95% confidence intervals, and altered no conclusions. Although there were some differences in perinatal variables between those with and without cerebral palsy data, adjustment for perinatal variables also had little effect on the OR or its 95% CI, and altered no conclusions. As two years of age may be too early to be sure of a diagnosis of cerebral palsy,[11,12] we will reassess the 2016-17 cohort later in childhood for cerebral palsy, which will then allow a more valid comparison of rates of cerebral palsy with earlier eras. Because we could not access all medical records, we do not have data on the dose or timing of antenatal magnesium sulphate, which may be important with respect to treatment effects. The sample sizes are not large and the confidence intervals of our estimates are

wide. Given the limitations, our results require corroboration from other population-based cohorts of infants born <28 weeks' gestational age.

When new treatments are introduced clinically following positive results from RCTs, data on their translation into clinical practice and effects on target outcomes rarely ensue. What we have attempted to do is to close the loop that started with the first evidence that antenatal magnesium sulphate might reduce rates of cerebral palsy in children born very low birthweight,[16] supported by positive data from biological studies,[17] to the completion of individual RCTs of magnesium sulphate neuroprotection, the results from which were first synthesised in a meta-analysis of aggregate data,[6] (and also in a subsequent individual participant-data meta-analysis[15]), and finally to the development and release of clinical practice guidelines.[7] The missing link to close the loop was to describe the translation of the guidelines into clinical practice, to determine how often magnesium sulphate was being used and its effects on rates of cerebral palsy in infants born <28 weeks' gestation, which is what we report in the current study.

We know that the data in the current observational study alone cannot prove that antenatal magnesium sulphate reduces the rate of cerebral palsy in children born <28 weeks' gestation because of the non-random exposure of individuals to magnesium sulphate. However, the previous RCTs and synthesis of their data in meta-analyses[6,15] already provide evidence of its effectiveness in neuroprotection of the fetus. The data in our current observational study is consistent with that evidence, and adjustment for potential confounding had little effect and altered no conclusions. Our primary intent in the current report was to document the translation of antenatal magnesium sulphate into clinical practice; not to prove that magnesium sulphate lowers rates of cerebral palsy in survivors born <28 weeks' gestation.

Just over 2/3 of actively managed infants born <28 weeks' gestation in Victoria were exposed to magnesium sulphate antenatally in 2016-17. How much more improvement is possible? It would be unrealistic to expect 100% of infants born <28 weeks' gestation to be exposed to magnesium sulphate because it requires an intravenous infusion, which takes time to administer safely to women. Many births <28 weeks occur too rapidly to even consider giving magnesium sulphate. Corticosteroids are simpler, safer and faster to administer than magnesium sulphate, but sometimes there is no time to even give corticosteroids. In our 2016-17 cohort just under 90% of actively managed infants had been

exposed to antenatal corticosteroids, in an environment where corticosteroids are considered routine for such pregnancies. Consequently, a rate of magnesium sulphate administration approaching that of antenatal corticosteroids might be desirable, but would be difficult to achieve in practice.

Monitoring of rates of magnesium sulphate administration occurs through databases, such as the Australian and New Zealand Neonatal Network (ANZNN). In 2017, 66% (726/1093) of infants <28 weeks' gestation who were registered with ANZNN and with complete date received some magnesium sulphate antenatally,[18] similar to the rate in our study. Individual units receive annual reports which they can benchmark against overall rates of administration in Australia and New Zealand to encourage action to improve their rate of administration of magnesium sulphate, if possible.

In conclusion, antenatal magnesium sulphate for fetal neuroprotection is being translated into clinical practice in Australia, but there is room for improvement as not 100% of infants are exposed. Importantly, antenatal magnesium sulphate is associated with lower population rates of cerebral palsy in infants born <28 weeks' gestation. Data from other population-based cohorts of infants born <28 weeks' gestation and from more mature infants exposed to antenatal magnesium sulphate neuroprotection would be desirable in future studies.

Table 1. Perinatal variables among survivors to 2 years of age compared between those who did and those who did not receive antenatal magnesium sulphate*

Variable	Magnesium sulphate N=147	No magnesium sulphate N=66	Contrast (95% CI)	*P*-value
Antenatal corticosteroids	143 (97%)	46/65 (71%)	†13.1 (4.18, 41.3)	<0.001
Inborn§	135 (92)	49 (74)	†3.90 (1.74, 8.76)	0.001
Pre-eclampsia	22 (15%)	4 (6%)	†2.67 (0.87, 8.17)	0.09
Multiple birth	37 (25%)	27 (41%)	†0.49 (0.26, 0.90)	0.022
Cesarean delivery	89 (61%)	41 (62%)	†0.89 (0.53, 1.43)	0.58
Male	83 (56%)	28 (42%)	†1.55 (0.84, 2.86)	0.16

Gestational age (weeks)	25.7 (1.2)	25.7 (1.2)	‡0.0 (-0.3, 0.3)	0.79
Birthweight (g)	846 (189)	848 (188)	‡6 (-52, 64)	0.84
Birthweight z-score	-0.09 (0.96)	0.02 (1.01)	‡0.05 (-0.32, 0.42)	0.78

*n=2 missing magnesium data. †Odds ratio or ‡mean difference. §born in a tertiary maternity hospital with a neonatal intensive care nursery. CI=confidence interval. Data are n (%), or mean (SD) unless otherwise specified

Table 2. Perinatal variables among survivors to 2 years of age compared between those who did and those who did not have follow-up data on cerebral palsy

Variable	Follow-up data on cerebral palsy N=172	No follow-up on cerebral palsy N=43	Contrast (95% CI)	*P*-value
Antenatal corticosteroids	156 (91%)	35/42 (83%)	*1.95 (0.75, 5.10)	0.17
Antenatal magnesium sulphate	125/171 (73%)	22/42 (52%)	*2.47 (1.23, 4.94)	0.011
Inborn‡	157 (91)	49 (74)	*5.05 (2.21, 11.6)	<0.001
Pre-eclampsia	25 (15%)	1 (2%)	*7.14 (0.94, 54.3)	0.057
Multiple birth	49 (28%)	16 (37%)	*0.67 (0.33, 1.36)	0.27
Cesarean delivery	105 (61%)	26 (60%)	*1.02 (0.52, 2.03)	0.94
Male	89 (52%)	22 (51%)	*1.02 (0.52, 2.00)	0.95
Gestational age (weeks)	25.6 (1.3)	26.0 (1.0)	†-0.4 (-0.8, 0.0)	0.048
Birthweight (g)	836 (188)	895 (182)	†-57 (-121, 7)	0.08
Birthweight z-score	-0.08 (0.97)	-0.01 (0.99)	†-0.06 (-0.40, 0.27)	0.70

*Odds ratio or †mean difference. ‡born in a tertiary maternity hospital with a neonatal intensive care nursery. CI=confidence interval.

Data are n (%), or mean (SD) unless otherwise specified

References

1. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. *Acta Paediatr.* 2005;94(3):287-294.
2. Doyle LW, Roberts G, Anderson PJ. Outcomes at age 2 years of infants <28 weeks' gestational age born in Victoria in 2005. *J Pediatr.* 2010;156(1):49-53.
3. Cheong JLY, Olsen JE, Huang L, et al. Changing consumption of resources for respiratory support and short-term outcomes in four consecutive geographical cohorts of infants born extremely preterm over 25 years since the early 1990s. *BMJ Open.* 2020;10(9):e037507.
4. Cheong JLY, Anderson PJ, Burnett AC, et al. Changing neurodevelopment at 8 years in children born extremely preterm since the 1990s. *Pediatrics.* 2017;139(6):e20164086.
5. Galea C, McIntyre S, Smithers-Sheedy H, et al. Cerebral palsy trends in Australia (1995-2009): a population-based observational study. *Dev Med Child Neurol.* 2019;61(2):186-193.
6. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev.* 2009(1):CD004661.
7. The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. Antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, infant and child:National clinical practice guidelines. Adelaide: The University of Adelaide; 2010.
8. Bain E, Bubner T, Ashwood P, Crowther CA, Middleton P, Team WP. Implementation of a clinical practice guideline for antenatal magnesium sulphate for neuroprotection in Australia and New Zealand. *Aust N Z J Obstet Gynaecol.* 2013;53(1):86-89.
9. Gatman K, May R, Crowther C. Survey on use of antenatal magnesium sulphate for fetal neuroprotection prior to preterm birth in Australia and New Zealand - Ongoing barriers and enablers. *Aust N Z J Obstet Gynaecol.* 2020;60(1):44-48.
10. Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev.* 2010(11):CD000025.
11. Stanley FJ. Using cerebral palsy data in the evaluation of neonatal intensive care: a warning. *Dev Med Child Neurol.* 1982;24(1):93-94.

12. Australian Cerebral Palsy Register. *Report of the Australian Cerebral Palsy Register Birth years 1995-2012.* 2018. Page 15.
13. *Stata/IC 16.1 for Windows.* College Station, TX: Stata Corp LLC; 2020.
14. Rubin DB. *Multiple imputation for nonresponse in surveys.* New York: Wiley; 1987.
15. Crowther CA, Middleton PF, Voysey M, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. *PLoS Med.* 2017;14(10):e1002398.
16. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics.* 1995;95(2):263-269.
17. Marret S, Doyle LW, Crowther CA, Middleton P. Antenatal magnesium sulphate neuroprotection in the preterm infant. *Sem Neonatal Fetal Med.* 2007;12(4):311-317.
18. Chow SSW, Creighton P, Chambers GM, Lui K. *Report of the Australian and New Zealand Neonatal Network 2017.* Sydney: ANZNN;2019.