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Magnesium sulphate and perinatal mortality and morbidity in very-low-birthweight infants born between 24 and 32 weeks of gestation in Japan

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ABSTRACT

Objective: Maternal exposure to magnesium sulphate has a neuroprotective effect in premature infants. This study aimed to examine this neuroprotective effect and the dose–response relationship in very-low-birthweight infants born between 24 and 32 weeks of gestation.

Study design: A retrospective cohort study compared the rates of mortality and brain damage between three groups: no magnesium sulphate, low-dose (<50 g) magnesium sulphate and high-dose (≥50 g) magnesium sulphate.

Results: Japanese maternal and neonatal databases were linked using six key parameters from 2003 to 2007. Of 298,514 deliveries, 9101 were very-low-birthweight infants. Among these, full matching was possible for 5562 infants. Of the fully-matched infants, 3763 were born between 24 and 32 weeks of gestation, and 1813 (48%) were followed-up beyond 18 months. A multivariate analysis of the data, including gestational age, sex, fetal growth restriction, antenatal steroids and low pH (<7.1), showed that the low-dose group had no beneficial effects in terms of a reduction in mortality or incidence of brain damage (cerebral palsy or mental retardation). The high-dose group showed a significantly higher mortality rate [odds ratio (OR) 1.9, 95% confidence interval (CI) 1.2–2.9]. A stratified subgroup analysis of infants born between 28 and 32 weeks of gestation showed that survivors in the low-dose group had significantly lower rates of cerebral palsy (OR 0.4, 95% CI 0.2–0.98) and brain damage (OR 0.2, 95% CI 0.1–0.9), while the high-dose group did not show any significant changes.

Conclusion: This study found that antepartum exposure to magnesium sulphate did not reduce the infant mortality rate or influence neurological outcomes. However, among infants born between 28 and 32 weeks of gestation, rates of cerebral palsy and brain damage were found to be significantly lower among survivors in the low-dose group.

Introduction

A recent meta-analysis of five trials and 6145 infants revealed that administration of magnesium sulphate ($MgSO_4$) before birth is beneficial for preterm infants as it significantly decreases the incidence of cerebral palsy (CP) and gross motor dysfunction without increasing infant mortality [1]. As such, $MgSO_4$ is recommended for neuroprotection of preterm infants for women at risk of imminent delivery. However, concerns have been raised regarding the slight increase in infant mortality following antenatal administration of $MgSO_4$ [2]. Maternal administration of $MgSO_4$ may be associated with adverse outcomes in a dose–response manner as adverse neonatal outcomes have been associated with higher ionized magnesium concentrations in umbilical cord blood [3]. However, the duration and timing of antenatal $MgSO_4$ administration with respect to the reduction in neurological damage has yet to be investigated extensively [4].

In Japan, $MgSO_4$ has been used as a tocolytic agent and an anti-eclamptic agent, but not as a neuroprotective agent until recently.

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Some investigators have adopted long-term (>48 h) tocolysis in an effort to extend pregnancy as close as possible to term unless obstetric indications occur, thus suggesting possible exposure to high-dose magnesium in utero. Under these conditions, some women experienced short-term (low-dose) exposure, while others experienced long-term (high-dose) exposure to $MgSO_4$. Thus, this retrospective study sought to investigate the neuroprotective effects of $MgSO_4$ and its dose–response relationship in premature infants using national databases.

Materials and methods

This study was approved by the Ethics Committee of the University of Miyazaki, Faculty of Medicine as a retrospective case–control study (Ref. No. 2014-138).

The Perinatal Committee of the Japan Society of Obstetrics and Gynaecology has a programme to register 60,000 deliveries per year for clinical studies. Similarly, the Neonatal Research Network in Japan has a database on neonatal outcomes. These two databases had been linked previously to follow low-birthweight infants (<1500 g) from 2003 to 2007; 40 institutions had been recruited to participate and contribute to both databases [5]. These 40 institutions were either secondary or tertiary perinatal centres that accepted referral cases for maternal or fetal indications. They all had neonatal intensive care units and their survival rates for premature infants in the study period were within acceptable limits. Six key parameters were involved in both databases for linkage: date of birth, sex, birth weight, gestational age (in weeks) at birth, maternal age at delivery, and the institution's name. Specific details have been reported elsewhere [5]. From 298,514 deliveries between 2003 and 2007, the number of very-low-birthweight infants (<1500 g) was 9101 (Fig. 1). Among these, full matching was possible for 5562 infants (61.1%). Multifetal pregnancies, except diamniotic twins, and infants with congenital abnormalities were excluded from this study. Of the fully-matched infants, 3763 were born between 24 and 32 weeks of gestation, and 1813 (48%) were followed-up for at least 18 months.

This study analyzed the effect of antenatal $MgSO_4$ administration on infant death and brain damage, particularly CP and mental retardation (MR). CP was diagnosed according to a proposed definition [6] at ≥18 months of age. Infants with moderate or severe types of CP were included. Mental retardation was defined as DQ <70 using the Kyoto Scale of Psychological Development [7], in which the details of cognitive impairment, language or performance were unclarified in the present study. The DQ score is strongly correlated with the corresponding composite score of Bayley III in very-low-birthweight infants at 18 months of age [7]. These diagnoses were confirmed by specialists in paediatric neurology in each of the 40 institutions.

The dose of $MgSO_4$ was categorized into three groups to examine the dose–response relationship: no-magnesium group, low-dose (<50 g) group and high-dose (≥50 g) group. The dose was determined arbitrarily as the clinically relevant dose is near 50 g; 4 g for the loading dose and 1 g/h for 48 h for the maintenance dose. This administration protocol was used for the prevention of preterm labour and pre-eclampsia/eclampsia. Therefore, the low-dose group represented short-term use of $MgSO_4$ (≤24–48 h) and the high-dose group represented long-term use of $MgSO_4$. It was presumed that women in the low-dose group received approximately 25–50 g of $MgSO_4$. Antenatal $MgSO_4$ administration for neuroprotection was not performed during the study period.

This study also analyzed several important clinical prognostic covariates for neurological damage in the premature infants, which included gestational age, sex, antenatal corticosteroids, fetal growth restriction (<10th percentile of the Japanese standard curve) and low umbilical arterial pH values (<7.1). Perinatal deaths included neonatal and infant deaths, but not fetal deaths. Apart from gestational age (continuous variable), dichotomous variables (absence = 0, presence = 1) were used for multivariate analysis using Statistical Package for the Social Sciences (IBM Corp., Armonk, NY, USA). A multiple logistic regression analysis was used to determine the effect of clinical covariates. One-way analysis of variance (ANOVA) with Dunnett's post hoc test was used to compare numerical values between the control value (no-magnesium group) and the other values (low-dose and high-dose groups). One-way ANOVA with Tukey's post hoc test was used to compare three subgroups of gestational age and three subgroups of birth weight. The Kruskal–Wallis test was used for non-parametric comparisons. $p < 0.05$ was considered to indicate statistical significance. Data are expressed as mean + standard deviation.

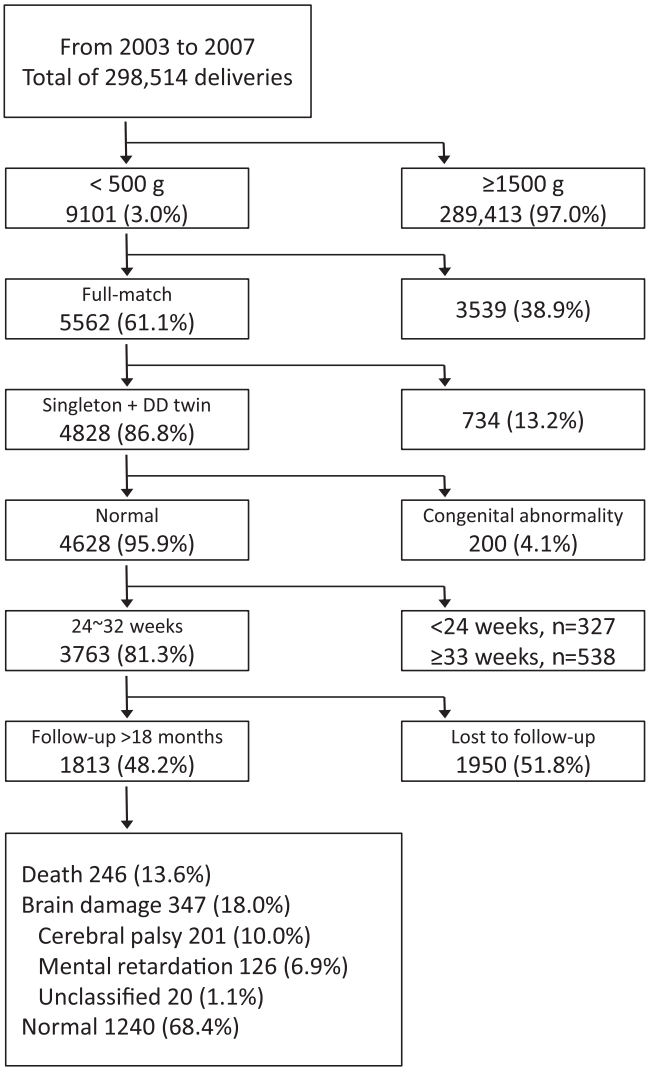

Fig. 1. Study flowchart. DD, diamniotic.

Results

The total dose of maternally administered $MgSO_4$ was 0 g (no-magnesium group, $n = 1300$), <50 g (low-dose group, $n = 237$), ≥50 g (high-dose group, $n = 259$) or unknown ($n = 17$). After excluding the infants who received an unknown dose of $MgSO_4$, 1796 infants were included to study the effect of $MgSO_4$ dose on infant outcome. Among these 1796 infants, $MgSO_4$ had been used for prevention of eclampsia in 113 cases and for tocolysis in