Maternal adverse effects with different loading infusion rates of antenatal magnesium sulphate for preterm fetal neuroprotection: the IRIS randomised trial

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Objective To evaluate a slower (compared with a standard) infusion rate of the loading dose of magnesium sulphate for preterm fetal neuroprotection as a strategy to reduce maternal adverse effects.

Design Randomised controlled trial.

Setting South Australian maternity hospital.

Population Fifty-one women at <30 weeks of gestation, where birth was planned or expected within 24 hours.

Methods Women received a loading infusion of 4 g of magnesium sulphate over either 60 or 20 minutes (followed by maintenance of 1 g/hour until birth, or for up to 24 hours).

Main outcome measures Any maternal adverse effects associated with the infusion.

Results Overall, 71% of women experienced adverse effects during the first hour of their infusion; the difference between groups was not significant [15/25 (60%) 60-minute loading; 21/26 (81%) 20-minute loading; risk ratio (RR) 0.74; 95% confidence interval (95% CI) 0.51–1.08]. Although no serious maternal complications occurred, adverse effects led to three women ceasing the loading treatment (1/25 in the 60-minute loading group; 2/26 in the 20-minute loading group; RR 0.52; 95% CI 0.05–5.38). Women in the 60-minute loading group experienced significantly less warmth and flushing at 20 minutes into the infusion (7/25 in the 60-minute loading group; 15/26 in the 20-minute loading group; RR 0.49; 95% CI 0.24–0.99). No other differences between groups for maternally reported and clinical adverse effects were shown.

Conclusions A slower rate of administering the loading dose of magnesium sulphate did not reduce the occurrence of maternal adverse effects overall. Flushing and warmth at 20 minutes into the infusion was reduced with a slower infusion.

Keywords Adverse effect, antenatal, clinical trial, magnesium sulfate, magnesium sulphate, preterm.

Introduction

Infants born preterm (before 37 weeks of gestation) are at an increased risk of mortality. 1,2 Although the survival rate of these infants has improved substantially over time, survival can be associated with complex, lifelong neurosensory disabilities, 3,4 including cerebral palsy, blindness, deafness, and developmental delay. 1,5 The social and economic costs associated with preterm birth and its sequelae are considerable. 6 Following observational data in the 1990s suggesting associations between exposure to magnesium sulphate in utero and reductions in intraventricular haemorrhage, cerebral palsy, and neonatal mortality, 6,7 five randomised controlled trials were conducted assessing magnesium sulphate for preterm fetal neuroprotection. 8–12 Meta-analysis of these trials supported a neuroprotective role for magnesium sulphate, showing a 32% relative reduction in the risk of cerebral palsy (RR 0.68; 95% CI 0.54–0.87; 6145 infants). 13
Given the widespread use of magnesium sulphate in obstetrics to prevent and treat eclampsia, for acute tocolysis, and for maintenance tocolysis, the associated maternal adverse effects are widely recognised. Whereas life-threatening adverse effects are considered to be extremely rare in obstetrics, severe consequences of magnesium toxicity are known: respiratory arrest may occur, along with altered cardiac function, cardiac arrest, and death. The ‘well recognised’, more commonly reported problems at the injection site. Importantly, significantly more women receiving magnesium sulphate ceased therapy because of these adverse effects (RR 3.26; 95% CI 2.46–4.31; three trials; 4847 women). The importance of assessing strategies to reduce maternal adverse effects during administration, and in turn to reduce the cessation rate of this beneficial therapy, has been highlighted in the relevant Cochrane review, and in the Australian and New Zealand Clinical Practice Guidelines recommending antenatal magnesium sulphate for fetal neuroprotection. To date, there have been no randomised controlled trials comparing the different infusion rates of the loading dose of antenatal magnesium sulphate. The IRIS Trial (Different Infusion Rates of Magnesium Sulphate Prior to Preterm Birth) aimed to compare the effects of two different rates of administering the loading dose of magnesium sulphate, given to women at risk of preterm birth before 30 weeks of gestation for fetal neuroprotection, on maternal adverse effects during the infusion.

Methods

Participants

Women with a single or twin pregnancy at <30 weeks of gestation at the Women’s and Children’s Hospital, Adelaide, South Australia, who gave informed consent, were eligible for the IRIS Trial if birth was planned or expected within 24 hours, as per the current Australian and New Zealand, and South Australian Clinical Practice Guidelines. A best estimate of gestational age was made at trial entry derived from the menstrual history and early ultrasound. Women were not eligible if they were in the second stage of labour, had already received magnesium sulphate therapy in this pregnancy, or had any of the following contraindications to magnesium sulphate: absent patellar reflexes; hypocalcaemia; respiratory rate of <16 breaths/minute; renal failure; or urine output of <100 ml during the last 4 hours.

Randomisation

The IRIS Trial protocol was approved by the Children, Youth and Women’s Health Services Human Research Ethics Committee (REC1651/2/2013). All participants were given written information on the study, and gave informed, signed consent before random assignment to either the 60-minute loading group, or the 20-minute loading group. The randomisation sequence was computer generated, with stratification by plurality, and treatment allocated by the telephone randomisation service at the University of Adelaide.

Interventions

Women randomised to the 60-minute loading group were administered a loading infusion of 4 g of magnesium sulphate intravenously over 60 minutes, whereas women randomised to the 20-minute loading group were administered a loading infusion of 4 g over 20 minutes. Both groups were administered a maintenance infusion of 1 g per hour intravenously until birth (if occurring within 24 hours), or for up to 24 hours, as per the clinical practice guidelines. In the event that birth did not occur within 24 hours, the infusion was ceased. The midwives, who could not be blinded to the treatment group allocation, reduced the rate of the infusion at 20 minutes for women in the 20-minute loading group, and after 1 hour for women in the 60-minute loading group. Midwives and obstetricians were asked not to discuss treatment group allocation with the women.

The women’s pulse rate, blood pressure, and respiratory rate were measured manually and recorded before initiating the infusion, at the end of 20 minutes of the infusion, and after the first hour of the infusion. Maternally reported adverse effects and any serious clinically observed effects were recorded by the attending midwives 20 and 60 minutes after commencement. The midwives asked the women an open-ended question regarding side effects experienced after 20 minutes and after 1 hour. If the loading infusion was stopped before treatment was complete, the time and date of cessation were recorded along with the reason for cessation. The total dose of magnesium sulphate administered prior to birth was recorded.

Data were recorded using trial-specific forms, and additional demographic and clinical outcome information was collected from the medical records. The care that women and infants received was otherwise according to standard practice at the hospital.
Outcomes
The primary outcome was the occurrence of any maternal adverse effects attributed to the magnesium sulphate infusion (maternally reported and clinically observed), including: arm discomfort; blurred vision; dizziness; headache; mild nausea; mouth dryness; muscle weakness; palpitations; sleepiness; sweating; warmth over body; respiratory depression (a decrease in respiratory rate of >4 breaths/minute from baseline); tachycardia (pulse rate of >160 beats/minute or pulse rate increase of >20 beats/minute from baseline); or other.
Secondary outcomes included any serious adverse cardiorespiratory effects of the infusion (defined as respiratory arrest, cardiac arrest, or death), cessation of treatment for maternal adverse effects attributed to the infusion, other adverse cardiorespiratory effects of the infusion (defined as a respiratory rate of <16 breaths/minute, or a decrease in diastolic blood pressure of >15 mmHg), maternal self-reported and clinical adverse effects of the infusion, and the total dose (g) of magnesium sulphate given prior to birth.

Sample size
A sample size of 48 women (24 in each group) would detect an absolute percentage reduction in the occurrence of any maternal adverse effects of 36%, from 89% in the 20-minute loading group [as found by the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO4), Crowther and colleagues 2003]¹⁰ to 53% in the 60-minute loading group, with 80% power and a two-tailed z = 0.05. Allowing for a 5% loss, we aimed to recruit 51 women in total.

Statistical analysis
Analyses were performed using intention-to-treat principles, blind to the allocated treatment, with the use of SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Analysis of all available data was performed for each outcome. Binary outcomes were analysed using log-binomial regression, to give risk ratios (RRs) and 95% confidence intervals (95% CIs). The Fisher’s exact test was used to calculate P-values where it was not possible to calculate RRs because of zero events in one treatment group. Continuous outcomes, if approximately normally distributed, were analysed using linear regression, to give differences in means and 95% CIs, and the Wilcoxon rank-sum test was used for skewed outcomes. All reported P-values were two-sided, and the level of statistical significance was 5%. For adverse effects measured over time, two analysis approaches were taken. First, a new outcome indicating whether the outcome of interest occurred at either time point was defined for the analysis. Second, where the outcome was sufficiently common, the repeated measurements were analysed using generalised estimating equations with an exchangeable working correlation structure. Models initially included treatment, time, and their interaction. If the interaction was significant, and for the primary outcome, separate estimates of treatment effect were calculated for the two time points (20 minutes and 60 minutes). Where no evidence of an interaction was identified, the interaction was removed from the model and the overall treatment effect, assumed to apply at each time point, was calculated.

Results
Of the 51 women enrolled in the IRIS Trial, 25 were allocated to the 60-minute loading group and 26 women were allocated to the 20-minute loading group (Figure 1). Approximately 40% of all women who gave birth before 30 weeks of gestation in the participating hospital during the study period were enrolled. Study outcome data were obtained up to birth for all 51 women. There was one stillbirth after randomisation in the 20-minute loading group, with cause of death classified as fetal growth restriction associated with evidence of reduced vascular perfusion on Doppler studies (Perinatal Society of Australia and New Zealand Perinatal Death Classification 8.1).²⁴

Baseline maternal and pregnancy characteristics
Most baseline maternal characteristics were similar between groups (see Table S1), and reflect the eligible high-risk population. The median gestational age at entry was 28 weeks. Over 50% of women were in their first pregnancy, 25% had experienced a previous preterm birth, and 10% had experienced a perinatal death. The reasons women were at risk of very preterm birth included preterm prelabour rupture of membranes (37%), preterm labour (35%), pre-eclampsia (31%), intrauterine growth restriction (22%), chorioamnionitis (16%), and antepartum haemorrhage (16%). Women in the 60-minute loading group were more likely to be at risk of preterm birth as a result of preterm prelabour rupture of membranes and preterm labour (48% versus 27% and 52% versus 19%, respectively).

Treatment
The majority of women (49/51) received some of the loading infusion [25 women (100%) in the 60-minute loading group and 24 women (92%) in the 20-minute loading group], with the full loading dose given to 23 women (92%) in the 60-minute loading group and 22 women (85%) in the 20-minute loading group (Figure 1). The median time from randomisation to birth was 5.6 hours (interquartile range, IQR = 1.9–20.1 hours) in the 60-minute loading group and 8.7 hours (IQR = 3.1–18.6 hours) in the 20-minute loading group (P = 0.52).
Primary outcome
Maternal adverse effects associated with the magnesium sulphate infusion occurred in 60% of women in the 60-minute loading group (15/25), and in 81% of the women in the 20-minute loading group (21/26); this difference was not statistically significant (RR 0.74; 95% CI 0.51–1.08; Table 1). Considering the two time points when maternal adverse effects were assessed (after 20 minutes and after 60 minutes), there was evidence of a significant treatment by time interaction (P = 0.01). When separate estimates of treatment effect were calculated for each of the two time points, however, no statistically significant differences between groups were observed (Table 1).

Secondary outcomes
There were no serious maternal adverse effects (death, cardiac arrest, or respiratory arrest) in either treatment group (Table 2). From the clinical observations, only one (4%) woman in the 60-minute loading group experienced a decrease in diastolic blood pressure of >15 mmHg from

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Table 1. Any maternal adverse effects of the magnesium sulphate infusion (primary outcome)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>60-minute loading n = 25</th>
<th>20-minute loading n = 26</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>Interaction P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse effects</td>
<td>15 (60.0)</td>
<td>21 (80.8)</td>
<td>0.74 (0.51–1.08)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Adverse effects over time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 minutes</td>
<td>14 (56.0)</td>
<td>20 (76.9)</td>
<td>0.73 (0.48–1.09)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>60 minutes</td>
<td>14 (56.0)</td>
<td>11 (42.3)</td>
<td>1.32 (0.75–2.34)</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>

Values are n and %.

*Treatment by time interaction P-value.
baseline. In the 20-minute loading group, two (8%) women experienced a decrease in diastolic blood pressure of >15 mmHg from baseline, and three (14%) women experienced a respiratory rate of <16 breaths/minute (Table 2).

Adverse effects led to the loading infusion being stopped in three women: one woman (4%) in the 60-minute loading group and two women (8%) in the 20-minute loading group \((P = 0.58; \text{Table 2})\). The reasons for the infusion being ceased were arm discomfort and/or problems at the intravenous site (one woman in each group), and other maternal discomfort, including warmth (one woman in the 20-minute loading group).

The most commonly reported adverse effects included arm discomfort (52% in the 60-minute loading group versus 65% in the 20-minute loading group), warmth over body (36% versus 62%), mouth dryness (12% versus 31%), mild nausea (12% versus 27%), and sleepiness (8% versus 19%). No significant differences between groups were observed for any maternally reported adverse effects or clinical observations (Table 2). There was evidence of a treatment by time interaction for only two of the adverse effects: warmth or flushing and arm discomfort (Table 3). When warmth or flushing was assessed at the two time points separately, it was observed that at 20 minutes, significantly fewer women in the 60-minute loading group (seven, 28%) experienced warmth and flushing as compared with women in the 20-minute loading group (15, 58%; RR 0.49; 95% CI 0.24–0.99; \(P = 0.046\)); however, the groups were similar at 60 minutes. Although a significant treatment by time interaction was identified for arm discomfort \((P = 0.02)\), when separate estimates of treatment effect were calculated for each of the two time points, no statistically significant difference between groups was observed at either time point.

The median total magnesium sulphate dose administered prior to birth was 7.00 g (IQR 4.50–9.00 g) in the 60-minute loading group and 7.75 g (IQR 5.00–13.00 g) in the 20-minute loading group \((P = 0.31)\).

### Birth outcomes

There were no important differences seen between the treatment groups for outcomes relating to birth. Gestational age at birth was similar in the 60-minute loading group (median 26.9 weeks, IQR 25.7–29.3 weeks) and 20-minute loading group (median 28.3 weeks, IQR 27.1–29.1 weeks). More than half of all women gave birth by caesarean section [60-minute loading group, 14 (56%); 20-minute loading group, 19 (73%)]. There was no substantial difference between the groups in the mean (SD)

### Table 2. Secondary maternal outcomes assessed during treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>60-minute loading (n = 25)</th>
<th>20-minute loading (n = 26)</th>
<th>RR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not Estimable</td>
<td></td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not Estimable</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not Estimable</td>
<td></td>
</tr>
<tr>
<td>Any respiratory rate of &lt;16 breaths/minute**</td>
<td>0 (0.0)</td>
<td>3 (13.6)</td>
<td>Not Estimable*</td>
<td>0.11</td>
</tr>
<tr>
<td>Any diastolic blood pressure decrease of &gt;15 mmHg</td>
<td>1 (4.0)</td>
<td>2 (7.7)</td>
<td>0.52 (0.05–5.38)</td>
<td>0.58</td>
</tr>
<tr>
<td>Loading infusion ceased for adverse effects</td>
<td>1 (4.0)</td>
<td>2 (7.7)</td>
<td>0.52 (0.05–5.38)</td>
<td>0.58</td>
</tr>
<tr>
<td>Any warmth over body</td>
<td>9 (36.0)</td>
<td>16 (61.5)</td>
<td>0.59 (0.32–1.07)</td>
<td>0.08</td>
</tr>
<tr>
<td>Any arm discomfort</td>
<td>13 (52.0)</td>
<td>17 (65.4)</td>
<td>0.80 (0.50–1.27)</td>
<td>0.34</td>
</tr>
<tr>
<td>Any mouth dryness</td>
<td>3 (12.0)</td>
<td>8 (30.8)</td>
<td>0.39 (0.12–1.31)</td>
<td>0.13</td>
</tr>
<tr>
<td>Any mild nausea</td>
<td>3 (12.0)</td>
<td>7 (26.9)</td>
<td>0.45 (0.13–1.53)</td>
<td>0.20</td>
</tr>
<tr>
<td>Any sleepiness</td>
<td>2 (8.0)</td>
<td>5 (19.2)</td>
<td>0.42 (0.09–1.95)</td>
<td>0.27</td>
</tr>
<tr>
<td>Any sweating</td>
<td>2 (8.0)</td>
<td>4 (15.4)</td>
<td>0.52 (0.10–2.59)</td>
<td>0.42</td>
</tr>
<tr>
<td>Any blurred vision</td>
<td>0 (0.0)</td>
<td>2 (7.7)</td>
<td>Not Estimable*</td>
<td>0.49</td>
</tr>
<tr>
<td>Any palpitations</td>
<td>2 (8.0)</td>
<td>2 (7.7)</td>
<td>Not Estimable*</td>
<td>0.49</td>
</tr>
<tr>
<td>Any headache</td>
<td>2 (8.0)</td>
<td>1 (3.8)</td>
<td>2.08 (0.20–21.52)</td>
<td>0.54</td>
</tr>
<tr>
<td>Any dizziness</td>
<td>1 (4.0)</td>
<td>1 (3.8)</td>
<td>1.04 (0.07–15.74)</td>
<td>0.98</td>
</tr>
<tr>
<td>Any muscle weakness</td>
<td>1 (4.0)</td>
<td>1 (3.8)</td>
<td>1.04 (0.07–15.74)</td>
<td>0.98</td>
</tr>
<tr>
<td>Any respiratory depression***</td>
<td>1 (4.3)</td>
<td>0 (0.0)</td>
<td>Not Estimable*</td>
<td>1.00</td>
</tr>
<tr>
<td>Any maternal tachycardia***</td>
<td>1 (4.3)</td>
<td>2 (9.5)</td>
<td>0.46 (0.04–4.68)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Values are \(n\) and %, unless stated otherwise.

\*\(P\)-value based on Fisher’s exact test.

\**n = 23, 60-minute loading; n = 22, 20-minute loading.

\***n = 23, 60-minute loading; n = 21 20-minute loading.
birthweight of the infants [60-minute loading group 958 g (352 g); 20-minute loading group 971 g (429 g)].

Discussion

Main findings
In this randomised trial of two infusion rates for administering the loading dose of antenatal magnesium sulphate to women at risk of preterm birth, for fetal neuroprotection at <30 weeks of gestation, no statistically significant difference between treatment groups was observed for the primary outcome of any maternal adverse effects of treatment. Although a significant treatment by time interaction was identified for this outcome, indicating that the trial treatments had a time-dependent effect on ‘any maternal adverse effects’, when separate estimates of treatment effect were calculated at 20 minutes and at 1 hour, no significant differences between groups were observed.

Our findings indicated no clear differences in the risks of minor maternally reported and clinically assessed adverse effects between treatment groups, except for warmth or flushing when assessed at 20 minutes into the infusion, which was experienced by significantly fewer women receiving the slower loading infusion.

Strengths and limitations
The high rate of minor adverse effects for women receiving magnesium sulphate (71% overall) observed in the IRIS Trial is broadly consistent with the high rates reported for women receiving magnesium sulphate for fetal neuroprotection in two large randomised trials: one from Australia and New Zealand (ACTOMgSO₄) that recruited 1062 women (89%); and one from the USA (BEAM) that recruited 2241 women (77%). Based on the ACTOMgSO₄ trial, however, we anticipated a higher rate of any maternal adverse effects than was observed, which limited our statistical power to detect the expected 36% reduction in the occurrence of our primary outcome. To detect the 36% absolute reduction from the observed 81% rate of any maternal adverse effects in the 20-minute loading group, with an 80% power, 33 women per group would have been required.

With utmost care taken to ensure that the randomisation procedures were secure and to reduce selection bias, baseline imbalances observed between treatment groups when considering reasons women were at risk of preterm birth were considered reflective of the trial’s sample size. Although such differences were believed to be unlikely to influence the maternal outcomes reported in this analysis, any imbalances will be important to consider when assessing later health outcomes for the infants.

As the methods used to monitor and detect adverse effects are known to greatly influence the adverse effect frequencies reported, for example, with active methods such as the use of checklists yielding substantially higher frequencies than more passive methods, care was taken to ensure consistency, with all women being asked an open-ended question at each of the time points at which adverse effects were assessed during the infusion. A limitation of the IRIS Trial is that we were not able to blind midwives and obstetricians to treatment group allocation; although all study personnel were asked not to discuss or reveal

<table>
<thead>
<tr>
<th>Table 3. Secondary maternal outcomes assessed over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Warmth over body</td>
</tr>
<tr>
<td>At 20 minutes</td>
</tr>
<tr>
<td>At 60 minutes</td>
</tr>
<tr>
<td>Arm discomfort</td>
</tr>
<tr>
<td>At 20 minutes</td>
</tr>
<tr>
<td>At 60 minutes</td>
</tr>
<tr>
<td>Mouth dryness</td>
</tr>
<tr>
<td>At 20 minutes</td>
</tr>
<tr>
<td>At 60 minutes</td>
</tr>
<tr>
<td>Mild nausea</td>
</tr>
<tr>
<td>At 20 minutes</td>
</tr>
<tr>
<td>At 60 minutes</td>
</tr>
<tr>
<td>Sleepiness</td>
</tr>
<tr>
<td>At 20 minutes</td>
</tr>
<tr>
<td>At 60 minutes</td>
</tr>
</tbody>
</table>

*Treatment by time interaction P-value.
treatment group allocation, and analyses were conducted blind, it may have been possible for women to deduce their group allocation.

**Interpretation**
We are not aware of any other trials assessing the rates of infusion of the loading dose of antenatal magnesium sulphate, nor of any trials comparing two regimens for the administration of antenatal magnesium sulphate for fetal neuroprotection. One non-randomised comparative study conducted in the USA recruited 144 women with pre-eclampsia: 47 women received a 10-g intramuscular loading dose followed by a continuous intravenous infusion of 1 g per hour, and 97 women received a 10-g intramuscular loading dose, followed by a 2-g ‘intravenous push’ every 1–2 hours. Of women receiving the ‘intravenous push’, 93% experienced transient, moderate falls in blood pressure, accompanied by heat and flushing, and 79% experienced respiratory effects, from a slowing of respiration, to shallow and slow breathing, to complete apnoea. No women receiving the continuous infusion experienced these effects. Although there were methodological limitations associated with this trial, including the absence of randomisation and blinding, and the incomplete reporting of adverse effects, the findings supported the use of a slow intravenous infusion as compared with a ‘push’ technique.

Reassuringly, and consistent with the findings from the relevant Cochrane systematic review, and from other published literature from randomised trials, no serious maternal complications (death, cardiac arrest, or respiratory arrest) were observed among women in the IRIS Trial. Adverse effects did, however, lead to treatment cessation for three women (6%) in our study, and although treatment was not stopped for life-threatening adverse effects (rather, treatment ceased for arm discomfort and/or warmth), this finding highlights the continued need to evaluate strategies to increase comfort for women receiving this therapy in order to reduce early cessation of this beneficial treatment for preterm infants.

Although this study was not designed to compare the neuroprotective benefits of the two regimens used, the median times between randomisation and birth for both groups in the IRIS Trial (60-minute loading group, 5.6 hours; 20-minute loading group, 8.7 hours) were similar to the times reported in two of the large randomised controlled trials upon which the Australian and New Zealand Clinical Practice Guideline recommendations regarding timing were made. These guidelines recommend magnesium sulphate be administered when early preterm birth is planned or definitely expected within 24 hours, and when birth is planned for treatment to be commenced as close to 4 hours before birth as possible.

The IRIS Trial is the first to assess strategies intended to reduce maternal adverse effects associated with antenatal magnesium sulphate for fetal neuroprotection, and contributes to continuing, critical research surrounding the optimal regimen for administration. In addition to evaluating methods to reduce maternal adverse effects and therapy cessation, important questions remain related to the minimum effective dose required for fetal neuroprotection, whether a single loading dose may be sufficient or if maintenance is necessary, and the optimal duration of treatment.

**Conclusion**
This study showed that a slower rate of administering the loading dose of magnesium sulphate prior to very preterm birth at <30 weeks of gestation for fetal neuroprotection did not reduce the occurrence of maternal adverse effects overall, and did not reduce therapy cessation; however, maternal flushing and warmth at 20 minutes into the infusion was reduced with the slower infusion. Further strategies to reduce maternal adverse effects and therapy cessation require evaluation; an additional study assessing a slower (compared with a standard) infusion rate of the loading dose, with increased power, may be warranted.

**Disclosure of interests**
P.J.A. and L.N.Y. declare no conflicts of interest. E.S.B., P.F.M., and C.A.C. were authors of the Cochrane review ‘Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth’. C.A.C. was the principal investigator for the Australasian Collaborative Trial of Magnesium Sulphate (ACT-MgSO4). Two authors (P.F.M. and C.A.C.) were members of the Guideline Development Panel for the Australian National Health and Medical Research Council-approved ‘Antenatal Magnesium Sulphate Prior to Preterm Birth for Neuroprotection of the Fetus, Infant and Child National Clinical Practice Guidelines’.

**Contribution to authorship**
C.A.C. and P.F.M. conceived, designed, and initiated the trial. E.S.B. contributed to the study design, and coordinated the trial, enrolling participants and collecting the data, in collaboration with C.A.C., P.F.M., and P.J.A. Both L.N.Y. and E.S.B. analysed the data, and all authors participated in the interpretation of the results. E.S.B. wrote the first draft and all authors commented on and contributed to subsequent drafts.

**Details of ethics approval**
This study was approved by the Children, Youth and Women’s Health Services Human Research Ethics Committee.

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(ref. no. 1651/2/2013). All participants gave written informed consent. This study is registered with the Australian New Zealand Clinical Trial Registry ACTRN12605000765628.

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Acknowledgments
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Supporting Information
Additional Supporting Information may be found in the online version of this article:
Table S1. Characteristics of women in the 60- and 20-minute loading groups at trial entry.

References
Commentary on ‘Maternal adverse effects with different loading infusion rates of antenatal magnesium sulphate for preterm fetal neuroprotection: the IRIS randomised trial’

The offspring of mothers who receive magnesium sulphate prior to early preterm birth are more likely to be alive in childhood and free of cerebral palsy than the offspring of mothers who don’t receive magnesium sulphate (Doyle LW et al. Cochrane Database Syst Rev 2009;1:CD004661). By one estimate, the systematic use of magnesium sulphate could prevent as many as 1000 cases of disabling cerebral palsy each year in the USA alone (Rouse DJ. Am J Obstet Gynecol 2009;200:610–12). Magnesium sulphate is inexpensive, readily available, easy to administer, and – when used properly – safe. But to say that it is well tolerated would be to stretch the truth. The majority of women who receive it report noisome flushing or a general feeling of warmth, and a substantial minority experience pain at the infusion site. In the first robust randomised trial of magnesium sulphate for neuroprotection, the infusion was discontinued for minor side effects in 14.6% of women allocated to the active drug, compared with 5.3% in those allocated to placebo (Crowther CA et al. JAMA 2003;290:2669–76). In the second, the respective rates were 4.2 and 1.4% (Rouse DJ et al. N Engl J Med 2008;359:895–905).

Clearly, discontinuation of any therapy will undermine its effectiveness, and magnesium sulphate for fetal neuroprotection is not exempt from this reality. Thus, the trial of Bain et al. is welcome, because it asks an important question: can magnesium sulphate be made more tolerable by slowing its bolus infusion from 20 to 60 minutes? Unfortunately, the answer provided by this trial is ‘no’. Although there were fewer adverse maternal effects observed in the 60-minute group, the 95% confidence interval for the relative risk of adverse effects includes one. This may be because, with only 51 participants, the study was underpowered (although the authors failed to acknowledge it, but should have, the intended sample size when they originally registered the trial was 140 women). Or it may be that there really is no difference between the two infusion rates.

It is tempting to give the benefit of doubt to the slower infusion, and chalk the non-significant result up to a type-II statistical error. This would be a mistake, however. The effectiveness data published come from trials in which the bolus infusion was administered over 20–30 minutes. A slower infusion rate might compromise the effectiveness of the treatment. So before condoning a slower rate, we should at least have convincing evidence that doing so will result in a substantially lower rate of therapy discontinuation.

Disclosure of interests
I have no conflicts of interest to declare.

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