High Versus Low Dose of Magnesium Sulfate as Initial Tocolytic Agent for Preterm Labour in Symptomatic Placenta Previa

Original Article

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ABSTRACT

Objective: To assess the efficacy and safety of alternative magnesium sulfate regimens used as single tocolytic therapy for preventing preterm labor in patients with symptomatic placenta previa and subsequent changes in cervical length.

Methods: The study was a randomized clinical trial conducted from December 2020 to August 2022 at Assiut Women's Health Hospital, Egypt, including pregnant women from 28 to 37 weeks of gestation with a singleton fetus in PTL and symptomatic placenta previa. The eligible women were randomized to either (group 1 or 2). The primary outcome was evaluating the efficacy of two different regimens of magnesium sulfate in postponing delivery in patients with P.P. in PTL for 48 hours and changes in cervical length.

Results: Clinical and pregnancy prolongation data showed no significant difference between the two therapy regimens. The high-dose group had a considerably longer cervical length (cm) at 48 hours (p<0.001). The low-dose group had a lower 4-hour magnesium serum level (3.98±0.60 vs. 4.80±0.91; p<0.001). Furthermore, when comparing subgroups based on obesity, our analysis revealed a significant increase in non-obese women delivering after 48 hours in high and low groups. Cervical length after 48 hours (cm) was also increased in the non-obese high-dose group (p<0.030). Non-obese pregnancies treated with high-maintenance tocolysis achieve a therapeutic level of magnesium than obese patients(36.1% vs.6.9%, p=0.007).

Conclusions: A high magnesium sulfate regimen in symptomatic preterm P,P in non-obese women may be related to potential clinical prolongation of pregnancy, an increase in cervical length, and achieving therapeutic magnesium levels.

Key Words: Cervical length; magnesium sulfate; magnesium level; placenta previa; tocolysis.

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INTRODUCTION

Placenta previa is adisease in which the placenta grows on or near the internal os. Placenta previa can be threatening for both the mother and the baby. It can cause PTL, which leads to a higher neonatal mortality and morbidity rate. Placenta previa can lead to the death of the mother. In developed countries, the rate of maternal death is 0.03%[1].

Placenta previa patients may have clinical or subclinical uterine contractions. Both may be associated with vaginal bleeding. Symptomatic placenta previa can be treated with medicines that inhibit uterine contractions[3]. Tocolytic medications reduce uterine contractions, preventing preterm labor. They include beta-adrenergic agonists, calcium channel blockers, magnesium sulfate, oxytocin receptor antagonists, progesterone, and prostaglandin synthesis inhibitors[2].

Magnesium sulfate (MgSO4-7H2O) has the same tocolytic effects as beta-mimetic drugs, but it has less of an immediate effect on the heart and blood vessels of the mother. It lowers the amount of calcium inside cells, preventing contracting[4].

Not enough data was released about other primary healthcare outcomes for mothers and babies, such as birth less than 48 hours after administering magnesium sulfate (a severe composite infant outcome or a composite serious mother outcome). Furthermore, there is not much evidence that magnesium sulfate tocolytic helps prolong pregnancy and reduce premature births.

The present study aimed to evaluate the effectiveness and safety of different magnesium sulfate regimens when used as a single tocolytic therapy to avoid premature labor in women with placenta previa and changes in the cervix length. Additionally, investigate the effect of maternal obesity on the effectiveness of the treatment.

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PATIENTS AND METHODS

This study was a single-blinded randomized clinical trial, registered on clinical trial (clinical trial.gov NCT04599868), Conducted from the 1st of December 2020 to the 20th of August 2022. At Assiut Women's Health Hospital, Egypt, on pregnant women presented with PTL and bleeding per vagina diagnosed as placenta previa. The study was approved by Assiut Medical School Ethical Review Board (IRB 17101293).

Patients were included in the trial if they met the following criteria: singleton pregnancy, gestational age between 28 and 37 weeks, placenta previa with preterm uterine contractions (3 contractions in 10 minutes), and the ability to provide informed permission. We excluded the patients with placental abruption, placenta previa with a severe attack of bleeding necessitating immediate delivery, clinical criteria of intrauterine infection, IUGR, fetal anomalies, fetal distress, IUFD, PROM, treatment with any tocolytic agent before maternal transport, inability or refusal to provide informed consent, and women with any contraindication for the use of magnesium sulfate as patients with renal failure.

All patients were maintained in bed during the initial evaluation. Demographic data were collected, including patient age, gravidity, parity, maternal history of previous placenta previa or preterm labor, gestational age at admission and delivery, and history of any uterine surgery. Current or past history of renal problems, history of treatment with any tocolytic agent before attendance to our center.BMI was calculated for all patients.

All patients underwent clinical examination. Measurement of blood pressure and pulse to evaluate the hemodynamic stability of patients, and the temperature was also measured to help to exclude chorioamnionitis. The number of uterine contractions in 10 minutes and their duration were evaluated. Offensive vaginal discharge and bleeding were assessed by inspection of soaked pads and the number of blood clots. We asked about the presence or absence of cervical cerclage.

Ultrasound examination was done for all patients to determine the fetus's viability. There number (singleton or twin or higher order pregnancy), placental site to diagnose placenta previa and its degree, fetal weight and fetal biometry were measured to exclude IUGR, amniotic fluid, and cervical length also measured.NST was done for all patients to exclude fetal distress.

The length of the cervix was measured with a transvaginal ultrasound probe placed in the anterior fornix of the vagina while the bladder was empty. The cervix was measured three times along the line made by the interface of the mucosal surface, with calipers placed at the notches made by the internal and external os.

Randomization

Computer-generated random number allocation with consecutively numbered opaque envelopes assigned patients to one of two magnesium sulfate therapy schedules. After meeting the entrance criteria and providing written consent, patients were assigned to treatment groups by selecting the next numbered envelope.

Intervention

All patients who met the criteria for inclusion in the study received a 4 g intravenous loading dose of magnesium sulfate on 150 ml saline over 20 minute period. Patients then received maintenance therapy with magnesium sulfate at either 1g / h (low dose group) or 2g/h (high dose group), depending on random assignment.

Patients of both groups were assessed hourly for pulse and blood pressure, contraction frequency, and vaginal bleeding. With strict monitoring for urine output, tendon reflexes in the form of knee jerk and respiratory rate for early detection of symptoms of magnesium sulfate toxicity.

Patients in whom bleeding continued and became severe and affected hemodynamic stability and contractions did not subside or developed manifestations of toxicity were considered to have treatment failure, and tocolytic therapy was discontinued and managed according to our hospital protocol for these patients.

Successful tocolysis was marked by postponing delivery for 48h - till administration of dexamethasone - and occurrence of fewer than four contractions per hour; each should be less than 30 seconds and stopping of bleeding or reaching 37 weeks. Once adequate tocolysis was achieved, or therapy was judged to be failed according to the criteria described here, magnesium infusion was discontinued.

All patients received dexamethasone to enhance fetal lung maturity. Four doses of dexamethasone were administrated as 6 mg /12h intramuscular over 48 h. The patient did not receive prophylactic antibiotics during tocolysis but received penicillin for group B streptococcal prophylaxis if delivery is imminent

RH status was determined for all patients, and those with (-ve) RH received anti - D, to prevent ISO immunization.

Cervical length was measured after 24 h and 48 h from the administration of magnesium sulfate in both groups. Maternal serum magnesium was measured at admission and after 4 hours after administration of magnesium sulfate, 2 ml of blood were collected and centrifuged at 2000-3000 revolutions / min. Serum magnesium level was measured by Dimension Rxl Max clinical chemistry system. Patients of both groups were assessed for their neonatal outcomes,

including deaths, gestational age at delivery, and fetal birth weight. Apgar score at five minutes, and neonatal ICU admission and duration of admission.

Study outcomes

The primary outcomes

1. Evaluate the efficacy of different regimens 0f magnesium sulfate in postponing delivery in patients with .placenta previa in preterm labor for 48 h.

2. Different regimens of magnesium sulfate and changes in cervical length (at admission and after 24 h and 48 h)

Secondary outcomes, such as birth weight and gestational age at delivery. Apgar score at five minutes, admission to the neonatal intensive care unit, and length of admission are also evaluated.

Sample size calculation

Based on determining the primary outcome variable, the estimated minimum required sample size is 130 patients (65 in each group). We calculated the sample size using G*power software 3.1.9.2., based on the following assumptions: The primary outcome variable is the efficacy of low-dose vs. high-dose MgSO4 in postponing preterm labor in cases of placenta previa. As no studies had been conducted to study this, we hypothesized that medium effect size was found for large doses (expected to postpone delivery more hours than low doses). A primary statistical test is a t-test to detect the difference between two groups.

Alpha = 0.05 Power = 0.80 Effect size = 0.5 Allocation ratio= 1

Statistical analysis

All data were analyzed using a statistical package for social science (SPSS software Chicago, IL, USA, version 25.) Comparison between categorical variables in both groups was done by Chi-square test. Continuous variables were compared using Mann–Whitney U test (two groups) or Kruskal–Wallis test (more than two groups). The Pearson correlation test calculated the correlation analysis of variables. For statistical analysis, we tested the data for normality by the Shapiro-Wilkes test. A two-sided $P<0.05$ was considered statistically significant.

RESULTS

Analysis of data between two study groups (high and low dose MgSO4)

We recruited 130 patients from one center in one country from 2020 through 2022. The CONSORT flowchart of the patients is shown in (Figure 1). The key sociodemographic feature of enrolled participants was the equal distribution of both groups. There is no statistically significant difference between the studied groups as regards their age, residence, parity, BMI, and obesity class, with the mean age of High dose MgSO4 group being 32.03 ±6.03 years versus 32.38 ±5.36 years among Low dose MgSO4 group. Pregnant women demonstrated higher BMI (30.76 ±4.88 vs. 30.09 ±5.83) in both groups (Table 1). All enrolled participants completed the study, and there were no withdrawals.

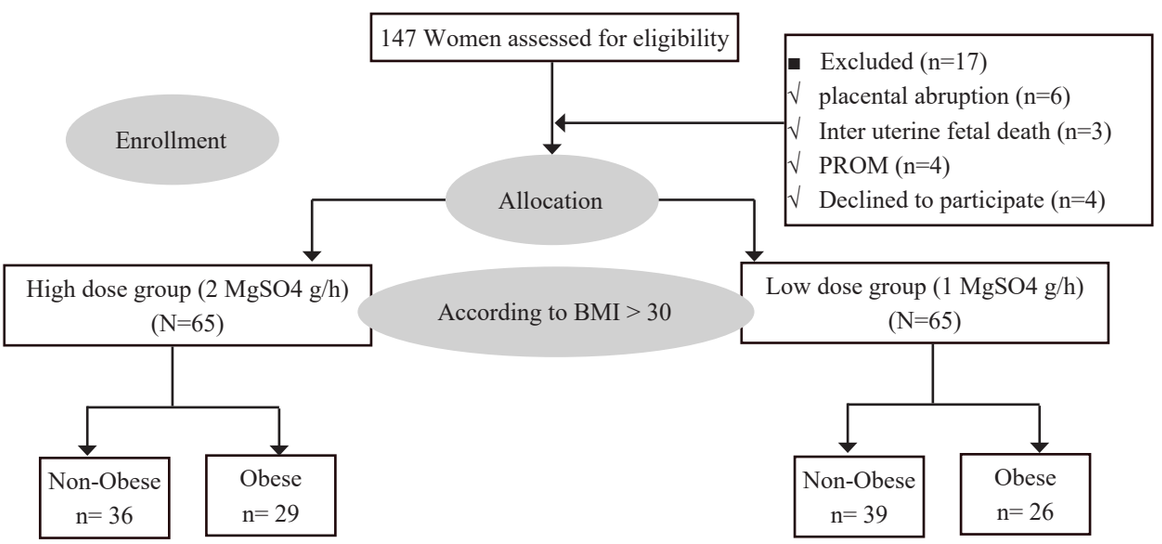

Fig. 1: The CONSORT flowchart of the patients.

Table 1: Demographic data in the two studied groups

Variables		Group				*p value*
		High dose MgSO4 (N=65)		Low dose MgSO4 (N=65)		
Age (years)		32.03 ± 6.03		32.38 ± 5.36		0.645
BMI (kg/m2)		30.76 ± 4.88		30.09 ± 5.83		0.204
		n	%	n	%	
Residence	rural	20	30.8%	25	38.5%	0.461
	urban	45	69.2%	40	61.5%	
Parity	Primigravida	6	9.2%	5	7.7%	0.753
	Multigravida	59	90.8%	60	92.3%	
Obesity class	Non obese	36	55.4%	39	60.0%	0.782
	obese I	16	24.6%	13	20.0%	
	obese II	9	13.8%	7	10.8%	
	obese III	4	6.2%	6	9.2%	

Prolongation of pregnancy in study groups showed that there was a non-significant difference in regards to Gestational age at first attack of bleeding (weeks) (34.11 ±1.24 versus 33.69 ±1.53 weeks, p = 0.055), Gestational age at delivery (weeks) (35.31 ±1.96 versus 35.15 ±1.77 weeks, p=0.427) and time from tocolysis to delivery (days) (12.51 ±8.40 versus 12.05 ±9.37 days, p=0.647). Delivery within 48 hours of the onset of bleeding was 16.9% versus 24.6% in the high-dose MgSO4 and low-dose MgSO4 groups, respectively (Table 2).

There was a significant improvement in mean cervix length in the two groups, from (2.16) in the Low dose of MgSO4 group at admission to (2.55) 48 hours later of follow-up and from (2.18) in the High group dose of MgSO4 group at admission to (2.85) at 48 hours later of follow up; otherwise, there was no significant difference. Also, each group had a highly significant difference (P <0.001) between admission time and other times; however, not clinically significant (Table 2).

Our study means Mg level was in the Low dose of MgSO4 group (3.77 ±0.60) at admission and (3.98 ±0.60) at the 4 hours follow-up examination, while in the high dose of MgSO4 group, the mean Mg level was (3.94 ±0.40) at admission and (4.80 ±0.91) at the four-hour follow-up examination. There was a non-significance difference (P>0.05) between both groups at admission but significant after 4 hours (P<0.05). There was a high significance difference (P<0.000) regarding the significant difference between baseline and 4 hours in each group. Moreover, Cases receiving a low dose had a lower serum magnesium level than those receiving a 6-gram as maintenance and were less likely to achieve a therapeutic level (7.7% vs. 23.1%) (Table 3).

It was found that was no statistically significant difference concerning blood transfused, number of full-term babies, neonatal ICU admission, Apgar score at five minutes <7, and fetal weight (gm). In this study, we can see that blood transfused was 9.2% versus 13.8%, the number of full-term babies was 13.8% versus 10.8%, neonatal ICU admission was 7.7% versus 15.4%, and Apgar scores at five minutes <7 6.2% versus 12.3% in comparing high dose MgSO4 group versus low dose MgSO4 group. No patients in any of the groups had admission to ICU. Mean fetal weight (gm). (2271.02 ±166.64 vs 2257.57 ±189.19) in high dose vs. low dose of MgSO4 groups (Table 4).

Table 2: Prolongation of pregnancy and cervical length in the two studied groups

Variables		Group				*p value*
		High dose MgSO4 (N=65)		Low dose MgSO4 (N=65)		
Gestational age at first bleeding (weeks) Mean ±SD Median (range)		34.11 ±1.24 34.00 (28.00-36.00)		33.69 ±1.53 34.00 (28.00-36.00)		0.055
Gestational age at delivery (weeks) Mean ±SD Median (range)		35.31 ±1.96 36.00 (34.00-37.00)		35.15 ±1.77 35.00 (34.00-37.00)		0.427
Time from tocolysis to delivery (days) Mean ±SD Median (range)		12.51 ±8.40 15.00 (1.00-42.00)		12.05 ±9.37 13.00 (1.00-42.00)		0.647
		n	%	n	%	
Delivery	<48 h from first bleeding	11	16.9%	16	24.6%	0.280
	>48 h from first bleeding	54	83.1%	49	75.4%	
Cervical length at admission (cm) Mean ±SD Median (IQR)		2.18 ±0.43 2.20 (1.40-3.10)		2.16 ±0.32 2.00 (1.50-3.00)		0.644
Cervical length after 24 hours (cm) Mean ±SD Median (IQR)		2.37 ±0.44 2.40 (1.60-3.30)		2.27 ±0.43 2.30 (1.20-3.10)		0.262
Cervical length after 48 hours (cm) Mean ±SD Median (IQR)		2.85 ±0.35 2.90 (1.90-3.70)		2.55 ±0.25 2.50 (2.20-3.20)		<0.001*
P- value for within groups		<0.001*		<0.001*		

*Statistically significant as $p<0.05$.

Table 3: Mg level before and after treatment in the two studied groups

Variables	Group				*p value*
	High dose MgSO4 (N=65)		Low dose MgSO4 (N=65)		
Mg level at admission (mg/dl) Mean ±SD Median (IQR)	3.94 ±0.40 4.00 (4.00-4.20)		3.77 ±0.60 3.89 (3.60-4.00)		0.065
Mg level after 4 hours (mg/dl) Mean ±SD Median (IQR)	4.80 ±0.91 4.60 (4.60-4.80)		3.98 ±0.60 4.00 (3.90-4.30)		<0.001*
	n	%	n	%	
Achieve a therapeutic level of Mg (4.8-8.4) mg/dl	15	23.1%	5	7.7%	0.015*

*Statistically significant as $p<0.05$.

Table 4: Maternal and fetal outcomes in the two studied groups

Variables	Group				RR (95%CI)	*p value*
	High dose MgSO4 (N=65)		Low dose MgSO4 (N=65)			
	n	%	n	%		
Blood transfused	6	9.2%	9	13.8%	0.780 (0.409-1.486)	0.410
Number of full term babies	9	13.8%	7	10.8%	1.145 (0.715-1.834)	0.790
Neonatal ICU admission	5	7.7%	10	15.4%	0.639 (0.306-1.335)	0.272
Apgar score at five minutes <7	4	6.2%	8	12.3%	0.467 (0.133-1.636)	0.364
Fetal weight (gm)	2271.02 ±166.64		2257.57 ±189.19			0.668

Analysis of Data Between Two Study Subgroups (High and Low Dose Mgso4) as A Function of Bmi (Obese and Non-Obese)

The mean time from tocolysis to delivery (days) was prolonged to 15.00 ±5.32 days in non-obese compared to 9.41 ±10.40 days in obese subjects in the high-dose group. Moreover, in the low-dose magnesium sulfate group, in the present study, the mean magnesium sulfate dose was increased by 13.67 ±8.08 days in the non-obese and by 9.62 ±10.75 days in the obese, with a statistically significant difference between sub-groups within the same group. From our results in the high-dose magnesium sulfate group, we can see that delivery <48 h from first bleeding was 5.6% versus 31.0% in non-obese and obese pregnant women. While the low-dose magnesium sulfate group, it is clear that among pregnant women who were not obese and those who were obese, the delivery rate within 48 hours of the first bleeding was 15.4% versus 38.5% (Table 5).

Table 5: Prolongation of pregnancy in the study subgroups

Variables		Group							
		High dose MgSO4 (N=65)				Low dose MgSO4 (N=65)			
		Non obese (N=36)		Obese (N=29)		Non obese (N=39)		Obese (N=26)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gestational age at first bleeding (weeks)		34.31	0.58	33.86	1.73	33.67	1.51	33.73	1.59
p-value			0.940				0.695		
Gestational age at delivery (weeks)		35.81	0.79	35.03	1.18	35.44	0.99	35.12	1.21
p-value			0.040*				0.441		
Time from tocolysis to delivery (days)		15.00	5.32	9.41	10.40	13.67	8.08	9.62	10.75
p-value			<0.001*				0.030*		
		n	%	n	%	n	%	n	%
Delivery from first bleeding	≤48 hrs.	2	5.6%	9	31.0%	6	15.4%	10	38.5%
	>48 hrs.	34	94.4%	20	69.0%	33	84.6%	16	61.5%
p-value			0.002*				0.035*		

*Statistically significant as $p<0.05$.

The most surprising aspect of the data is the cervical length. There were no statistically significant differences ($P>0.05$) between the subgroups at any point in time in either the high or low magnesium sulfate dose groups, except after 48 hours (P 0.05) between non-obese and obese patients in the high dose group (p=0.030). The mean cervix length in the two subgroups in high dose from (2.23 ±0.51) in the non-obese women at admission to (2.94 ±0.41) 48 hours later of follow-up and from (2.12 ±0.31) in the obese women at admission to (2.76 ±0.26) at 48 hours later of follow-up.

There was no statistically significant difference ($P>0.05$) between the two subgroups in the high and low magnesium sulfate groups at admission. But after 4 hours, the non-obese and obese patients in the high-dose group showed a significant difference ($P<0.05$). Non-obese patients that received a high dose had a higher serum magnesium level than obese patients that received a 6-gram load and were more likely to reach a therapeutic level (36.1% vs. 6.9%).

Correlation Between Mg Level and Other Variables (Bmi and Apgar Score <7)

We found a moderate negative correlation between Mg level change (Δ) with level BMI (r = -0.391) and Apgar score <7 (r = -0.330) among high dose MgSO4 cases, and it was statistically significant ($p < 0.001$ and p=0.007).

DISCUSSION

Few published studies support prescribing a tocolytic in patients of preterm symptomatic placenta previa, even though this treatment significantly prolongs pregnancy. These results (Besinger *et al*., 1995) reported that 112 women were randomly assigned to receive tocolysis or no tocolysis[5]. Tocolysis in symptomatic placenta previa was related to a clinically significant delay in premature birth. Tocolysis significantly improved clinical indicators, such as the time between admission and birth (39.2 versus 26.9 days, p 0.02). Similar findings were reported by (Sharma *et al*., 2004) found that there was a significant correlation between the usage of tocolysis in symptomatic placenta previa and a lengthening of the duration of pregnancy (25.33 vs. 14.47 days, P-0.05)[6].

Contrary to expectations, this study showed that in a multicenter randomized controlled trial, maintenance tocolysis with nifedipine was compared to placebo in 109 women who had received 48 hours of tocolysis and antenatal corticosteroids because of placenta previa

with antepartum bleeding[7]. No significant changes in the pregnancy length or the baby's health were seen. So, maintenance tocolysis to keep a pregnancy going longer is not advised. However, suppose you have signs like uterine contractions or bleeding before birth. In that case, you should use tocolysis carefully for up to 48 hours (to allow administration of corticosteroids or transfer of care)[7-9].

These studies tend to prove a relationship between the use of tocolysis and prolongation in pregnancy. Consequently, we estimated the difference between high and low dose MgSO4 tocolysis on prolongation of pregnancy, the mean (SD) gestational age at randomization was 34.11 weeks (1.2 weeks) in the high dose MgSO4 group and 33.69 weeks (1.5 weeks) in the low dose MgSO4 group. Gestational age at delivery was similar between groups, with a mean (SD) of 35.31 weeks (1.5 weeks) for the high-dose MgSO4 group and 35.15 weeks (1.7 weeks) for the low-dose MgSO4 group (p = 0.427). Both groups had similar rates of pregnancy prolongation (mean (SD): 12.51 days (8.4 days) for the high dose MgSO4 group and 12.05 days (9.3 days) for the low dose MgSO4 group; p = 0.647. In the present study, delivery <48 h from first bleeding was 16.9% versus 24.6% in the high-dose MgSO4 group versus the low-dose MgSO4 group.

According to cervix length, There was a non-significant difference (*P*>0.05) between both groups at different times except after 48 hours (*P*<0.05). There was a significant difference (*P*<0.000) regarding Cervical length between baseline and different times in each group, but still not clinically significant. These results reflect those of (Rozenberg *et al*., 2004), who also found that on admission, the median (IQR) cervical length was 18 (13, 22) mm. After tocolysis was terminated, the median (IQR) variance in cervical length was 3 (0, 8) mm, ranging from -13 to 26 mm[10]. In a study of 214 patients with arrest Preterm Labor, 109 patients received magnesium sulfate and had a cervical length (2.3 ±0.9) at randomization and (2.6 ± 1.2) at the 48 hours' follow-up examination[11]

Our study Mg level before and after treatment reported a non-significant difference (*P*>0.05) between both groups at admission. However, after 4 hours, there was a significant difference (*P* <0.05). There was a significant difference (*P* <0.001) between Mg levels before and after treatment in each group. This difference is comparable to differences between low and high doses in Mg level reported by (Westermann *et al*., 2022), who reported that women who received a load of 4 g of magnesium had a lower serum magnesium level (3.99 ±0.68) compared to those who received a load of 6 g of magnesium (4.37 ±0.71) and had a decreased chance of reaching a therapeutic level (12.9% vs. 27.6%)[12].

From maternal and fetal outcomes data, there was no significant difference (*P*>0.05) between both study groups regarding all variables. This comes in agreement with a study by (Khalifa *et al*., 2019) that reported that patients with preeclampsia were given either a loading dose of MgSO4 or a loading dose plus a maintenance dose for 12 or 24 hours[13]. There was no significant difference between the two groups' effects on the mother and baby. This outcome is contrary to (Behrad *et al*., 2003), who found that no patients had their therapy stopped due to side symptoms such as respiratory depression, severe hypotension, or pulmonary edema. In terms of birth weight (P= 0.01), 5-minute Apgar scores (P= 0.018), percent of the neonatal need for neonatal intensive care unit (NICU), number of days spent in NICU (P= 0.013), and severe neonatal morbidity like respiratory distress syndrome (P= 0.01), the results in pregnancies randomized to receive high-dose magnesium sulfate were significantly different from the low dose group[14].

Other clinical reviews and toxicology studies (Ciarkowski&Stalburg, 2010; Hunter and Gibbins, 2011; Alauddin *et al*., 2011) also show that the drug is safe to use for its intended purposes, in the recommended doses, and according to a standard protocol for giving the drug and keeping an eye on it. The results of this comprehensive review add to what is known about how often and how harmful side effects are when the drug is used correctly[15-17].

Until this point in our analysis, we found that magnesium sulfate treatment at a low dose was just as effective as treatment at a high dose, with no difference regarding adverse effects.

In terms of the amount of magnesium in the blood, the effect of the magnesium sulfate dose calculated using the actual body weight was the same as that calculated using the corrected ideal body weight in obese people. Changes in the pharmacokinetics of many medications are caused by increased fat tissue and muscle mass[18]. Also, diseases that are linked to obesity reduce this population's physiological reserves[19]. Even though magnesium sulfate is helpful in many areas of medicine, it has side effects like pulmonary edema, so it is essential to assess the effect of obesity on the achieved therapeutic dose of magnesium sulfate and its effect on the primary outcome of delayed delivery >48 h from first bleeding.

For more analysis, patients were divided into subgroups according to obesity. Regarding time from tocolysis to delivery (days) in the high-dose magnesium sulfate group, in the present study, there was a significant difference concerning time from tocolysis to delivery (days) and delivery when compared between subgroups according to obesity.

Regarding cervical length (cm), except for after 48 hours (P 0.05) between non-obese and obese patients in high dose group (p=0.030), there was no statistically

significant difference (P>0.05) between the subgroups at any point in time in both high and low magnesium sulfate dose groups.

Additionally, there was a non-significant difference (P>0.05) between both subgroups at the admission Mg level in the high and low mgso4 groups. However, after 4 hours, there was a significant difference (P <0.05) between non-obese and obese patients in the high-dose group. A recent study (De Zoysa *et al*., 2022) found that women receiving a 4-g load obese women were less likely to achieve a therapeutic level than non-obese women. Among women receiving a 6-g load, obese women were less likely to achieve a therapeutic level than non-obese women[20]. Interestingly, the results of another RCT in obese women with preeclampsia, the alternative dosing schedule of a 6g IV loading dose followed by a 2g/hr IV maintenance dose is more likely to reach therapeutic serum magnesium concentrations defined as at least 4.8 mg/dL[21]. The time needed to reach a steady state and maternal weight is correlated linearly. BMI significantly influences magnesium levels, and obese women (especially those with BMI > 30 kg/m2) may experience subtherapeutic magnesium levels[22].

Finally, in our results cases with high doses of MgSO4, there was a moderately negative correlation between Mg level change ((Δ)) and level BMI and Apgar score, which was statistically significant. The results of our study support the results of previous retrospective trials and prospective pharmacokinetic modeling, which show that the dose needs to increase with BMI to get serum magnesium concentrations that are the same as those in pregnant women with the average body weight, no matter what threshold is used to define a therapeutic serum magnesium concentration[23].

Similar attitudes to neuroprotective efficacy expressed by (Vilchez *et al*., 2018) in this study evaluated that increasing the dose of MgSO4 in obese moms may improve neuroprotective efficacy without causing an increased risk to the mother[24]. Considering the cost of analyzing this association, the current analysis may serve as the foundation for reasonable practice. Magnesium's neuroprotective effects may be multifaceted. Magnesium influences brain injury pathways. Magnesium reduces excitotoxic calcium-induced damage as a non-competitive NMDA antagonist. Magnesium reduces extracellular glutamate during ischemia, lowering excitotoxicity. Magnesium reduces calcium influx through voltage-gated channels, reducing apoptosis[25].

Magnesium decreases oxidative stress and pro-inflammatory cytokines interleukin-6 and TNF- alpha. Magnesium shortage raises endothelial nitric oxide, promoting endothelial dysfunction. This could entail decreased calcium influx, phagocytic cell activation, neurotransmitter release, or nuclear factor kappa B suppression[26].

Strengths and limitations

The investigators who analyzed and reported the outcomes were blinded to the identity of the participants and the results, which minimized observer bias. Additionally, according to our knowledge, assessment of the effect of obesity and Mgso4 dose effect on patients in preterm labor and symptomatic placenta previa has not been researched before. Our study was carried out on a balanced cohort regarding baseline characteristics; despite its strengths, the study has some problems that need to be considered as it is a small study that only looked at one center.

CONCLUSIONS

Using two different magnesium sulfate regimens does not improve maternal or perinatal outcomes nor lengthen the duration of pregnancy. According to the findings of this study, treatment with high magnesium sulfate in cases with non-obese symptomatic preterm previa may be related to clinically significant lengthening of pregnancy and increased cervical length. Compared to loading maintenance of 1 g/h, a maintenance dose of 2 g/h of magnesium sulfate produces a therapeutic level 4 hours after delivery with significantly greater reliability.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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