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# Antenatal Magnesium Sulfate for Preterm Neuroprotection: A Single-Center Experience from Kuwait Tertiary NICU

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**Keywords**
Preterm · Magnesium sulfate · Newborn infant · Neuroprotection

**Abstract**

***Objectives:*** The study aimed to evaluate the impact of antenatal exposure of magnesium sulfate ($MgSO_4$) on short- and long-term outcomes in preterm neonates born less than 32 weeks gestation. ***Methods:*** Single-center retrospective cohort study of 229 neonates born between 24 and 32 weeks gestation was conducted from January 2018 through December 2018 in a level III neonatal care unit in Kuwait. Antenatal $MgSO_4$ exposure was collected from the medical records, and the indication was for neuroprotection effect. Brain MRI was done on 212 neonates (median gestational age 36 weeks), and brain injury was assessed using the Miller's score. Neurodevelopmental outcome was assessed by Bayley-III scales of infant development at 36 months corrected age ($N = 146$). The association of exposure to MgSO4 with brain injury and neurodevelopmental outcomes was examined using multivariable regression analysis adjusting for gestational age at MRI and variables with $p$ value <0.05 on univariate analysis. ***Results:*** Among the 229 neonates, 47 received antenatal $MgSO_4$. There were no differences between the groups in gestational age and birth weight. $MgSO_4$ exposure was not associated with an increased risk of necrotizing enterocolitis, chronic lung disease, retinopathy of prematurity, and mortality. The incidence of cerebellar hemorrhage was significantly less in the $MgSO_4$ group (0% vs. 16%, $p$ value = 0.002). Neonates who received $MgSO_4$ had lower risks of grade 3–4 intraventricular hemorrhage (IVH) adjusted OR 0.248 (95% CI: 0.092, 0.66), $p = 0.006$; moderate-severe white matter injury (WMI) adjusted odd ratio 0.208 (95% CI: 0.044, 0.96), $p = 0.046$; and grade 3–4 IVH and/or moderate-severe WMI adjusted OR 0.23 (95% CI: 0.06, 0.84), $p = 0.027$. Neurodevelopmental assessment at 36 months corrected age showed better motor (adjusted beta coefficient 1.08 [95% CI: 0.099, 2.06]; $p = 0.031$) and cognitive composite scores (adjusted beta coefficient 1.29 [95% CI: 0.36, 2.22]; $p = 0.007$) in the $MgSO_4$ group. ***Conclusion:*** Antenatal exposure to $MgSO_4$ in preterm neonates less than 32 weeks was independently associated with lower risks of brain injury and better motor and cognitive outcomes.



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## Introduction

Cerebral palsy (CP) is the most common physical disability of childhood, has lifelong ramifications on physical and mental health, and can also negatively affect the later social and academic performance of the child [1]. Premature neonates are at higher risk of developmental disability, including CP, the incidence of which is inversely proportional to the gestational age. The rate of CP among extreme prematurity survivors ranges from 7 to 14%, which is many folds higher than the general population [2, 3]. Globally, it is estimated that up to 8% of global preterm babies have a neurological impairment, 3% of which have moderate to severe impairment [4]. Therefore, any neuroprotective intervention in this high-risk group has a long-term benefit in reducing the overall burden of neurodisability.

Apart from antenatal steroids, antenatal magnesium sulfate ($MgSO_4$), given to mothers at risk of preterm labor, is shown to be neuroprotective and reduces the incidence of CP [5, 6]. Multiple meta-analyses, including recently published individual patient data meta-analysis, which is considered the highest quality meta-analysis, have shown its efficacy in reducing the motor disability and CP when given to mothers in preterm labor with the intention for neuroprotection and not for maternal indications [7–9]. Many prominent professional bodies worldwide have endorsed antenatal $MgSO_4$ supplementation for preterm neuroprotection; however, penetration in clinical practice is still low [10, 11]. Concern was raised about a possible association with increased fetal and neonatal mortality, neonatal necrotizing enterocolitis (NEC), and neonatal spontaneous intestinal perforation, all of which were refuted in the later studies and systematic reviews [8, 12, 13]. Despite its proven efficacy, relative safety, and cost-effectiveness, clinicians are slow to embrace this in clinical practice [14, 15]. We introduced antenatal magnesium supplementation for neuroprotection in our hospital in the year 2018; however, adoption for this new intervention among the clinicians was slow, resulting in only a smaller proportion of babies receiving it. The present study describes the important neonatal clinical outcome and the long-term neurodevelopment follow-up of cohort of neonates exposed to antenatal $MgSO_4$ therapy during this period, with the aim of developing local data, to encourage the practitioners to adopt antenatal magnesium into practice.

## Methods

We retrospectively reviewed the charts of all the preterm infants born at gestation <32 weeks admitted to NICU during January 2018 and December 2018, Farwaniya Hospital, Kuwait. Obstetrical medical records were reviewed for all the infants, and two groups are formed based on those who received antenatal $MgSO_4$ for neuroprotection indication and those who did not receive but were eligible.

$MgSO_4$ for neuroprotection was introduced in our center in the year 2018; however, the policy was not fully implemented until August 2018 as per published international guidelines [10]. Before 2018, $MgSO_4$ was mainly used for preeclampsia prophylaxis and treatment.

*Inclusion Criteria*

Population

Preterm infants born at gestation <32 weeks receiving antenatal $MgSO_4$ specifically indicated for neuroprotection and not for maternal indication like preeclampsia or tocolysis were compared to the cohort of preterm neonates admitted during the same period who did not receive $MgSO_4$ for neuroprotection.

*Exclusion criteria*

We excluded neonates with known congenital anomalies, chromosomal anomalies, congenital infections, and syndrome, which are likely to affect the development outcome, and those with incomplete medical records lacking details.

*Outcomes*

Primary Outcome

Incidence of brain injury on MRI, before discharge, including intraventricular hemorrhage (IVH) as per Papile classification and white matter injury (WMI) according to Miller scoring [16].

Secondary Outcome

Neurodevelopmental impairment assessed Bayley Scales of Infant and Toddler Development-III (BSID-III) at 36 months chronological age. Brain MRI (1.5 or 3 Tesla) was performed before discharge at mean age 36 weeks, after swaddling and feeding or procedural sedation with 25–50 mg/kg chloral hydrate. Besides the standard T1- and T2-weighted images, fluid attenuated inversion recovery, apparent diffusion coefficient and diffusion-weighted image sequences were also obtained. The MRI images were interpreted by an experienced neuroradiologist who was unaware of the intervention. WMI was classified according to Miller's scoring system into mild WMI (<3 areas of abnormal T1 signal intensity), moderate (>3 areas of abnormal T1 signal intensity and <5% hemispheric involvement), and severe (>5% of the hemisphere involved) [16]. The presence of cerebellar hemorrhage was also recorded. The diagnosis of a patent ductus arteriosus (PDA) was according to the echocardiographic diagnosis of a hemodynamically significant PDA (HsPDA) requiring pharmacological or surgical treatment. Systemic hypotension was defined as systolic or diastolic or mean blood pressure below the 3rd centile for age or requiring inotropic support. Chronic lung disease (CLD) was defined as oxygen requirement beyond 36 weeks PMA, NEC classified as stages 2 and 3 as per Bell's staging, retinopathy of prematurity (ROP) as per the International Classification of ROP (International Committee for the Classification of Retinopathy of Prematurity, 2005).

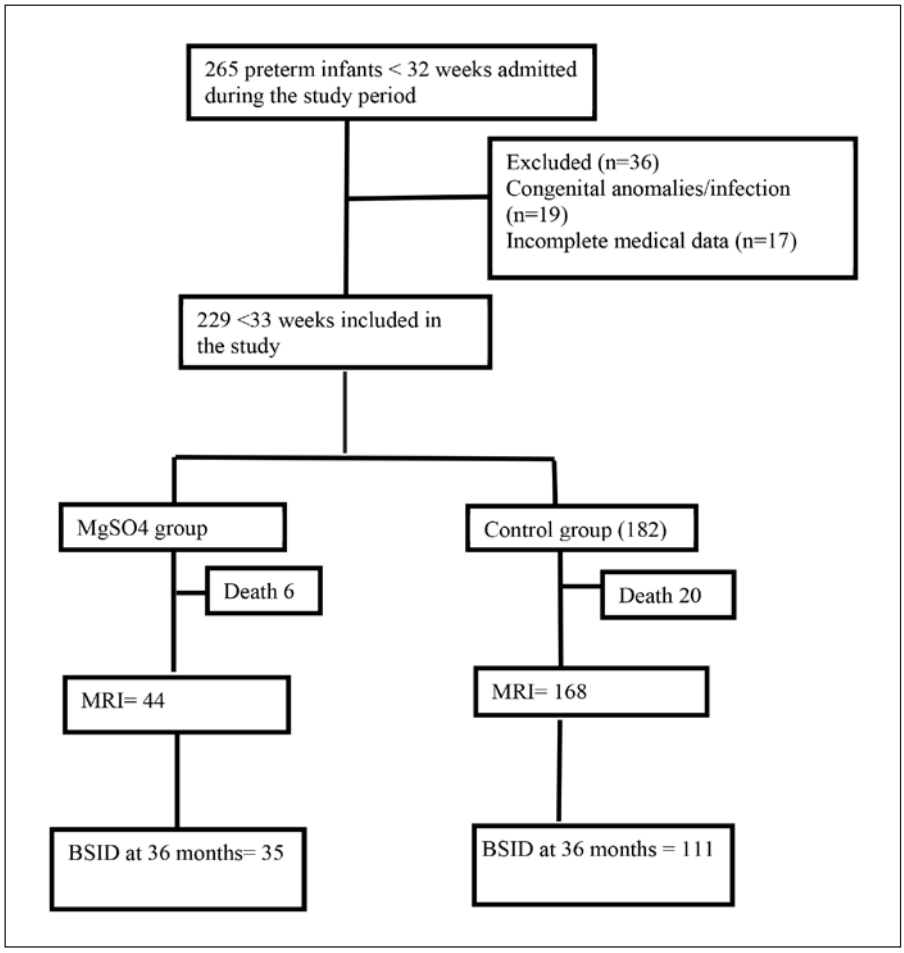


**Fig. 1.** Study flowchart.

All the preterm infants were followed up in the neurodevelopment outpatient clinic after discharge from NICU. At 36 months of age, a complete neurodevelopment assessment was performed with the Bayley Scales of Infant and Toddler Development-III (BSID-III) [17]. A composite score is calculated. Mild development impairment is classified as composite score <85, and a moderate developmental delay was designated to a worst composite score of 70–84 in ≥1 of the 3 domains, whereas a score of <70 for any of the 3 domains or when unable to assign a score owing to severe mental deficiency or CP (appraised using the Gross Motor Function Classification System (GMFCS)) was termed as severe delay [18, 19]. The GMFCS evaluates the gross motor function of children and youth with CP considering their ability to initiate basic movements like sitting and ambulation (walking or wheeled mobility). All the assessors were certified pediatric occupational therapists, physical therapists, and developmental specialists and were blinded to the intervention.

*Statistical Analysis*

Statistical analysis was performed using Stata 14 software (Stata Corporation, College Station, TX, USA). We used the $\chi^2$ test and Mann-Whitney test for categorical and continuous data, respectively, with a statistical significance of $p < 0.05$. The association between $MgSO_4$ exposure and other clinical variables with MRI results and neurodevelopmental outcomes was tested with univariate logistic regression. In addition, multivariate logistic and linear regression analyses were carried out on significantly different variables between the groups.

## Results

There was a total of 265 very preterm infants admitted during the study period, out of which 47 preterm neonates received antenatal $MgSO_4$ for neuroprotection. The flow diagram illustrates the enrolment and follow-up, and the attrition rate is depicted in Figure 1. The maternal and neonatal characteristics, including SNAP score at admission, were comparable in all aspects. A total of 39 pregnant women received bolus of 4 g of $MgSO_4$, while eight mothers received less than 4 g. No women received multiple courses of $MgSO_4$. The mean cumulative infusion dose of $MgSO_4$ was 4.5 g (range 8.5–16.5 g). There were no differences in the maternal characteristics be-

**Table 1.** Maternal and neonatal demographic characteristics, birth, and neonatal outcome

| Variables | Antenatal $MgSO_4$ (*N* = 47) | Control (*N* = 182) | *p* value |
|---|---|---|---|
| Maternal characteristics | | | |
| Age, median (IQR), years | 28 (25–32) | 27 (25–33) | 0.121 |
| Gestational diabetes, *N* (%) | 2 (4.2) | 18 (10) | 0.382 |
| Pregnancy induced hypertension, *N* (%) | 4 (8.5) | 15 (8.2) | 1 |
| Histopathological chorioamnionitis, *N* (%) | 2 (4.2) | 10 (5.5) | 0.981 |
| Antenatal steroids, *N* (%) | 40 (85.1) | 158 (86.8) | 0.132 |
| Neonatal characteristics | | | |
| Gestational age, median (IQR), weeks | 28 (27–30) | 27 (26–30) | 0.214 |
| Birth weight, median (IQR), g | 970 (820–1,217) | 1,022 (824–1,285) | 0.552 |
| Twin birth, *N* (%) | 13 (27.7) | 68 (37.4) | 0.215 |
| Caesarean section, *N* (%) | 30 (63.8) | 105 (58) | 0.065 |
| Male, *N* (%) | 27 (57.4) | 103 (56.6) | 0.104 |
| 5-min Apgar score, median (IQR) | 8 (8–7) | 7 (5–8) | 0.251 |
| Resuscitation details, *N* (%) | | | |
| PPV only | 15 (32) | 39 (21.5) | |
| PPV and intubation | 15 (32) | 95 (52) | 0.01 |
| Chest compression±epinephrine | 1 (2) | 8 (4) | |
| Any resuscitation at birth | 31 (65.9) | 142 (78) | 0.085 |
| SNAP score, median (IQR) | 9 (5–19) | 9 (0–17) | 0.917 |
| Needs for surfactant, *N* (%) | 28 (68) | 108 (70) | 0.849 |
| HsPDA, *N* (%) | 18 (38) | 84 (46) | 0.411 |
| Hypotension, *N* (%) | 2 (4.2) | 24 (13) | 0.065 |
| Early onset sepsis, *N* (%) | 11 (23) | 38 (21) | 0.696 |
| NEC stage >2, *N* (%) | 0 | 9 (5) | 0.21 |
| Spontaneous intestinal perforation, *N* (%) | 0 (0) | 0 (0) | 0 |
| CLD, *N* (%) | 6 (12) | 34 (17) | 0.396 |
| ROP, *N* (%) | 5 (10) | 30 (16) | 0.371 |

Values are expressed as number (*N*) and percentage (%) or median and interquartile range (IQR). Any resuscitation at birth defined as the need for PPV or intubation or chest compression ± epinephrine. PPV, positive pressure ventilation; SNAP, Score for Neonatal Acute Physiology; HsPDA, hemodynamically significant patent ductus arteriosus; NEC, necrotizing enterocolitis; CLD, chronic lung disease; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage.

tween the groups. There was a higher birth rate by caesarean section in the $MgSO_4$ group (63.8% vs. 58%; $p$ = 0.065). However, there were no differences between the groups in gestational age, birth weight, or 5-min Apgar score. Fewer neonates in the MgSO4 group required intubation at birth (32% vs. 52%) or chest compression ± epinephrine (2% vs. 4%) ($p$ = 0.01). However, the overall need for positive pressure ventilation (PPV) and/or chest compression in either group was not significantly different ($p$ < 0.085). There was a lower incidence of early hypotension in the $MgSO_4$ group compared to those in the control group (4.2% vs. 13%; $p$ = 0.065) (Table 1).

The first-week brain ultrasound showed a significant reduction in any IVH, grade 1–2 IVH, and severe grade 3–4 IVH in the $MgSO_4$ group ($p$ = 0.001). MRI data were available for 212 infants (magnesium 44 and control 168). There was a significant reduction in the prevalence of any IVH in the $MgSO_4$ group (grade 1&2 20 [11.9%] vs. 3 [6.8%] and severe grade 3&4 IVH 65 [39%] vs. 7 [16%] $p$ = 0.004) at 36 weeks. Additionally, there was a substantial reduction in the moderate to severe WMI score on MRI (33 [19%] vs. 2 [4.2%] $p$ = 0.02). $MgSO_4$ administration was not associated with an increase in neonatal mortality before discharge (20 [11%] vs. 6 [12.7%] $p$ = 0.369). There were no differences in the incidence of HsPDA, sepsis, NEC, CLD, and ROP between the two groups (Table 2).

Neurodevelopmental outcomes at 36 months corrected age were completed in 146 children (magnesium 35 [85% of the survived] and control 111 [69% of the survived]). The median motor score was 103 (interquartile

**Table 2.** Primary and secondary neonatal outcomes

| | $MgSO_4$ group | Control group | *p* value |
|---|---|---|---|
| Primary outcome | | | |
| Brain MRI, *N* = 212 | *N* = 44 | *N* = 168 | |
| Grade 1–2 IVH, *N* (%) | 3 (6.8) | 20 (11.9) | 0.01 |
| Grade 3–4 IVH, *N* (%) | 7 (16) | 65 (39) | 0.004 |
| Mild WMI, *N* (%) | 10 (22.7) | 23 (13.7) | 0.07 |
| Moderate-severe WMI, *N* (%) | 2 (4.2) | 33 (19) | 0.02 |
| Cerebellar hemorrhage, *N* (%) | 0 | 27 (16) | 0.002 |
| Week one head ultrasound | *N* = 47 | *N* = 182 | |
| Normal | 34 (72) | 92 (50.5) | |
| Grade 1–2 IVH | 3 (6.4) | 19 (10.4) | 0.003 |
| Grade 3–4 IVH | 10 (17) | 71 (39) | |
| Any IVH | 13 (27.6) | 90 (54.4) | 0.001 |
| Mortality before discharge, *N* (%) | 6 (12.7) | 20 (11) | 0.369 |
| Secondary outcomes | | | |
| Bayley-III composite score at 36 months corrected age, *N* = 146 | *N* = 35 | *N* = 111 | |
| Motor composite score, median (IQR) | 107 (97–112) | 97 (85–107) | 0.002 |
| Language composite score | 103 (94–109) | 94 (83–106) | 0.096 |
| Cognitive composite score | 110 (100–115) | 100 (95–110) | 0.013 |
| CP | 1 (2.8) | 26 (23.4) | 0.02 |

Values are expressed as number (*N*) and percentage (%) or median and interquartile range (IQR). IVH, intraventricular hemorrhage; WMI, white matter injury.

**Table 3.** Crude and adjusted analysis of the risk of brain injury in the $MgSO_4$ group versus control group

| | Crude odd ratio (95% CI); *p* value | *Adjusted odd ratio (95% CI); *p* value | **Adjusted odd ratio (95% CI); *p* value |
|---|---|---|---|
| Grade 3–4 IVH | 0.299 (0.126–0.712); 0.006 | 0.341 (0.142–0.823); 0.017 | 0.248 (0.0926, 0.66); 0.006 |
| WMI moderate to severe | 0.194 (0.044–0.846); 0.029 | 0.241 (0.070–0.827); 0.024 | 0.208 (0.044, 0.969); 0.046 |
| Grade 3–4 IVH on USG | 0.32 (0.16–0.64); 0.002 | 0.36 (0.17–0.74); 0.006 | 0.38 (0.18–0.78); 0.009 |
| Grade 3–4 IVH or moderate to severe WMI | 0.22 (0.065–0.745); 0.015 | 0.200 (0.045–0.882); 0.034 | 0.231 (0.063, 0.844); 0.027 |

IVH, intraventricular hemorrhage; WMI, white matter injury. * Adjusted for gestational age, birth weight. ** Adjusted for gestational age, birth weight, mode of delivery, need for resuscitation, and hypotension.

region [IQR]: 94–110), language score 109 (IQR: 100–118), and cognitive score 100 (IQR: 95–110). The median motor score 107 (IQR: 97–112) and median cognitive score 110 (IQR: 100–115) were significantly higher in the neonates antenatally treated with $MgSO_4$ ($p = 0.002$ and $p = 0.013$, respectively). Moreover, $MgSO_4$ was associated with lower risk of CP (2.8% vs. 23.4%, $p = 0.02$). However, there was no significant difference in the language score between the two groups (Table 2).

In the regression analysis models, adjusting for gestational age and birth weight, the use of $MgSO_4$ was significantly associated with the lower odds of severe grade 3–4 IVH (OR = 0.341, 95% CI: 0.142–0.823), moderate-severe WMI (OR = 0.241, 95% CI: 0.070–0.827), and the composite outcome of IVH or WMI (OR = 0.2, 95% CI: 0.045–0.882) (Table 3). Moreover, the tendency of the lower odds of grade 3–4 IVH, moderate to severe WMI, and composite outcomes of IVH or WMI in the $MgSO_4$ group persisted after regression analysis for gestational age, birth weight, mode of delivery, need for resuscitation (Table 3).

Similarly, in multivariate regression analysis of the BSID score, antenatal $MgSO_4$ exposure is associated with significantly greater odds of better motor BSID score

**Table 4.** Crude and adjusted analysis of neurodevelopmental outcome (BSID score) at 36 months corrected age (*N* = 146)

| Composite score | Crude β coefficient (95% CI); *p* value | *Adjusted β coefficient (95% CI); *p* value | **Adjusted β coefficient (95% CI); *p* value |
|---|---|---|---|
| Motor | 1.42 (0.436–2.41); 0.005 | 1.4 (0.44–2.38); 0.004 | 1.08 (0.0997–2.06); 0.031 |
| Language | 2.05 (−4.1–8.2); 0.511 | 2.65 (−3.44–8.7); 0.391 | 3.56 (−2.59–9.73); 0.254 |
| Cognitive | 1.09 (0.206–1.9); 0.016 | 1.17 (0.296–2.05); 0.009 | 1.29 (0.363–2.225); 0.007 |

* Adjusted for gestational age and birth weight. ** Adjusted for gestational age, birth weight, need for resuscitation at birth (intubation or chest compression), and hypotension.

(1.42 [95% CI: 0.436, 2.41] *p* value; 0.005) and better cognitive score (1.09 [95% CI: 0.206, 1.9], *p* value; 0.016). The significant difference persisted even after adjustment for gestation age and birth weight and need for resuscitation and hypotension (Table 4).

## Discussion

This is the largest neonatal follow-up study from the Middle East with detailed MRI evaluation and neurodevelopment assessment for the use of $MgSO_4$ for neuroprotection in preterm infants. We found a significant reduction in any IVH, severe grade 3 and 4 IVH in the first week which persisted in MRI examination before discharge. Furthermore, there was substantially less mild and severe WMI on MRI in the $MgSO_4$ group. Moreover, neurodevelopment follow-up at 36 months, there was a significant improvement in the motor and cognition score, which remained significant on multivariate regression analysis.

Our findings are consistent with conclusions of other landmark trials done before and add to the existing knowledge [6, 20–22]. We found a significant reduction in the incidence of IVH on the first-week brain ultrasound and MRI before discharge, which was in contrast to earlier reports of no significant reduction in IVH [23, 24]. This result is more consistent with the recent meta-analysis of 7 pooled studies, which showed a trend toward lower IVH relative risk 0.80 (95% CI: 0.63–1.03) [25]. We did multivariate logistic regression analysis for known confounding variables (gestational age, birth weight, and resuscitation) and found the result to be valid. Our neurodevelopment follow-up showed an improved motor score of BSID at 3 completed years in MgSO4 exposed neonates, which is significant even on multivariate regression consistent with all other meta-analysis suggesting a reduction in CP [7, 8, 13]. Additionally, we found improved cognitive scores on a follow-up which was also significant in regression analysis. This finding needs to be taken with caution due to the high attrition rate on follow-up. In our study, need for PPV at birth was more elevated in $MgSO_4$ exposed neonates; however, overall need for PPV and intubation or chest compression was significantly less than the control group. Nevertheless, Apgar score at birth and need for any resuscitation were not different in both the groups, which is similar to other studies and meta-analyses [8].

We did not find any other neonatal adverse effect attributable to magnesium consistent with other studies and meta-analysis [7, 8, 13, 25]. Interestingly, in our cohort, neonates exposed to antenatal $MgSO_4$ experienced significantly lesser hypotension in the immediate postnatal period and required lesser vasopressor support. The effect of $MgSO_4$ on preterm hemodynamic blood flow is an area of active and ongoing research. Magnesium, a potent calcium antagonist, can cause vasodilation in the mother and is reported to cause a decrease in systemic vascular return, hypotension in the immediate postnatal period without affecting the ejection fraction or cardiac performance; however, these effects are short-lived [26]. Our findings hence will be further explored in future clinical trials.

The strength of our study includes a relatively large sample size, blinded radiological MRI assessment by standardized tool, as a surrogate marker of brain injury, and standardized long-term neurodevelopment follow-up at 36 months. We chose 36 months for the end point of neurodevelopment follow-up, as compared to 24 months commonly followed in other neonatal studies, as we believe that neurodevelopment impairment is better defined at a later age than earlier. There are also few significant limitations to our study. There is significant selection bias as the choice of intervention was based on

clinicians' discretion. This is a retrospective cohort study, data are collected from electronic records, and human errors cannot be ruled out. All mothers received magnesium as per protocol, irrespective of their BMI, and we did not check serum magnesium level in the mother; therefore, we could not comment on the adequacy or superiority of the magnesium regime/protocol. Though the radiologist performing the MRI was blinded to the treatment received, the neurodevelopment assessment performed was unblinded. Although we could manage almost 93% MRI before discharge, many were lost to follow-up at 36 month follow-up (15% in magnesium group vs. 31% in the control group) for neurodevelopment assessment. This high attrition rate is mainly due to the predominant migrant population-based demography of Kuwait, which is unique to the region. We did not find any significant difference in the neonatal side effects, especially NEC and SIP, as reported by some smaller studies [12, 27]. However, the incidence of this was very low in our population, and our study is not powered for this.

## Conclusion

These data from our single-center experience with $MgSO_4$ are encouraging and should boost the confidence of practitioners both obstetric and perinatologists, in prescribing it for preterm neuroprotection. Further population-based, multi-centric quality improvement studies involving extreme preterm infants should be carried out in the region to improve the diffusion of $MgSO_4$ for preterm neuroprotection in clinical practice.

## Statement of Ethics

This paper adheres to the law of data protection and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was not required as this was conducted using retrospective data. This study was approved by the Ministry of Health of Kuwait ethics review board (2018/1462).

## Conflict of Interest Statement

The authors declare no conflict of interest.


## Funding Sources

No funding sources have been used.


## Author Contributions

Mariam Ayed and Amal Ayed conceptualized the study, and collected and analyzed the data. Mariam Ayed, Javid Ahmed, and Kiran More were involved in the writing of manuscript and critically reviewing the draft. Hamid Hussain, Ammar AlQurashi, and Najla Alrajaan were involved in data collection and drafting the manuscript. Final manuscript was approved by all the authors. Mariam Ayed is the corresponding author and is responsible for the accuracy of the data.

## Data Availability Statement

All data regarding the case presented are included in this. Further inquiries can be directed to the corresponding author.

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