

Effects of Different Doses of Antenatal Magnesium Sulfate Exposure on Short-Term Outcomes of Preterm Infants < 32 weeks: A Retrospective Cohort Study

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Research Article

Keywords: Magnesium sulfate, Premature infants, Infant, extremely premature, Intracranial hemorrhage, Ductus arteriosus, patent, Cohort studies

Posted Date: September 28th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10612075/v1>

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Additional Declarations: No competing interests reported.

Abstract

Objective To investigate the effects of different doses of antenatal magnesium sulfate exposure on short-term outcomes of preterm infants < 32 weeks gestation and to analyze the differences in its effects across gestational age subgroups.

Methods Preterm infants < 32 weeks gestation born at the Affiliated Zhangzhou Hospital of Fujian University between June 2023 and December 2025 were retrospectively enrolled. Infants were divided into low-dose group (≤ 30 g), high-dose group (> 30 g), and non-exposure group based on cumulative antenatal magnesium sulfate dosage. Multivariable logistic regression was used to identify risk factors for death within 1 week after birth. Subgroup analyses were performed by gestational age (<28 weeks and 28–31⁺6 weeks) to compare the differences in primary outcomes (death within 1 week, grade III–IV intracranial hemorrhage(IVH)) and secondary outcomes (bronchopulmonary dysplasia(BPD), hemodynamically significant patent ductus arteriosus(hs PDA), necrotizing enterocolitis(NEC), retinopathy of prematurity(ROP), etc.) between the magnesium sulfate exposure group and the non-exposure group.

Results A total of 451 preterm infants were enrolled, including 143 (31.7%) in the low-dose group, 21 (4.7%) in the high-dose group, and 287 (63.6%) in the non-exposure group. Multivariable logistic regression showed that antenatal magnesium sulfate exposure was an independent protective factor for death within 1 week after birth (OR=0.197, 95%CI: 0.051–0.759, P=0.018). Gestational age subgroup analysis revealed that in the <28 weeks subgroup, the mortality rate within 1 week in the magnesium sulfate exposure group was significantly lower than that in the non-exposure group [5.1% (2/39) vs. 24.0% (18/75), P=0.024], while the incidence of grade III–IV IVH showed no significant difference between the two groups (P=0.931). In the 28–31⁺6 weeks subgroup, there were no significant differences between the two groups in mortality within 1 week (0.8% vs. 2.4%, P=0.509) or grade III–IV IVH (0% vs. 2.4%, P=0.194). Regarding complications, in the 28–31⁺6 weeks subgroup, the incidence of hsPDA at 2 weeks in the magnesium sulfate exposure group was significantly lower than that in the non-exposure group (3.9% vs. 12.0%, P=0.013), while the incidence of ROP was significantly higher (20.6% vs. 8.7%, P<0.001). In the <28 weeks subgroup, no significant differences were observed in any complication between the two groups (P>0.05).

Conclusions Antenatal magnesium sulfate exposure significantly reduces the risk of death within 1 week in preterm infants < 32 weeks gestation, and this protective effect is mainly concentrated in extremely preterm infants < 28 weeks.

Introduction

Premature infants, especially extremely preterm infants with a gestational age < 32 weeks, face risks of severe complications such as IVH, white matter injury, respiratory distress syndrome(RDS), and PDA due to the extreme immaturity of their organ systems, resulting in significantly higher case fatality rates and disability rates compared to full-term infants¹. Prenatal administration of magnesium sulfate has been confirmed by multiple randomized controlled trials and meta-analyses to have definitive fetal neuroprotective effects, significantly reducing the risk of cerebral palsy in preterm infants. Cochrane systematic reviews indicate that prenatal magnesium sulfate exposure can reduce the risk of cerebral palsy in preterm infants by approximately 31% and decrease the composite outcome of death or cerebral palsy². Based on this, both the American College of Obstetricians and Gynecologists (ACOG)³ and China's preterm birth guidelines⁴ recommend the use of magnesium sulfate for pregnant women with threatened preterm labor before 32 weeks of gestation to protect the fetal central nervous system.

However, aside from neuroprotective benefits, the effects of prenatal magnesium sulfate on other systems of preterm infants remain highly controversial. As a calcium ion antagonist, magnesium sulfate relaxes vascular smooth muscle. Some studies suggest that prenatal magnesium sulfate may delay the natural closure of the ductus arteriosus,

increasing the risk of hspDA^{5 6}. Additionally, research has indicated that magnesium sulfate exposure may cause adverse effects such as neonatal respiratory depression, feeding intolerance, and intestinal injury⁷. However, studies from the Canadian Neonatal Network and others have not found that prenatal magnesium sulfate exposure increases the incidence of neonatal necrotizing enterocolitis or hspDA^{8 9}, suggesting that the safety of magnesium sulfate requires further validation.

It is noteworthy that the clinical use of magnesium sulfate in obstetrics varies, not only for fetal neuroprotection but also widely for treating preeclampsia/eclampsia and inhibiting preterm labor contractions. Different purposes lead to significant differences in dosage and duration: the total dose for neuroprotection is typically $\leq 30\text{g}$, while cumulative doses for treating preeclampsia or inhibiting contractions can exceed 50g ¹⁰. Theoretically, different doses of magnesium sulfate exposure may have differential effects on various systems of preterm infants, but previous studies have mostly analyzed prenatal magnesium sulfate exposure as a whole, with few stratified analyses based on dosage. This study aims to investigate the effects of different doses of prenatal magnesium sulfate exposure on short-term outcomes (focusing on death within 1 week, intracranial hemorrhage, patent ductus arteriosus, etc.) in preterm infants < 32 weeks through a retrospective cohort study, and to analyze risk factors for death within 1 week in preterm infants.

Methods

2.1 Study Subjects and Data Collection

2.1.1 Study Design and Subjects

This study is a retrospective cohort study. Preterm infants with a gestational age of <32 weeks who were born at the Affiliated Zhangzhou Hospital of Fujian Medical University and admitted to the Neonatal Intensive Care Unit (NICU) from June 2023 to December 2025 were included. Inclusion criteria: (1) Gestational age at birth <32 weeks; (2) Born at this hospital; (3) Transferred to the NICU within 2 hours after birth. Exclusion criteria: (1) Complicated with chromosomal abnormalities, congenital abnormalities, or genetic metabolic diseases; (2) multiple pregnancy; (3) Incomplete clinical data. This study was approved by the Institutional Review Board (IRB) of Zhangzhou Affiliated Hospital of Fujian Medical University, with a waiver of informed consent ;

(2026LWB274).

2.1.2 Exposure Definition and Grouping

The included preterm infants were divided into three groups based on the cumulative total dose of antenatal magnesium sulfate. The cumulative total dose was calculated from electronic medical records (loading dose + maintenance dose $\times$ duration of administration).

(1) Low-dose group: Cumulative total dose of antenatal magnesium sulfate $\leq 30\text{ g}$.

(2) High-dose group: Cumulative total dose of antenatal magnesium sulfate $>30\text{ g}$.

(3) No-use group: Mothers did not receive any form of magnesium sulfate before delivery.

2.1.3 Data Collection

Using the hospital's electronic medical record system, standardized data collection forms were used to retrospectively collect the following perinatal and neonatal clinical.

Perinatal data: Hypertensive disorders of pregnancy (including preeclampsia/eclampsia), gestational diabetes mellitus (GDM), premature rupture of membranes, use of antenatal corticosteroids, mode of delivery (cesarean delivery or vaginal delivery), cumulative dose of magnesium sulfate before delivery;

Data at birth of preterm infants: Gestational age, sex, birth weight, small for gestational age (SGA), 1-minute Apgar score, venous blood magnesium concentration within 48 hours after birth (measured by direct spectrophotometry);

Clinical outcome indicators:

Primary outcomes: (1) Death within 1 week after birth (death from any cause within 7 days after birth); (2) Grade III–IV IVH; (3) Periventricular leukomalacia (PVL).

Secondary outcomes: Neonatal respiratory distress syndrome (NRDS), BPD, hsPDA, NEC, ROP, pulmonary hemorrhage, pulmonary hypertension, cholestasis, sepsis, days of invasive mechanical ventilation.

2.1.4 Diagnostic Criteria

(1) Grade III–IV IVH and PVL: Confirmed by cranial ultrasound or MRI (MRI), with diagnostic criteria referring to *Practical Neonatology* (5th edition)¹¹.

(2) BPD: Diagnostic criteria referring to the 2018 revised criteria of the National Institute of Child Health and Human Development (NICHD)¹².

(3) hsPDA: Diagnosed when all the following conditions are met : ☐ Cardiac color Doppler ultrasound confirms left-to-right shunt; ☐ Left atrial-to-aortic root ratio (LA/AO) >1.3; ☐ Patent ductus arteriosus diameter >1.5 mm; ☐ Presence of at least one of the following clinical manifestations: heart murmur, bounding pulse, tachycardia, worsening respiratory status, or increased precordial activity.

(4) NRDS, NEC, and ROP: Diagnostic criteria all referring to *Practical Neonatology* (5th edition)¹¹.

(5) SGA was defined as birth weight below the 10th percentile for gestational age.¹³

2.1.5 Statistical Methods

SPSS 27.0 statistical software was used for data organization and analysis. Measurement data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed measurement data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and group comparisons were performed using the t-test. Non-normally distributed measurement data were expressed as median (Q1, Q3), and group comparisons were performed using the Mann-Whitney U test. Count data were expressed as cases (%), and group comparisons were performed using the Chi-square test (χ^2 test) or Fisher's exact test. A two-sided $P < 0.05$ was considered statistically significant. Multivariate logistic regression analysis was used to analyze risk factors for death within 1 week in preterm infants.

Results

3.1 Participant Flow and Baseline Characteristics

A total of 496 preterm infants with gestational age < 32 weeks who met the inclusion criteria during the study period were initially screened. After excluding 9 cases with chromosomal abnormalities, congenital malformations, or inherited metabolic diseases, 21 cases with multiple pregnancy and 15 cases with incomplete clinical data, 451 infants were finally enrolled for analysis. Based on the cumulative total dose of antenatal magnesium sulfate, infants were

divided into three groups: low-dose group (≤ 30 g) with 143 cases (31.7%), high-dose group (>30 g) with 21 cases (4.7%), and non-exposure group with 287 cases (63.6%). For further analysis of complications among surviving infants, cases with death within 1 week after birth ($n=26$) and those with withdrawal of treatment after 1 week ($n=3$, all from the non-exposure group) were excluded, resulting in 422 infants included in the complication analysis. The participant flow chart is shown in Figure 1.

Comparison of maternal and infant baseline characteristics among the three groups is presented in Table 1. In terms of baseline characteristics, there were significant differences among the three groups in gestational age, serum magnesium concentration, magnesium sulfate dosage, cesarean section rate, gestational hypertension, and SGA incidence ($P < 0.05$), while no significant differences were observed in birth weight, sex, gestational diabetes mellitus, antenatal corticosteroid use, or 1-minute Apgar score < 7 ($P > 0.05$). There was a significant difference in gestational age among the three groups ($H=11.734$, $P=0.003$). The high-dose group had the largest median gestational age [30.9 (29.7, 31.4) weeks], the low-dose group had the smallest [29.4 (28.0, 31.3) weeks], and the non-exposure group was [29.9 (28.0, 31.3) weeks].

Serum magnesium concentrations differed significantly among the three groups ($H=91.763$, $P < 0.001$), with the highest level in the high-dose group [1.06 (0.89, 1.28) mmol/L], followed by the low-dose group [0.95 (0.87, 1.04) mmol/L], and the lowest in the non-exposure group [0.82 (0.74, 0.91) mmol/L]. The cumulative magnesium sulfate dosage in the high-dose group was significantly higher than that in the low-dose group [54.0 (34.5, 75.0) g vs. 10.0 (9.0, 19.0) g, $Z=-7.841$, $P < 0.001$]. The incidence of gestational hypertension (100%) and cesarean section rate (100%) in the high-dose group were significantly higher than those in the low-dose group (11.2%, 49.0%) and the non-exposure group (7.0%, 56.1%), with statistically significant differences ($\chi^2=153.787$ and 19.370, respectively, both $P < 0.001$). The incidence of SGA in the high-dose group was 33.3%, significantly higher than that in the low-dose group (4.2%) and the non-exposure group (7.7%) ($\chi^2=21.727$, $P < 0.001$).

Table 1 Comparison of baseline characteristics among different magnesium sulfate dosage groups

Characteristics	Low-dose group n=143	High-dose group n=21	Non-exposure group n=287	Z/ χ^2 /t	pvalue
GA M Q 1, Q3 week	29.4 28.0 31.3	30.9 29.7, 31.4	29.9 28.0 31.3	11.734	0.003
BW M Q 1, Q3 g	1200 990 1400	1250 965, 1576	1300 1020 1550	3.414	0.181
Serum magnesium M Q 1, Q3 mmol/L	0.95 0.87, 1.04	1.06 0.89, 1.28	0.82 0.74, 0.91	91.763	0.001
Male [n (%)]	92 64.3	10 47.6	161 56.1	3.701	0.157
Magnesium sulfate dosage M Q 1, Q3 g	10.0 9.0, 19.0	54.0 34.5, 75.0	—	44.408	0.001
Cesarean section [n (%)]	70 49.0	21 100.0	161 56.1	19.370	0.001
Gestational hypertension [n (%)]	16 11.2	21 100.0	20 7.0	153.787	0.001
GDM [n (%)]	49 34.3	6 28.6	79 27.5	2.090	0.352
Grade III–IV IVH [n (%)]	3 2.1	0 0	9 3.1	0.999	0.459*
Antenatal corticosteroid use [n (%)]	105 73.4	16 76.2	187 65.2	3.649	0.161
SGA [n (%)]	6 4.2	7 33.3	22 7.7	21.727	0.001
Death within 1 week of birth [n (%)]	3 2.1	0 0	23 8.0	7.496	0.009
1-minute Apgar score < 7 [n (%)]	40 28	5 23.8	98 34.1	2.315	0.314

GA-gestational age, BW-birth weight, SGA-small for gestational age, GDM-gestational diabetes

Mellitus, IVH-intraventricular hemorrhage.*Fisher's exact test.

3.2 Comparison of Primary Outcomes among Different Dosage Groups

Comparison of primary outcomes among the three groups is also shown in Table 1.

A total of 26 infants died within 1 week after birth, with an overall mortality rate of 5.8% (26/451). The mortality rates were 2.1% (3/143) in the low-dose group, 0% (0/21) in the high-dose group, and 8.0% (23/287) in the non-exposure group. The difference among the three groups was statistically significant ($\chi^2=7.496$, $P=0.009$). The non-exposure group had the highest mortality rate, followed by the low-dose group, and the high-dose group had the lowest.

The incidence of grade III–IV IVH was 2.1% (3/143) in the low-dose group, 0% (0/21) in the high-dose group, and 3.1% (9/287) in the non-exposure group. No significant difference was observed among the three groups (Fisher's exact test, $P=0.459$).

3.3 Risk Factors for Death within 1 Week after Birth

Multivariable logistic regression analysis with stepwise backward elimination was performed to identify risk factors for death within 1 week after birth. The dependent variable was death within 1 week (death=1, survival=0), and the independent variables included gestational age, birth weight, mode of delivery (cesarean section=1, vaginal delivery=0), gestational diabetes mellitus, gestational hypertension, 1-min Apgar score < 7, SGA, antenatal corticosteroid use, and antenatal magnesium sulfate exposure (exposed=1, non-exposed=0). (Table 2).

1-Each 1-week increase in gestational age was associated with an approximately 41% reduction in the risk of death within 1 week (OR=0.589, 95%CI: 0.376–0.922, P=0.021). Cesarean section was a protective factor against death within 1 week (OR=0.196, 95%CI: 0.052–0.743, P=0.017). Antenatal magnesium sulfate exposure reduced the risk of death within 1 week by approximately 80% (OR=0.197, 95%CI: 0.051–0.759, P=0.018). A 1-min Apgar score < 7 significantly increased the risk of death within 1 week (OR=5.005, 95%CI: 1.570–15.957, P=0.006).

Table 2 Multivariable logistic regression analysis of risk factors for death within 1 week after birth (stepwise backward elimination)

Variables	β coefficient	Standard error	Wald χ^2	P value	OR 95%CI
BW	0.002	0.001	1.300	0.254	1.002 0.999-1.004
GA	0.529	0.229	5.360	0.021	0.589 0.376-0.922
Cesarean section	1.631	0.680	5.747	0.017	0.196 0.052-0.743
GDM	0.208	0.624	0.111	0.739	0.812 0.239-2.761
Gestational hypertension	0.074	1.411	0.003	0.958	0.929 0.059-14.743
1-minute Apgar score < 7	1.610	0.592	7.411	0.006	5.005 1.570-15.957
Antenatal dexamethasone use	0.290	0.500	0.337	0.562	0.748 0.281-1.993
Antenatal magnesium sulfate use	1.622	0.687	5.577	0.018	0.197 0.051-0.759

GA-gestational age, BW-birth weight, GDM-gestational diabetes mellitus;

3.4 Subgroup Analysis by Gestational Age

To further explore the effects of antenatal magnesium sulfate exposure on short-term outcomes across different gestational age subgroups, the 451 enrolled infants were divided into two subgroups: < 28 weeks (n=114) and 28–31⁺⁶ weeks (n=337). Comparisons of primary outcomes and complications between the magnesium sulfate exposure group (low-dose + high-dose) and the non-exposure group within each subgroup are presented in Table 3.

3.4.1 Primary Outcomes in the Overall Population (n=451)

In the < 28 weeks subgroup: The mortality rate within 1 week in the magnesium sulfate exposure group was significantly lower than that in the non-exposure group [5.1% (2/39) vs. 24.0% (18/75), $\chi^2=6.317$, P=0.024]. The incidence of grade III–IV IVH showed no significant difference between the two groups [7.7% (3/39) vs. 5.3% (4/75), Fisher's exact test, P=0.931].

In the 28–31⁺⁶ weeks subgroup: There were no significant differences between the magnesium sulfate exposure group and the non-exposure group in mortality within 1 week [0.8% (1/128) vs. 2.4% (5/209), $\chi^2=1.178$, P=0.509] or grade III–IV IVH [0% vs. 2.4% (5/209), Fisher's exact test, P=0.194].

These findings suggest that the protective effect of antenatal magnesium sulfate on early survival is primarily concentrated in extremely preterm infants < 28 weeks.

3.4.2 Complications and Clinical Outcomes in Surviving Infants (n=422)

After excluding cases with death within 1 week and withdrawal of treatment after 1 week, comparisons of complications and clinical outcomes between the magnesium sulfate exposure group and the non-exposure group within each gestational age subgroup are presented in Table 3.

Baseline characteristics:

In the < 28 weeks subgroup, there were no significant differences between the exposure and non-exposure groups in gestational age [26.7 (25.8, 27.6) weeks vs. 27.0 (26.0, 27.7) weeks, $Z=-0.657$, $P=0.511$] or birth weight [900 (765, 990) g vs. 910 (750, 1048) g, $Z=-0.165$, $P=0.869$]. Serum magnesium concentration was significantly higher in the exposure group [0.99 (0.92, 1.06) mmol/L vs. 0.88 (0.81, 0.93) mmol/L, $Z=-4.332$, $P < 0.001$].

In the 28–31⁺⁶ weeks subgroup, the exposure group had significantly lower gestational age [29.9 (29.1, 31.0) weeks vs. 30.8 (29.6, 31.4) weeks, $Z=-3.845$, $P < 0.001$] and birth weight [1450 (1300, 1662) g vs. 1650 (1200, 1650) g, $Z=-3.305$, $P < 0.001$] than the non-exposure group. Serum magnesium concentration was also significantly higher in the exposure group [0.94 (0.85, 1.07) mmol/L vs. 0.82 (0.75, 0.91) mmol/L, $Z=-7.330$, $P < 0.001$].

Complications:

(1) < 28 weeks subgroup: No significant differences were observed between the two groups in the incidence of sepsis (13.5% vs. 19.6%, $P=0.627$), RDS (97.3% vs. 100%, $P=0.834$), pulmonary hemorrhage (16.2% vs. 8.9%, $P=0.461$), pulmonary hypertension (5.4% vs. 10.7%, $P=0.470$), BPD (66.7% vs. 67.9%, $P=0.905$), hsPDA at all time points (1 week: 54.1% vs. 55.3%, $P=0.902$; 2 weeks: 30.6% vs. 32.7%, $P=0.828$; 1 month: 12.1% vs. 18.5%, $P=0.431$), ROP (27.0% vs. 50.0%, $P=0.088$), PVL (18.9% vs. 16.1%, $P=0.706$), or NEC (2.7% vs. 5.4%, $P=1.000$). Although ROP incidence in the exposure group showed a trend toward being lower than that in the non-exposure group (27.0% vs. 50.0%), the difference did not reach statistical significance ($\chi^2=4.870$, $P=0.088$). The duration of invasive mechanical ventilation also showed no significant difference between the two groups [14 (1, 42.5) days vs. 8 (1, 36.8) days, $Z=-0.169$, $P=0.866$].

(1) 28–31⁺⁶ weeks subgroup: The incidence of hsPDA at 2 weeks in the magnesium sulfate exposure group was significantly lower than that in the non-exposure group [3.9% (5/127) vs. 12.0% (24/202), $\chi^2=7.722$, $P=0.013$]; hsPDA at 1 month also showed a trend toward lower incidence in the exposure group [0% vs. 5/202 (2.5%), Fisher's exact test, $P=0.051$]. However, the incidence of ROP was significantly higher in the exposure group [20.6% (26/127) vs. 8.7% (17/202), $\chi^2=17.168$, $P < 0.001$]. No significant differences were found between the two groups in the incidence of sepsis (9.4% vs. 7.9%, $P=0.629$), RDS (93.7% vs. 86.6%, $P=0.066$), pulmonary hemorrhage (3.1% vs. 3.0%, $P=1.000$), pulmonary hypertension (0.8% vs. 3.0%, $P=0.256$), BPD (22.8% vs. 18.8%, $P=0.378$), hsPDA at 1 week (29.1% vs. 35.1%, $P=0.258$), PVL (19.7% vs. 23.3%, $P=0.444$), or NEC (5.5% vs. 4.5%, $P=0.665$). The duration of invasive mechanical ventilation also showed no significant difference between the two groups [0 (0, 1) days vs. 0 (0, 2) days, $Z=-0.423$, $P=0.672$].

Table 3 Comparison of outcomes between magnesium sulfate exposure and non-exposure groups stratified by gestational age

28					28~31 ⁺⁶			
n=451	MgSO ₄ group n=39	Non-MgSO ₄ group n=75	χ^2	P value	MgSO ₄ group n=128	Non-MgSO ₄ group n=209	χ^2	P value
Death within 1 week [n (%)]	25.1	1824.0	6.317	0.024	10.8	52.4	1.178	0.509
Grade III–IV IVH [n (%)]	37.7	45.3	0.248	0.931*	00	52.4	3.108	0.194*
n=422	MgSO ₄ group n=37	Non-MgSO ₄ group n=56	Z/ χ^2 /t	P value	MgSO ₄ group n=127	Non-MgSO ₄ group n=202	Z/ χ^2 /t	P value
GA M Q 1, Q ₃ weeks	26.725.8 27.6	27.026.0 27.7	0.657	0.511	29.929.1 31.0	30.829.6 31.4	3.845	0.001
BW M Q 1, Q ₃ g	900765 990	910750 1048	0.165	0.869	1450 1300,1662	1650 1200,1650	3.305	0.001
Serum magnesium [M (Q1, Q3), mmol/L]	0.99 0.92,1.06	0.88 0.81,0.93	4.332	0.001	0.94 0.85,1.07	0.82 0.75,0.91	7.330	0.001
Sepsis [n (%)]	513.5	1119.6	0.588	0.627	129.4	167.9	0.234	0.629
RDS [n (%)]	3697.3	56100	1.530	0.834	11993.7	17586.6	4.097	0.066
Pulmonary hemorrhage [n (%)]	616.2	58.9	1.135	0.461*	43.1	63.0	0.009	1.000*
Pulmonary hypertension [n (%)]	25.4	610.7	0.799	0.470*	10.8	63.0	1.791	0.256*
BPD [n (%)]	2466.7	3867.9	0.014	0.905	2922.8	3818.8	0.778	0.378
hsPDA at 1 week [n (%)]	2054.1	3155.3	0.015	0.902	3729.1	7135.1	1.279	0.258
hsPDA at 2 weeks [n (%)]	1130.6	1832.7	0.047	0.828	53.9	2412.0	7.722	0.013
hsPDA at 1 month [n (%)]	412.1	1018.5	0.621	0.431	00	50.5	3.851	0.051
ROP [n (%)]	1027	2850	4.870	0.088	2620.6	178.7	17.168	0.001
PVL [n (%)]	719.4	916.4	0.143	0.706*	2519.7	4723.3	0.585	0.444*
NEC [n (%)]	12.7	35.4	0.381	1.000*	75.5	94.5	0.188	0.665*

Invasive mechanical ventilation [M (P ₂₅ , P ₇₅), days]	14 (14, 42.50)	8 (14, 36.75)	0.169	0.866	0 (0, 1)	0 (0, 2)	0.423	0.672
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*Fisher's exact test; The overall population analysis (n=451) included all enrolled participants. The complication analysis (n=422) excluded cases with death within 1 week (n=26) and withdrawal of treatment after 1 week (n=3, all from the non-exposure group). PVL analysis included infants who survived to completion of cranial imaging, with denominators as shown in the "complication analysis" rows for each subgroup. The analysis of hsPDA at 1 month further excluded infants who were discharged or died before 1 month of age.

Discussion

In this study, the mortality rate within one week was significantly lower in the prenatal magnesium sulfate exposure group of preterm infants compared to the non-exposure group. Multivariate regression analysis confirmed that prenatal magnesium sulfate is an independent protective factor against death within one week (OR=0.197, 95% CI: 0.051-0.759). This result is consistent with the conclusion of the Cochrane systematic review ², which summarized multiple randomized controlled trials and found that prenatal magnesium sulfate can reduce the risk of composite outcomes of death or cerebral palsy in preterm infants by approximately 30% and may reduce the risk of severe intracranial hemorrhage. This study further found that the protective effect of magnesium sulfate has significant gestational age differences—only in the subgroup of extremely preterm infants <28 weeks was a significant reduction in mortality observed (5.1% vs. 24.0%, P=0.024), while in the subgroup of 28-31⁺⁶ weeks, the difference in mortality between the two groups was not statistically significant (0.8% vs. 2.4%, P=0.509). This finding is consistent with relevant domestic research¹⁴ and further focuses the beneficiary population of this protective effect on extremely preterm infants <28 weeks. The possible reasons are: extremely preterm infants have extremely immature organ system development, especially the cerebrovascular autoregulation function is not yet perfect, and blood pressure fluctuations can easily lead to abnormal cerebral blood flow perfusion¹⁵; magnesium sulfate can exert multi-pathway neuroprotective effects by stabilizing vascular endothelial cells, inhibiting the release of inflammatory cytokines, reducing cerebral blood flow fluctuations, and antagonizing excitatory amino acid toxicity¹⁶, thereby providing greater absolute benefit in this high-risk population. The randomized controlled trial by Crowther et al. published in JAMA also found that the protective effect of magnesium sulfate on the composite outcomes of death and cerebral palsy in preterm infants at 30-34 weeks did not reach statistical significance¹⁷, which is consistent with the negative results in the larger gestational age subgroup in this study, suggesting that the neuroprotective benefits of magnesium sulfate are mainly concentrated in preterm infants with smaller gestational ages.

The gestational age stratification analysis in this study showed that in the two subgroups of <28 weeks and 28-31⁺⁶ weeks, there was no statistically significant difference in the incidence of grade III-IV IVH between the Magnesium sulfate exposure group and the non-exposure group, which is not entirely consistent with the conclusions of the Meta-analysis by Shepherd et al. ². This discrepancy may be attributed to the following reasons: First, the overall incidence of grade III-IV IVH in this study was low, lower than the reported incidence of IVH in Extremely premature infants in the literature¹⁸, which may be related to the refined monitoring strategies in the NICU and the high usage rate of Antenatal corticosteroids, and may also reflect the comprehensive level of perinatal management of preterm infants at this center. Second, the sample size of the subgroup analysis in this study was limited, which may be insufficient to detect minor differences between groups. Furthermore, a 2021 review by Ballabh¹⁵ pointed out that there are significant differences in the pathophysiological mechanisms and High-risk factors of Intracranial hemorrhages in preterm infants of different gestational ages. This study focused on extremely premature infants <32 weeks, and the responsiveness to

Magnesium sulfate may vary among different gestational age populations, necessitating further validation with larger sample sizes in the future.

Theoretically, magnesium sulfate, as a calcium ion antagonist, can relax vascular smooth muscle and delay ductus arteriosus closure¹⁹. However, this study found that in the 28–31⁺⁶ weeks subgroup, the incidence of hsPDA within 2 weeks was significantly lower in the magnesium sulfate-exposed group compared to the non-exposed group (3.9% vs. 12.0%, $P=0.013$), and the incidence of hsPDA at 1 month of age also showed a trend toward being lower than that in the non-exposed group (0% vs. 2.5%, $P=0.051$). In the <28 weeks subgroup, there were no significant differences in hsPDA incidence at any time point between the two groups. This finding contradicts the previous hypothesis that "magnesium sulfate may increase the risk of PDA"^{6,9}. A study by Okulu et al.⁹ published in 2024 also found that prenatal magnesium sulfate exposure for neuroprotection did not increase the risk of hsPDA in preterm infants <32 weeks. Although the number of cases in the high-dose group (>30 g) in this study was small, a reduced rather than increased risk of hsPDA was observed in the 28–31⁺⁶ weeks subgroup. Possible explanations include: the blood magnesium concentration in the magnesium sulfate-exposed group in this study was far below the concentration threshold reported in the literature to affect vascular smooth muscle tone²⁰; additionally, some studies have suggested that magnesium sulfate may indirectly promote the mature closure of the ductus arteriosus by inhibiting the inflammatory response, but this remains speculative and requires further research for validation²¹.

In the subgroup of 28 to 31⁺⁶ weeks, the incidence of ROP in the magnesium sulfate-exposed group was significantly higher than that in the non-exposed group, which is a finding worthy of attention and cautious interpretation. The occurrence of ROP is closely related to small gestational age, low birth weight, and oxygen exposure²². In this study, within the 28 to 31⁺⁶ weeks subgroup, the gestational age and birth weight of the magnesium sulfate-exposed group were significantly lower than those of the non-exposed group, meaning the exposed group itself was a high-risk population for ROP. Although this study excluded those who died within one week, inherent differences in gestational age and birth weight still existed between the groups, which may have led to differences in ROP incidence. After multivariate regression adjustment for gestational age and birth weight, whether magnesium sulfate exposure itself independently increases the risk of ROP still requires further analysis and confirmation.

In the <28 weeks subgroup, the incidence of ROP in the exposed group showed a trend of being lower than that in the non-exposed group. This trend was opposite to the results in the 28–31⁺⁶ weeks subgroup, which may be related to the small sample size of this subgroup or may suggest that the effect of magnesium sulfate on ROP is gestational age-dependent, warranting further investigation in future studies. Regarding other complications, this study did not find that magnesium sulfate exposure increased the risk of BPD, NEC, or sepsis, consistent with the findings of Shalabi et al.⁸ based on the Canadian Neonatal Network and the multicenter study by Ferreira et al.²³. For PVL, after including it in the complication analysis population (excluding those who died within one week), the incidence rates in the two groups showed no statistically significant differences in either the <28 weeks subgroup or the 28–31⁺⁶ weeks subgroup. This negative result may be related to the complexity of PVL pathogenesis, which involves multiple factors such as ischemia, infection/inflammation, and oxidative stress²⁴. The single neuroprotective mechanism of magnesium sulfate may be insufficient to completely block its occurrence pathway. There was also no significant difference in the number of days of invasive mechanical ventilation between the two groups, further supporting the good safety profile of antenatal magnesium sulfate within the neuroprotective dose range.

This study also has limitations: (1) It is a single-center retrospective study with a relatively small sample size, especially in the high-dose group (21 cases) and the <28 weeks subgroup (114 cases), which may affect the statistical power of some analyses; (2) Due to the inherent nature of retrospective studies, some potential confounding factors (e.g., detailed indications for maternal medication, specific decisions during labor, precise doses of neonatal oxygen

exposure) are difficult to fully collect and adjust for; (3) All pregnant women in the high-dose group had severe preeclampsia, with a significantly higher rate of SGA in this group, making it difficult to separate the effects of maternal disease from those of magnesium sulfate on preterm infant outcomes; (4) Long-term neurodevelopmental outcomes (e.g., cerebral palsy, cognitive dysfunction, etc.) of preterm infants were not collected, preventing assessment of the impact of different doses of magnesium sulfate exposure on long-term prognosis.

In summary, prenatal magnesium sulfate exposure significantly reduces the risk of death within one week in preterm infants <32 weeks, with this protective effect mainly concentrated in extremely preterm infants <28 weeks. In the 28–31⁺⁶ weeks subgroup, magnesium sulfate exposure was associated with a reduced incidence of hsPDA within two weeks, without increasing the risk of complications such as BPD or NEC. The increased incidence of ROP may be related to the smaller gestational age and greater oxygen exposure in the exposed group, rather than a direct toxic effect of magnesium sulfate, but this finding warrants clinical attention and further validation in future studies. Future multicenter, large-sample prospective studies, combined with long-term follow-up data, are needed to further verify the effects of different doses of magnesium sulfate exposure on the short- and long-term outcomes of very preterm infants, particularly its potential impact on complications such as ROP.

Abbreviations

IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; BPD: bronchopulmonary dysplasia; hsPDA: hemodynamically significant patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; RDS: respiratory distress syndrome; GA: gestational age; BW: birth weight; SGA: small for gestational age; GDM: gestational diabetes mellitus; NICU: neonatal intensive care unit; CI: confidence interval; OR: odds ratio.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Zhangzhou Affiliated Hospital of Fujian Medical University (Approval No.: 2026LWB274). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee. All patient data were anonymized prior to analysis to protect participant privacy.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request, due to privacy.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by no funders.

Authors' contributions

LLC initiated the study and wrote the manuscript. CWW performed the data analysis. HXL and WZH collected the data. XLP and WWC revised the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgements

None.

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Figures

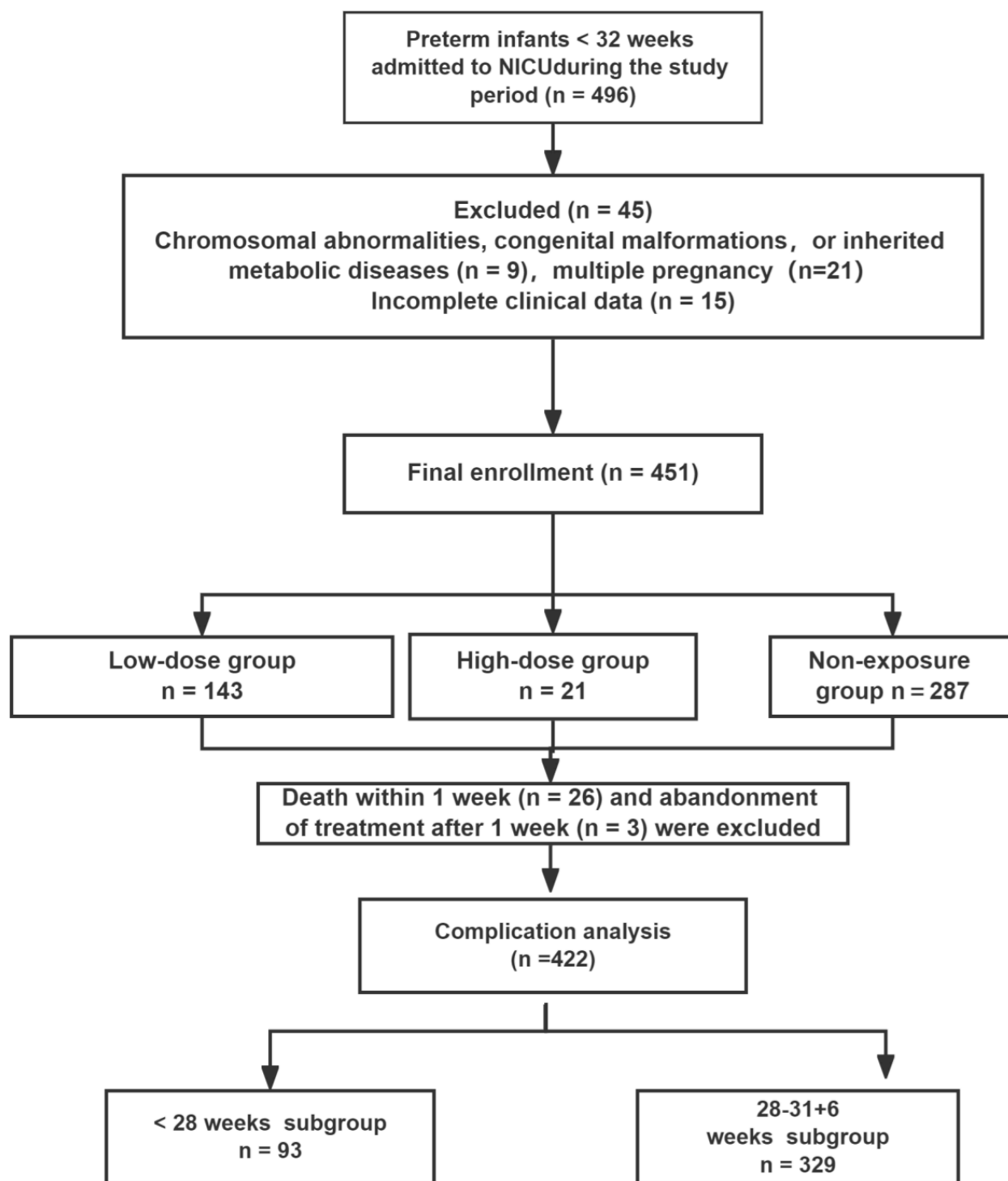


Figure 1

Participant flow chart