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ORIGINAL ARTICLE

Neonatal Effects of Maternal Magnesium Sulphate in Late Preterm and Term Pregnancies

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Abstract

Aim To compare the clinical, obstetric and neonatal parameters between patients with > 34-week gestation having severe preeclampsia receiving magnesium sulphate and those with > 34-week gestation with preeclampsia but not receiving magnesium sulphate.

Materials and Methods Single-centre prospective study studied 60 patients in each of the two groups. Magnesium sulphate was administered by Pritchard regimen as per standard protocol. Standard obstetric management was followed for both groups. In the severe preeclampsia/eclampsia group, maternal blood sample was analysed for serum magnesium levels. The duration of exposure, the amount of magnesium sulphate received and time elapsed between last dose of magnesium sulphate and delivery were all noted. Neonatal assessment was done. The various parameters including age, parity, blood pressure, mode of termination of pregnancy, NICU admission rate, incidence of hypotonia in the newborn and other neonatal parameters were tabulated and compared.

Results The two groups were comparable with respect to age and parity. Need for induction of labour was higher in the group with severe preeclampsia/eclampsia. Rate of LSCS and birth weights were comparable between the two groups. NICU admission rate and incidence of hypotonia were higher in those who received magnesium sulphate. Amount of

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magnesium sulphate received and total duration of magnesium sulphate did not correlate with NICU admission rates.
Conclusions Neonatal morbidity, in terms of higher NICU admission rates and hypotonia, is higher in patients receiving magnesium sulphate.

Keywords Magnesium sulphate · Neonatal · Neuroprotection · Hypotonia · NICU admission

Introduction

The use of magnesium sulphate as prophylactic anticonvulsant in severe preeclampsia and management of eclampsia is established and is proven to improve maternal outcomes. The use of magnesium sulphate as a neuro-protective agent in preterm deliveries is also approved. While the advantages for the neonates due to administration of magnesium sulphate in early preterm pregnancies are well established, whether such an advantage exists for late preterm deliveries and term deliveries is not clearly resolved. In this context, the focus of this study is the neonatal effects among women receiving magnesium sulphate for maternal indications.

Aims and Objectives

The aims and objectives of the study were as follows:

a. To document the clinical parameters.
   - Patients with $>$ 34-week gestation having severe preeclampsia receiving magnesium sulphate.
   - Patients with $>$ 34-week gestation having preeclampsia but not receiving magnesium sulphate.

b. To compare the obstetric and neonatal outcomes between the above groups.
c. To study the association between magnesium sulphate administration and neonatal outcomes.

Materials and Methods

A single-centre comparative study was conducted at a tertiary care hospital after due institutional ethics committee approval. Patients who were admitted to the labour ward with $\geq$ 34 weeks of live gestation were included. Sixty patients with preeclampsia/eclampsia receiving magnesium sulphate as per Pritchard regimen were included in one group. Sixty matched patients with preeclampsia, not requiring magnesium sulphate or any other anticonvulsants, were included in the other group. The study was done over 1 year. Standard definition of Pritchard regimen (magnesium sulphate injection given intravenous loading dose of 4 g over 10 min followed by 5 g as a deep intramuscular injection and maintenance therapy in the form of 5 g intramuscularly every 4 h, after ensuring the presence of patellar reflex; adequate urine output and no respiratory depression) was followed. Patients with any different dosages of magnesium sulphate due to any reasons, patients who required discontinuation of magnesium sulphate due to toxicity, those with chronic medical disorders and those with anomalous foetuses and antepartum haemorrhage or any other coexisting major obstetric problems were excluded. Due informed consent was obtained by the patients and relatives. Standard obstetric management of the patients was followed, and there was no change due to inclusion in the study. In both groups, the details recorded were age, parity status, previous history of preeclampsia, the presence of anaemia, severity of blood pressure, need for induction of labour, mode of delivery, birth weight outcomes and NICU admission rates. In the severe preeclampsia/eclampsia group, blood sample from the mother was analysed for serum magnesium levels. Blood samples were collected before delivery, immediately centrifuged to separate serum, and haemolysed samples were discarded. Serum magnesium level was done with the same kit, and similar methodology was followed for all patients. The duration of exposure to magnesium sulphate, the amount of magnesium sulphate received and time elapsed between last dose of magnesium sulphate and delivery were all noted. Neonatal assessment was done by the neonatologist as is usual protocol. To avoid bias, the biochemical technicians and the neonatologists were blinded to the study. Magnesium levels in neonate were not studied.

Statistical Analysis

Sample size calculation was based on the frequency of patients encountered in the department. Around 100 patients of severe preeclampsia/eclampsia are managed in the department over 1 year. Owing to possible fitting into exclusion criteria or denial of consent, 40% attrition was assumed and sample size was taken as 60 to be completed in 1 year.

Data were entered in the case record form, and comparison between test and control groups was done. Qualitative and quantitative tests—Chi-square test, Pearson's Chi-square test and Fishers exact test, were used. Results were tabulated and analysed.

Results

As shown in Table 1, majority of the patients belonged to the age groups 22–30. The two groups were comparable in this parameter. Among 120 patients, primigravida were 55% and multigravidae were 45% and the difference was

Table 1 Age and parity distribution

Classification	Severe preeclampsia group	Mild preeclampsia group	$n = 60$ in each	Comments
Age distribution				
18–22	14 (23.3%)	9 (15%)	23 (19.2%)	P value = > 0.05
22–26	30 (50%)	18 (30%)	48 (40%)	
26–30	7 (11.7%)	15 (25%)	22 (18.3%)	
30–34	6 (10%)	12 (20%)	18 (15%)	
Above 34	3 (5%)	6 (10%)	9 (7.5%)	
Parity distribution				
Primigravidae	38 (63.3%)	28 (46.7%)	66 (55.0%)	P value = 0.067
Multigravidae	22 (36.7%)	32 (53.3%)	54 (45%)	
No	26 (43.3%)	11 (18.3%)	37 (30.8%)	

Table 2 Severity of blood pressure, mode of delivery and birth weight distribution

Classification	Severe preeclampsia	Mild preeclampsia	Comments
Blood pressure			
< 120/80	5 (8.3%)	0	Blood pressure mentioned is the highest blood pressure recorded
120/80–140/90	9 (15.0%)	4 (6.7%)	
140/90–160/110	23 (38.3%)	47 (78.3%)	
> 160/110	23 (38.3%)	9 (15.0%)	
Mode of termination of pregnancy			
Induction	34 (56.7%)	43 (71.6%)	P value = 0.007
Spontaneous	26 (43.3%)	17 (28.4%)	
Mode of delivery			
Vaginal	48 (80.0%)	44 (73.3%)	P value > 0.05
LSCS	12 (20.0%)	16 (26.7%)	
Birth weight			
< 2 kg	9 (15.0%)	1 (1.7%)	$P = 0.071$
2–2.5 kg	24 (40.0%)	21 (35.0%)	
2.5–3 kg	20 (33.3%)	27 (45.0%)	
3–3.5 kg	6 (10.0%)	10 (16.7%)	
≥ 3.5 kg	1 (1.7%)	1 (1.7%)	

not significant. The two groups were comparable in respect of parity distribution. Among 49 patients who had previous pregnancy beyond 20 weeks (not presented in table), 33% had history of preeclampsia in previous pregnancy, while 37% did not. Hence, with respect to these parameters, the two groups were comparable.

As shown in Table 2, in 15% of patients in mild preeclampsia group, though the highest blood pressure recorded was more than 160/110 mmHg, it was a single-reading remote from delivery and they did not require magnesium sulphate administration.

Higher proportion ($P < 0.05$) of patients in the mild preeclampsia group required induction of labour when compared to the severe preeclampsia group. The rate of LSCS in both the groups was comparable. Low birth weight was observed in 45.8% in the severe preeclampsia group and 36.7% with mild preeclampsia. However, this difference was not statistically significant ($P = 0.071$).

There were no neonatal deaths in this study. As shown in Table 3, rate of NICU admission was 21.7% among neonates of mother receiving magnesium sulphate, which was significantly different than the 5% among those not receiving the same. 11.7% of neonates who were exposed to magnesium sulphate had hypotonia while only 1.7% neonates among those not exposed had hypotonia, which was statistically significant. These two findings form the crux of this article. 10% of neonates of mother receiving magnesium sulphate had respiratory distress, while only 3.3% neonates among not receiving the same had similar problem. This difference was not statistically significant. The time taken for meconium passage in neonatal life was similar between the two groups.

Table 3 Neonatal outcomes distribution

Classification	Test	Control	Comments
NICU admission			
Yes	13 (21.7%)	3 (5.0%)	$P = 0.007$
No	47 (78.3%)	57 (95.0%)	
Hypotonia			
Hypotonia	7 (11.7%)	1(1.7%)	$P = 0.028$
Normal tone	53 (88.3%)	59 (98.3%)	
Respiratory distress			
Yes	6 (10%)	2 (3.3%)	$P = 0.143$
No	54 (90%)	58 (96.7%)	
Meconium passage			
< 6 h	19 (31.7%)	19 (31.7%)	P value > 0.05
6–12 h	29 (48.3%)	36 (61.0%)	
More than 12 h	12 (20.0%)	5 (7.3%)	

As shown in Table 4, among 13 neonates with NICU admission, nine neonates were exposed to ≤ 24 g of magnesium sulphate in utero. There was no relation between the cumulative dosage of magnesium sulphate and rate of NICU admission. Similarly, ten neonates admitted to NICU were exposed to ≤ 18 h of magnesium sulphate. There was no relation between duration of exposure to magnesium sulphate and rate of NICU admission. The mean maternal serum magnesium level was 5.2 meq/l and a standard deviation of 1.6 meq/l. This range is well within therapeutic range. 48.3% of patients had magnesium level 4–6 meq/dl. The maternal magnesium level did not correlate with NICU admission rate. However, the time elapsed since administration of last dose of magnesium sulphate correlated with the NICU rate; the closer the last dose of magnesium sulphate the higher the rate of NICU admission.

Discussion

Magnesium sulphate is well established as the treatment of choice for prophylaxis of preeclampsia and for treatment of eclampsia. Maternal adverse effects are minimal, and safety is well established [1]. For the preterm foetuses, antenatal magnesium sulphate therapy acts as a neuroprotective agent and is now introduced in most guidelines [2]. However, systematic reviews opine that there is no evidence for administration of magnesium for neuro-protection of the term infant [3]. Hence, the study of the neonatal effects of magnesium sulphate—the apparently indispensable drug for maternal benefit—formed the basis of the study. The administration of magnesium sulphate, hence, raises concerns not only for the doctors but also for nurses and midwives [4]. In our study, the obstetric outcomes were comparable. Mode of delivery and birth weight remained comparable among the groups.

Neonatal Effects of Magnesium

NICU admission rate was 21.7%, which was much higher in the control group not receiving magnesium sulphate. This high rate is comparable to that reported by Greenberg et al. [5]. Similar results were found by the same authors in two different study cohorts also [6, 7].

In our study, the occurrence of neonatal hypotonia was around 11%, which is much higher than in the group not exposed to magnesium. The rate was 17% in the study by Das et al. [8]. In a large retrospective cohort study by Abbasi-Ghanavati et al. [9] also, occurrence of neonatal hypotonia corresponded to increasing neonatal magnesium levels.

In our study, the occurrence of respiratory distress was comparable among both groups. However, this finding is different from that reported by Greenberg and Riaz et al. where a higher rate of respiratory distress was found.

The time elapsed for meconium passage was similar among both groups. However, the slowing down effect of magnesium on the gastrointestinal system of the neonate is well established, with a study by Havranek et al. [10] reporting even effects on intestinal blood flow velocity.

Relation of NICU Admission Rate to Magnesium Levels

In our study, though the NICU admission rate was higher, there was no relation to the dose of magnesium sulphate or the duration of administration of the same. Our findings are different from Greenberg et al. [5], who found a duration-dependent and dose-dependent increase in the rate of NICU admission. A study conducted by Sherwin et al. [11] had

Table 4 Details of magnesium sulphate received (Dose, duration, duration between last dose and delivery; level before delivery)

	NICU admission yes	No NICU admission	
Total dose of magnesium received before time of delivery			
Only loading (14 g)	3 (18.8%)	13 (81.3%)	*P* value = 0.506
Loading + 1 dose (19 g)	5 (31.3%)	11 (68.8%)	
Loading + 2 doses (24 g)	1 (9.1%)	10 (90.9%)	
Loading + 3 doses (29 g)	0 (0.0%)	5 (100.0%)	
Loading + 4 doses (34 g)	3 (33.3%)	6 (66.7%)	
Loading + 5 doses (39 g)	1 (50.0%)	1 (50.0%)	
Loading + 7 doses (49 g)	0 (0.0%)	1 (100.0%)	
Duration of exposure to magnesium before delivery			
< 6 h	4 (23.5%)	13 (76.5%)	*P* value = 0.341
6–12 h	5 (31.3%)	11 (68.8%)	
12–18 h	1 (6.3%)	15 (93.8%)	
18 or more hours	3 (21.7%)	8 (78.3%)	
Time elapsed since last dose of magnesium before delivery			
1–2 h	6 (13.6%)	13 (68.4%)	*P* value = 0.0441
2–3 h	1 (6.7%)	14 (93.3%)	
3–4 h	1 (6.7%)	14 (93.3%)	
4–5 h	3 (37.5%)	5 (62.5%)	
> 5 h	2 (66.7%)	1 (33.3%)	
Maternal serum magnesium level just prior to delivery			
2–4 meq/dl	3 (21.4%)	11 (78.6%)	*P* value = 0.0964
4–6 meq/dl	5 (17.2%)	24 (82.8%)	
6–8 meq/dl	3 (30.0%)	7 (70.0%)	
8–12 meq/dl	2 (28.6%)	5 (71.4%)	

concluded that foetal effects due to use of magnesium sulphate can be correlated with magnesium levels. Higher maternal magnesium levels corresponded higher levels of foetal problems like lower Apgar score. It was also found that maternal and neonatal magnesium levels also show good correlation. However, a review article by Drassinower [12] concluded that magnesium sulphate exposure does not appear to increase need for neonatal resuscitation. But this was a study involving preterm neonates also.

In our study, a correlation was found between occurrence of NICU admission and the proximity of the time at which magnesium sulphate was administered, it is recommended that a trained neonatologist to be present when a baby exposed to magnesium during labour is delivering. The maximum duration for which magnesium sulphate was administered in our patient was 24 h. However, regimens of prolonged administration of the same (ranging up to many days) can cause bone problems in neonates [13].

Limitations of the Study

We did not study intrapartum foetal rate patterns. Duffy et al. [14] have shown that intrapartum foetal heart patterns are affected by magnesium sulphate administration. Importantly, they also concluded that there were no effects on overall neonatal outcomes. We did not study patients with intravenous regimen. However, Indian studies have proven the similarity in outcomes between intravenous and intramuscular regimens [15]. One of the limitations of the study is that it did not account for variables such as maternal BMI. It is being proven nowadays that maternal BMI has a significant bearing on the effect of magnesium sulphate and requires monitoring [16].

Differences in the effects of the drug between mild preeclampsia and severe preeclampsia may be due to differences in pharmacokinetics also. While Brookfield et al. have proven a difference in the pharmacokinetic properties between preeclampsia and non-preeclampsia, it can be inferred that such a difference may exist between severe and non-severe preeclampsia also and probably explains neonatal effects. This is to be considered in future studies [17]. The ideal study to test the effect of magnesium on neonatal outcomes would be one comparing the same with patients receiving other anticonvulsants. However, since magnesium is established as the *optimus unus* anticonvulsant, it would be difficult to perform such a study. Hence, the closest comparison group being mild preeclampsia not receiving magnesium sulphate was used in this study.

To conclude, even when the mode of delivery and birth weights were comparable, a higher NICU admission rate and a higher rate of neonatal hypotonia were observed. Thus the neonatal effects of administration of magnesium sulphate for maternal indication is definite.

Implications of the Study

A recent study was published in BJOG which surveyed practice of usage of magnesium in various institutions across many countries. It was found that the non-protocol-based use of magnesium sulphate was very high, especially in developing countries; and almost 24% of the usage was in mild preeclampsia, where its use may be questionable [18]. On the other hand, one recent review has stated that magnesium sulphate should be considered even in mild preeclampsia [19]. In this scenario, where magnesium sulphate use is widespread, with a hint at probable over usage, and likely expansion in the nature of use, our study assumes significance. Before such recommendations, the adverse effects on neonatal outcomes due to magnesium sulphate should be considered. Further studies may be required to study effects of different dosing patterns and routes of administration.

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Compliance with Ethical Standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Since it was a retrospective review of records, no informed consent was obtained from any patients for being included in the study. This article does not contain any studies with animal subjects.

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