Original Article

Doppler Velocimetry Changes After Administration of Magnesium Sulfate in Severe Preeclampsia : Mansoura Experience

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ABSTRACT

Aim: Intravenous administration of MgSO4 to pregnant women with severe preeclampsia to prevent seizures in pregnant females with severe preeclampsia.

Materials and Methods: This study was conducted at Mansoura University Hospital from November 2018 to December 2019. Doppler indices of uterine artery, umbilical artery (UA), fetal middle cerebral artery (MCA) were measured before, 20 minutes after IV loading dose of 6gm of MgSO4, and after administration of maintenance dose of 1gm/hr. of MgSO4 for 24 hours.

Results: There was a significant difference between maternal heart rate, systolic, diastolic and mean blood pressure before and 20 minutes after administration of loading dose of MgSO4 (*p value* < *0.001*) and a significant difference also before and after completing administration of maintenance dose of MgSO4 (*p value* < *0.001*). There was a significant difference between RI, PI, and S/D ratio of uterine artery, UA, and MCA before and 20 minutes after administration of loading dose of MgSO4 (*p value* < *0.001*) and a significant difference also between before and after 24 hours (*p value* < *0.001*). The cerebroumbilical ratio had significant change as regards RI and S/D. However, there was no significant change as regards PI. The decrease in Doppler parameters of MCA was more than the decrease in those of UA.

Conclusion: IV administration of the loading dose then the maintenance dose of MgSO4 resulted in decrease in Doppler indices of uterine artery, UA, fetal MCA and increased cerebroumbilical ratio indicating improved fetal cerebral perfusion and affinity of cerebral vessels to MgSO4.

Key Words: Doppler ultrasound, hypertension, magnesium sulfate, middle cerebral artery, preeclampsia, umbilical artery, uterine artery

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INTRODUCTION

Preeclampsia (PE) is a diseases of diffuse vascular endothelial dysfunction and vasoconstriction that takes place after 20 weeks of gestation and can manifest up to four to six weeks post-partum[1]. In developing nations, the incidence of the disease is reported to be 4-18%, with hypertensive disorders being the second most frequent obstetric cause of stillbirths in those regions and the second most common cause of direct maternal mortality globally[2].

Preeclampsia is defined as the presence of a systolic blood pressure (SBP) of 140 mm Hg or higher, or a diastolic blood pressure (DBP) of 90 mm Hg or higher, on two occasions at least four hours in between in a previously-normotensive patient after 20 weeks of pregnancy, associated with proteinuria of more than or equal to 0.3 gm in a 24-hour urine sample[3].

PE with severe features might be defined as the presence of one of the following criteria: SBP more than or equal to 160 mm Hg or DBP of more than or equal to 110 mm Hg, impaired hepatic function, progressive renal insufficiency ,new onset cerebral or visual disturbances, pulmonary edema, or thrombocytopenia (platelet count <100,000/µ L)[3].

Magnesium sulfate ($MgSO_4$) can be prescribed to pregnant women for different indications and, therefore, different physio pathologic roles, such as neuroprotection of the fetal brain, prevention of eclampsia, or tocolysis[4].

The action of MgSO4 on cerebral arteries is still debatable. MgSO4 might reduce the risk of cerebral hemorrhage and cerebral palsy in neonates and infants respectively. The protection against brain injury might result from blocking N-methyl-D-aspartate receptors, blocking calcium channels inhibiting the action of vasoconstrictor agents, and by direct arterio-dilator effect of Mg[5].

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Doppler ultrasound is thought to be a useful tool to predict the diagnosis of PE and unfavorable pregnancy prognosis. Uterine artery might be the most convenient vessel to be used for Doppler assessment of PE, as it might represent the vascular condition of the mother. Umbilical and fetal middle cerebral arteries are usually used for fetal status evaluation. Evaluating the changes in the arteries with Doppler ultrasound might reveal the fetal adaptation to the pathology[6].

However, studies investigating the hemodynamic actions of MgSO4 might be controversial. Some studies did not reveal any statistically significant difference in vascular resistance of umbilical artery, fetal middle cerebral artery, or uterine arteries on administering MgSo4[7,8]. However, other studies showed significant decrease of Doppler indices of umbilical, fetal MCA and uterine arteries[6,9,10]. Meanwhile, in other studies there were heterogenecity between the different indices[11-13].

It is crucial to study the hemodynamic impact of MgSO4 on uterine arteries, umbilical and fetal middle cerebral arteries Doppler velocimetry indices in patients with severe preeclampsia. This may further determine the hemodynamic effect of MgSO4, consolidate the use of $MgSO_4$, clarify the effect of different regimens of MgSO4 on maternal and fetal hemodynamics, enhance the use of maintenance dose of MgSO4 and help to define an accurate tool to monitor the fetus.

AIM OF THE STUDY

The aim of the study was to evaluate Doppler velocimetric parameters (resistance index [RI], pulsatility index [PI], and systolic/diastolic [S/D] ratio) of uterine, umbilical and fetal middle cerebral arteries prior to and after MgSO4 injection in pregnant females with severe preeclampsia.

PATIENTS AND METHODS

This Quasi-experiment study was conducted on 100 women diagnosed with severe preeclampsia admitted to the department of Obstetrics and Gynecology from November 2018 to December 2020.

Inclusion criteria: Gestational age 28 weeks or more. Diagnosed as severe preeclampsia[3]. Systolic blood pressure (SBP) more than 160 mmHg or diastolic blood pressure (DBP) more than 110 mmHg and proteinuria.Or SBP ≥140 mmHg or DBP ≥90 mmHg (with presence or absence of proteinuria) and one or more of the following signs: Serum transaminase level ≥2 times upper limit of normal for a specific, or both.<100,000 platelets/micro-L. Progressive renal impairment (serum creatinine > 1.1 mg/dL), or doubling of serum creatinine level without other kidney disorder; singleton pregnancy, patients not in labor.

Exclusion criteria: Multiple gestations.Fetal anomalies (diagnosed by ultrasound). IUGR. Maternal chronic disease especially DM, chronic HTN, renal disease, epilepsy and CNS lesion. Women with genital bleeding, abruption placentae, PROM, or absent or reverse end-diastolic flow in the UA (by Doppler ultrasound). Contraindications to use of MgSO4 especially hypersensitivity to MgSO4 or myasthenia gravis. Patients receiving antiplatelet drugs eg. Low dose Aspirin or Patients receiving anticoagulants eg. Heparin. Symptoms of severe disease-severe headache or persistent progressive headache, characteristic vision abnormalities, or epigastric/ right upper quadrant pain unresponsive to analgesics.

Ethical approval: The study was approved by the local institutional ethical committee and an informed oral written consent was taken from all participants after full explanation of the steps and significance of this study.

Study methods : After taking a verbal and written consents, patients admitted to MUH and meeting the criteria of selection were subjected to: Full history taking; Particularly manifestations including headache, visual affection, stomach pain, edema, oliguria and seizures (time and number). Physical examination; General, abdominal (obstetric) and pelvic examinations (if indicated). Accurate measurement of maternal blood pressure:

Blood pressure was acquired following at least five min of rest, with the case sitting with feet down and in a semi-reclining situation with back supported and with the arm supported and at heart level. A sphygmomanometer was utilized, with a cuff of 20 × 60 cm encircling at least 80 percentage of the upper arm. The initial audible sound (Korotkoff I) is the SBP and the disappearance of sound (Korotkoff V) is the DBP. However, if sounds were audible with the cuff deflated, which may occur in pregnancy, then Korotkoff IV (abrupt muffling) was utilized[14].

1st measure: for the diagnosis of severe preeclampsia just before administration of loading dose (6 gm) of magnesium sulfate. 2nd measure: just after intravenous administration of loading dose (6 gm) of magnesium sulfate. 3rd measure: after completing administration of maintenance dose.

Assessment of routine laboratory investigations. Complete blood count, blood group, RH, fasting blood sugar, 2-hour postprandial blood glucose, ALT, AST, serum creatinine and urine analysis. Assessment of fetal status; transabdominal obstetric ultrasound examination was done for verification of GA, viability, presentation, weight of the fetus, position and grade of placenta, liquor quantity, calculating PPB, and exclusion of multifetal gestation and fetal anomalies. Verification of GA was done via measurement of BPD, HC, AC, and FL. Fetal heart rate (FHR) was assessed by cardiotocography.

Doppler study; examinations were carried out dorsal position using Samsung Medison SONOACE R3 portable ultrasound machine (Medison Co., Ltd., Seoul, Korea) equipped with a Medison CN2-8 Convex [2-5 MHz] transabdominal probe. Scans of the vessels were acquired throughout fetal inactivity, in durations of apnea and in cases without uterine contractions[15]. Low frequency filters were utilized to minimize the risk of artifact owing to the vascular walls motions. The size of the volume sample was adjusted according to the vessel diameter and the angle of insinuation was <30 degree.

Umbilical artery Doppler: The uterine content is scanned to choose a space of amniotic cavity with many loops of cord. After that, utilizing a pulsed wave Doppler on a free loop of cord, the Doppler cursor line was aligned with the vessel axis with the angle of insinuation as close to zero as possible. The Doppler sample volume was then placed in the vascular lumen encompassing it and the waveforms were recorded[16].

Middle cerebral artery Doppler: It was estimated by acquiring the transverse aspect of brain of the fetus at the BPD level. The transducer was moved towards the skull base at the lesser wing of the sphenoidal bone level. By utilizing color flow image, the MCA was visualized as a great division of the circle of Willis, running antero-laterally between the anterior and the middle cerebral fossae. The Doppler cursor line was aligned with the vessel axis with the angle of insinuation as close to zero as possible[17].

Care should be taken to apply minimal pressure to the maternal abdomen with the transducer, as fetal head compression is associated with alterations of intracranial arterial waveforms[17].

Uterine artery Doppler: It was performed with the abdominal probe positioned 2 cm medial to the ASIS. Subsequently, the probe was guided laterally and downward in which the uterine artery passes beside the lateral wall of the uterus and color flow mapping function was then overlaid. The probe is tilted sideways but still maintaining its medial angulation, until the uterine artery is visualized as it crosses the external iliac artery, having originated from the internal iliac artery. The sample volume was positioned one cm below the point of apparent cross over before any branching of the uterine arteries[18].

The mean indices of the two uterine arteries were measured manually as the arithmetic mean between the corresponding indices of the left and right arteries. An early diastolic notch was present when there was a visibly defined upturn of the flow velocity waveform at the beginning of diastole[18].

For each studied vessel, when the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and then the Doppler indices (S/D ratio, RI, PI) generated automatically from the machine. At least the mean value of three different readings were taken before the last values were acquired.

1st evaluation: Before administration of loading dose (6 gm) of magnesium sulfate. 2nd evaluation: 20 minutes after intravenous administration of loading dose (6 gm) of magnesium sulfate over 20 minutes. 3rd evaluation: after completing administration of maintenance dose.

Regimen of magnesium sulfate: 10% magnesium sulfate heptahydrate ($MgSO_4$•7H2O) [Egyptian International Pharmaceutical Industries Company] ampoules were used.

The magnesium sulfate is administrated according to the regimen of six gm IV over twenty min as a loading dosage then by IVI at a rate of one gm / h for 24 hours [19].

Clinical assessment for magnesium toxicity was performed every four hours. The maintenance dosage was only given when a patellar reflex was found, respirations exceeded 12 breaths/minute and urine output exceeded 100 mL over four hours.

An ampoule containing 1 g (10 mL of a 10%solution) calcium gluconate was kept at the bedside to be utilized for IV injection as an antidote in patients with magnesium toxicity. Resuscitation and ventilator support were also available.

Follow up of the patients was done with registration of mode of delivery and neonatal outcome as regards Apgar score and NICU admission.

STATISTICAL ANALYSIS

IBM's SPSS statistics (Statistical Package for the Social Sciences) for windows (version 25, 2017) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution.

All tests were conducted with 95% confidence interval. P (probability) value < 0.05 was considered statistically significant. Charts were generated using SPSS' chart builder and Microsoft Excel for windows 2019.

Continuous Group differences : For pair-wise comparison of data (within subjects), the follow-up values were compared to their corresponding basal value using paired samples T-test or Wilcoxon matched pairs signed ranks test

Categorical Group differences : Comparison of follow-up data (within subjects) was conducted using Wilcoxon signed ranks test and McNemar test for ordinal and nominal data respectively.

RESULTS

The main characteristics of the participants including age, body mass index gravidity, and gestational age are represented in Tables 1. The age of the studied group ranged from 18 to 37 years with mean 25 years and SD ± 4.12, BMI ranged from 27 to 34 with mean 30 and SD ± 2.06 while gestational age ranged from 28 to 34 weeks with mean 32.04 weeks and SD ± 1.52.

There was a significant difference between maternal heart rate, systolic, diastolic and mean blood pressure before and 20 minutes after administration of loading dose of mg sulfate (*p value* < *0.001*) and a significant difference also before and after completing administration of maintenance dose of mg sulfate (*p value* < *0.001*) as shown in Tables 2 and 3.

There was a highly significant difference between RI, PI, and S/D ratio of uterine artery, UA, and MCA before and 20 minutes after administration of loading dose of mg sulfate (*p value* < *0.001*) and a highly significant difference also between before and after 24 hours (*p value* < *0.001*) as shown in Tables 4 and 6.

The cerebroumbilical ratio had significant change as regards RI and S/D. However, there was no significant change as regards PI.

The decrease in Doppler parameters of MCA was more than the decrease in those of UA as shown in Tables 7 and 8.

Neonatal outcome and mode of delivery was shown in Table 9 showing 89% elective C.S rate and 16% NICU admission rate.

Table 1: Age, BMI, Gravidity, and Gestational age of the studied patients

	Mean and SD	Median	Minimum	Maximum
Age	25.12 ± 4.12	24.00	18	37
BMI	30.04 ± 2.06	29.80	27	34
Gravidity	2.69 ± 1.14	3.00	1	5
Gestational age	32.04 ± 1.52	32	28	34

Data is expressed as mean and SD, median, Minimum, and Maximum.

Table 2: Basal and post-treatment maternal heart rate of the studied patients

Heart rate	All patients (n= 100)				
	Mean and SD	Median	Minimum	Maximum	*P*
Basal (beat/minute)	83.30 ± 11.79	84.00	55	108	-
20 minutes (beat/minute)	87.88 ± 8.9	88.75	65	105	< 0.001
24 hours (beat/minute)	88.06 ± 8.88	89.00	64	107	< 0.001

Data is expressed as mean and SD, median, Minimum, and Maximum. *P* is significant when < *0.05*.

Table 3: Basal and post-treatment systolic, diastolic and mean blood pressure of the studied patients

Blood pressure		All patients (n= 100)				
		Mean & SD	Median	Minimum	Maximum	*P*
SBP(mmHg)	Basal	170.6 ± 23.53	170	115	220	-
	20 minutes	156.6 ± 14.46	160	120	185	< 0.001
	24 hours	155.15 ± 16.04	155	110	195	< 0.001
DBP(mmHg)	Basal	102.7 ± 15.86	100	65	135	-
	20 minutes	93.5 ± 10.24	95	65	120	< 0.001
	24 hours	98.5 ± 11.29	100	65	130	0.005
MBP(mmHg)	Basal	147.97 ± 20.69	147.50	98	188	-
	20 minutes	135.54 ± 12.53	137	102	163	< 0.001
	24 hours	136.27 ± 13.94	137	95	173	< 0.001

Data is expressed as mean and SD, median, Minimum, and Maximum. *P* is significant when < *0.05*.

Table 4: Basal and post-treatment RI, PI, and S/D ratio of uterine artery

Studied Vessel	Doppler index	Study	Mean and SD	*P value*
Uterine artery	RI	Basal	0.68 ± 0.1	-
		20 minutes	0.6 ± 0.08	< 0.001
		24 hours	0.57 ± 0.08	< 0.001
	PI	Basal	1.02 ± 0.31	-
		20 minutes	0.97 ± 0.23	< 0.001
		24 hours	0.96 ± 0.24	< 0.001
	S/D	Basal	2.94 ± 0.58	-
		20 minutes	2.58 ± 0.44	< 0.001
		24 hours	2.56 ± 0.44	< 0.001

Data is expressed as mean and SD. *P* is significant when < *0.05*.

Table 5: Basal and post-treatment RI, PI, and S/D ratio of umbilical artery

Studied Vessel	Doppler index	Study	Mean and SD	*P value*
Umbilical artery	RI	Basal	0.68 ± 0.12	-
		20 minutes	0.6 ± 0.09	< 0.001
		24 hours	0.57 ± 0.08	< 0.001
	PI	Basal	1.02 ± 0.31	-
		20 minutes	0.97 ± 0.23	< 0.001
		24 hours	0.96 ± 0.24	< 0.001
	S/D	Basal	2.56 ± 0.48	-
		20 minutes	2.44 ± 0.37	< 0.001
		24 hours	2.37 ± 0.36	< 0.001

Data is expressed as mean and SD. *P* is significant when < 0.05.

Table 6: Basal and post-treatment RI, PI, and S/D ratio of fetal middle cerebral artery

Studied Vessel	Doppler index	Study	Mean and SD	*P value*
Middle cerebral artery	RI	Basal	0.71 ± 0.09	-
		20 minutes	0.59 ± 0.06	< 0.001
		24 hours	0.57 ± 0.06	< 0.001
	PI	Basal	1.42 ± 0.37	-
		20 minutes	1.4 ± 0.37	< 0.001
		24 hours	1.37 ± 0.39	< 0.001
	S/D	Basal	3.2 ± 0.58	-
		20 minutes	3.05 ± 0.56	< 0.001
		24 hours	3.05 ± 0.56	< 0.001

Data is expressed as mean and SD. *P* is significant when < 0.05.

Table 7: Changes in the studied arteries Doppler readings after $MgSO_4$ therapy

	Uterine artery	Umbilical artery	MCA
RI	-0.11 ± 0.05	-0.11 ± 0.08	-0.15 ± 0.09
PI	-0.14 ± 0.15	-0.05 ± 0.09	-0.06 ± 0.12
S/D	-0.38 ± 0.23	-0.15 ± 0.13	-0.18 ± 0.21

Data is expressed as mean and SD.

Table 8: Comparison of basal and post-treatment values of cerebroumbilical ratio

	Basal	After treatment	*P*
RI	0.96 ± 0.11	1.01 ± 0.12	0.002
PI	0.71 ± 0.07	0.71 ± 0.06	0.72
S/D	0.8 ± 0.07	0.78 ± 0.05	0.007

Table 9: Neonatal outcome and mode of delivery

		All patients (n= 100)
Mode of delivery	**Elective CS**	89 (89%)
	Induction	11 (11%)
Apgar	6	5 (5%)
	7	14 (14%)
	8	21 (21%)
	9	27 (27%)
	10	33 (33%)
NICU admission		16 (16%)

Data is expressed as percentage and frequency

DISCUSSION

Research in the last 15 years had demonstrated that preeclampsia is associated with impaired trophoblastic invasion of maternal spiral arteries leading to increased impendance to flow in uterine arteries[2].

Circulation disorders and insufficient placental perfusion in PE induce improper oxygen supply to the fetus with subsequent fetal distress. Evaluating the alterations in the arteries with Doppler ultrasound may reveal the adaptation of fetus with this situation[20].

Magnesium sulfate (MgSO4) can help prevent serious complications in severe preeclampsia[4]. It reduces the risk of eclampsia in antepartum and postpartum women, irrespective of the severity of preeclampsia[21]. It appears to have no fetal complication, but in response to MgSO4 administration, fetal brain perfusion might also alter. It protects against neonatal cerebral hemorrhage, decreases neuronal damage following brain injury and improves survival in extremely low-birthweight infants[22].

Magnesium acts in the extracellular space of vascular smooth muscle inhibiting transmembrane calcium transport, lowering the calcium intake and causing a reduction in the contractile actions of vasoactive agents. It also acts within the cell as a calcium antagonist, modulating the vasoconstrictor action. Thus, it has been recognized that extracellular concentrations of magnesium have role in influencing blood flow, vascular reactivity, and blood pressure in mammals. Hypomagnesaemia causes increased vasoconstriction and hypertension[23].

Unfortunately, 10 women couldn't complete the study. Three women complicated with Magnesium toxicity and managed accordingly while seven delivered within 24 hours; three of them due to fetal distress and four women had progressive course of PE and were uncontrolled.

The current study was done to assess Doppler velocimetric parameters (resistence index [RI], pulsatility index [PI], and systolic/diastolic [S/D] ratio) of uterine, umbilical and fetal middle cerebral arteries prior magnesium sulfate administration in pregnant females with severe preeclampsia and following it.

Our results showed a marked hemodynamic action of IV administration of 6g of MgSO4 in cases with severe preeclampsia following 20 minutes. Following drug infusion, there was a marked decrease in systolic and diastolic BP. In contrast, the maternal pulse increased following the infusion.

These results are similar to those reported by Belfort *et al*., Souza *et al*., and Maged *et al*., suggesting that acute administration of magnesium sulfate in women with severe PE decreases systemic vascular resistance and blood pressure, and increases cardiac output[6,7,10].

Rantonen *et al*., also clarified that following MgSO4 administration for management of seizures; only females with severe preeclampsia revealed a decrease in BP, while the maternal pulse was elevated[24].

In another study, Belfort *et al*., revealed a marked elevation in maternal pulse and a reduction in MAP, but no change in BP. May be owing to the limited number of patients involved in their research giving inaccurate outcomes[25].

Excessive sweating, nausea, flushing and hotness are common complications which occurred after injection of loading dose but these were short lasting.

In preeclampsia, there are abnormal wave forms of UA Doppler which show increase in resistance and decrease in perfusion. Abnormal UA waveform is a strong and independent predictor of fetal outcome[26].

Tarzamni *et al*., showed that the incidence of abnormal UA pulsatility index in both severe and mild preeclampsia is higher than in normotensive pregnant women[27].

The current study revealed a significant decrease in UA Doppler indices following administration of the loading dosage of MgSO4.

These results agree with the studies done by Souza *et al*., and Maged *et al*., who reported a reduction in UA Doppler indices following administration of 6g loading dose of MgSO4 in women with severe preeclampsia[9, 10].

Jamileh *et al*., also showed that after use of 6gm loading and 2g/hr maintenance dose of mg sulfate on 70 women pregnant up to 32 weeks gestational age, UA pulsatility index, resistance index and S/D were significantly decreased after MgSO4 injection[28].

Likewise, Belfort *et al*., 1995 reported that while in patients with normal BP levels the vasodilator action of MgSO4 is not apparent; in cases with PE this influence is marked[29]. That was confirmed when Houlihan *et al*., who studied in vitro effect of mg sulfate on human UA, revealed that MgSO4 encouraged vasodilator effect of the UA with subsequent reduction of vascular resistance[30].

On the contrary, Belfort *et al*., study assessing pregnant women with preeclampsia failed to show any significant reduction in the vascular resistance of the UA as measured by the pulsatility index[7].

Nevertheless, Farshchian *et al*., showed that after injection of 4g loading dose of MgSO4, the mean resistivity index (RI) of the UA showed a statistically significant reduction while the mean pulsatility index (PI) did not have statistically significant changes. Probably, these contradictory results are explained by the small sample size of the above mentioned study, together with the fact that women were not stratified according to severity and most cases consisted of mild preeclampsia; we recruited solely women with severe preeclampsia[12].

The cerebral circulation is a high-impedance bed with low-end diastolic flow. The fetal MCA resistance increases in normal pregnancy slightly and the increase is more substantial in preeclampsia and eclampsia. The administration of MgSO4, therefore, can have beneficial effects on the fetus and can increase perfusion[31].

Much controversy remains regarding the effect on the middle cerebral artery. The present study revealed a significant decrease in fetal middle cerebral artery Doppler indices following injection of the loading dosage of MgSO4.

Our results go hand in hand with Souza *et al*., and Maged *et al*., which found that MCA Doppler indices reveal marked reduction following injection of the 6g of MgSO4[6,10].

On the other hand, Belfort *et al*., Twickler *et al*., and Dasgupta *et al*., displayed that there was no marked reduction in vascular resistance of the fetal MCA. However, we should clarify that the difference in results may be owing to limited number of cases in the initial researches in addition to the concept that most of the pregnant females had mild degrees of PE[7,11,13].

In other studies, Keeley *et al*., and Kovac *et al*., showed increase in RI and PI of MCA respectively. But these studies were conducted for another therapeutic indication of mg sulfate, on women with preeclampsia with premature labour[32,33]. Likewise, Jamileh *et al*., found that the middle cerebral artery PI and RI were increased significantly after MgSO4 injection. These results may be due to the small sample size and use of MgSO4 for different therapeutic indications including women with absent EDV and revered EDV of UA[28].

Farshchian *et al*., also showed that after injection of 4g loading dose of magnesium sulfate, the pulsality index (PI) of the middle cerebral artery showed a statistically significant reduction. However, pre-and post-RI-cerebral did not have marked changes. The limitations of this research was the absence of a control group.

The limited number of cases was an additional limitation, which decreased the test power of PI-umbilical and RI-MCA below 80%[12].

In the present study, we noticed that the reduction in the Doppler velocimetry measurements of the MCA was higher than the reduction in the consequent measurements in the UA.

The affinity of cerebral vessels to MgSO4 was confirmed when Souza *et al*., reported that out of 44 patients with severe PE, 17% revealed alterations in MCA Doppler parameters in the fetus following MgSO4[9]. This results agree with Maged *et al*., which concluded also that degree of decrease in indices of MCA was greater than that of UA[10].

However, Houlihan *et al*., revealed that the vasodilator action of MgSO4 on the MCA is equal to the cord. Thus, the cord/brain percentage kept constant[30].

Several researches established the efficiency of Doppler US examination for evaluation of the fetal vascular condition and have introduced the cerebroumbilical ratio as a measurement in fetal blood supply evaluation. The cerebroumbilical ratio exhibit the alteration in fetal circulation and adaptations in the artery. It is also an adequate indicator for evaluating the fetal growth and prognosis, while the fetal MCA only does not have the identical value[34,35].

As for umbilical/middle cerebral ratios, in this study there was no significant change for PI after the use of MgSO4. However, there was significant difference as regards RI and S/D ratio, which indicates that the fetal blood supply and brain perfusion had improved.

Farshchian *et al*., stated that after injection of MgSO4, C/U ratio (MCA RI/UA RI) had a marked elevation indicating the improvement of fetal blood supply[12]. While Maged *et al*., stated that UA/MCA ratios were the same as regard to PI and RI but S/D ratio showed significant difference[10].

In other researches, Houlihan *et al*., and Souza *et al*., revealed that there is no noticed significant change prior and after the usage of MgSO4 as regards the UA/MCA percentage. This may be due to a mathematical cause. When it reduces the numerator and the denominator, the outcome keeps constant[6,30].

Preeclampsia is characterized by abnormal trophoblastic invasion of the maternal spiral arteries keeping these vessels as high resistance vessels. This can be detected by Doppler studies of the uterine arteries showing high resistance in these vessels[36].

In our study, statistically significant reductions were present in the PI, RI and S/D ratio of the uterine artery following administration of magnesium sulfate in patients with severe preelampsia.

These results agree with the studies done by Maged *et al*., and Jamileh *et al*., which noticed that there was a marked decrease of UA Doppler velocimetry measurements following injection of the first dosage of MgSO4 representing reduced vascular resistance[10,28].

Souza *et al*., also stated that in most of the 40 patients in the study a decrease occurred in the Doppler velocimetry indices of the arithmetical mean of the uterine arteries following infusion of magnesium sulphate, resulting in higher significance levels. Significance levels were lower, however, in isolated vessels. In many of these pregnant women, resistance was normal in the uterine artery ipsilateral to the placenta. Therefore, it is reasonable to speculate that vasodilatation did not occur in this artery, but only in the resistant side[6].

Another study confirmed that vascular resistance is greater in the uterine artery on the opposite side of the placenta and stated that the vasodilatation induced by MgSO4 might increase markedly in vessels with greater resistance[24].

While Schauf *et al*., and Kovac *et al*., suggested a decrease in the uterine artery RI and PI respectively; but, such change was insignificant and may be owing to the limited numbers in their studies[33,37].

None of the above-mentioned studies had evaluated the changes after completing the full dose of magnesium sulfate. The present study is the first study comparing UA, fetal MCA and uterine arteries Doppler indices following full dose of prophylactic MgSO4 in women with severe PE.

In our study, Doppler evaluation of the studied arteries after completing maintenance dose showed significant decrease in Doppler indices, which was more than the decrease obtained after 20 minutes after administration of loading dose of mg sulfate.

Jamileh *et al*., performed Doppler ultrasound after administration of 6g loading dose and 2g/hr maintenance dose of MgSO4 for 12 hours. However, inclusion criteria were different from ours as it included pregnant women up to 32 weeks candidate for use of MGSO4 for different therapeutic indications. It concluded that Intravenous administration of magnesium sulfate resulted in a decrease in PI and RI in UA and uterine artery, and an increase in MCA Doppler indices[28].

Schauf *et al*., evaluated RBCs deformability and blood flow of the uterus in pregnant females with PE or IUGR following the intravenous application of magnesium (1g/h) to 25 pregnant women with reduced uterine blood flow for a period of at least 24 hours. It concluded that a high IV dosage of magnesium over a period of 24 hours dilates the uterine arteries of pregnant women with PE and/or IUGR, increases uterine blood flow and improves the deformability of RBC[37].

We included in our study neonatal outcome as regards Apgar score and NICU admission, as a secondary outcome. Our results are similar to Rezavand *et al*., with 95% of neonates had Apgar score ≥ 7 while 5% of neonates had Apgar score < 7. However, NICU admission rate was 38% while in our study was 16%. This may be due to the small number of cases in the former study which used Pritchard regimen of MgSO4 on 21 pregnant women with severe PE[38].

CONCLUSION

IV administration of the loading dose then the maintenance dose of MgSO4 resulted in decrease in Doppler indices of uterine artery, UA, fetal MCA and increased cerebroumbilical ratio indicating improved cerebral perfusion and affinity of cerebral vessels to MgSO4.

RECOMMENDATION

We recommend multicenteric studies on larger number of patients to optimize safety for mother, fetus, and neonate.

MgSO4 effect on maternal-fetal circulation 12-24 hours after completing maintenance dosage should be studied to investigate whether MgSO4 actions are short-lived and transient.

REFERENCES

1. Redman CW, Sargent ILJS. Latest advances in understanding preeclampsia. 2005;308(5728):1592-4.

2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, *et al*. Global causes of maternal death: a WHO systematic analysis. 2014;2(6):e323-e33.

3. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstetrics and gynecology. 2019;133(1):e1-e25.

4. ACOG. Committee Opinion No. 573: Magnesium sulfate use in obstetrics. Obstetrics and gynecology. 2013;122(3):727-8.

5. Jung EJ, Byun JM, Kim YN, Lee KB, Sung MS, Kim KT, *et al*. Antenatal magnesium sulfate for both tocolysis and fetal neuroprotection in premature rupture of the membranes before 32 weeks' gestation. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018;31(11):1431-41.

6. Souza ASR, Amorim MMR, Coutinho IC, ANC, Marques de Souza Lima M, Noronha Neto C, Natal Figueroa JJHip. Effect of the loading dose of magnesium sulfate (MgSO4) on the parameters of Doppler flow velocity in the uterine, umbilical and middle cerebral arteries in severe preeclampsia. 2010;29(2):123-34.

7. Belfort MA, Saade GR, Moise KJ, Jr. The effect of magnesium sulfate on maternal and fetal blood flow in pregnancy-induced hypertension. Acta obstetricia et gynecologica Scandinavica. 1993;72(7):526-30.

8. Belfort MA, Saade GR, Yared M, Grunewald C, Herd JA, Varner MA, *et al*. Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulfate in patients with preeclampsia. 1999;181(2):402-7.

9. Souza ASR, Amorim MMR, Coêlho ICN, Lima MMdS, Noronha Neto C, Figueroa JNJRdAMB. Doppler of the umbilical and fetal middle cerebral arteries after magnesium sulfate in preeclampsia. 2008;54(3):232-7.

10. Maged AM, Hashem AM, Gad Allah SH, Mahy ME, Mostafa WA, Kotb AJHip. The effect of loading dose of magnesium sulfate on uterine, umbilical, and fetal middle cerebral arteries Doppler in women with severe preeclampsia: a case control study. 2016;35(1):91-9.

11. Twickler DM, McIntire DD, Alexander JM, Leveno KJJO, Gynecology. Effects of magnesium sulfate on preterm fetal cerebral blood flow using Doppler analysis: a randomized controlled trial. 2010;115(1):21-5.

12. Farshchian N, Rezavand N, Mohammadi SJJocis. Effect of magnesium sulfate on Doppler parameters of fetal umbilical and middle cerebral arteries in women with severe preeclampsia. 2012;2.

13. Dasgupta S, Ghosh D, Seal SL, Kamilya G, Karmakar M, Saha D. Randomized controlled study comparing effect of magnesium sulfate with placebo on fetal umbilical artery and middle cerebral artery blood flow in mild preeclampsia at >/= 34 weeks gestational age. The journal of obstetrics and gynaecology research. 2012;38(5):763-71.

14. Ngene NC, Moodley J. Blood pressure measurement in pregnancy and in hypertensive disorders of pregnancy: devices, techniques and challenges. Cardiovascular journal of Africa. 2019;30(2):120-9.

15. Maulik D, Figueroa R. Absent end-diastolic velocity in the umbilical artery and its clinical significance. Doppler ultrasound in obstetrics and gynecology: Springer; 2005. p. 375-86.

16. Maulik D. Doppler sonography: a brief history. Doppler ultrasound in obstetrics and gynecology: Springer; 2005. p. 1-7.

17. Vyas S, Nicolaides K, Bower S, Campbell SJBAIJoO, Gynaecology. Middle cerebral artery flow velocity waveforms in fetal hypoxaemia. 1990;97(9):797-803.

18. Woodward PJ, Kennedy A, Sohaey R. Diagnostic Imaging: Obstetrics E-Book: Elsevier Health Sciences; 2016.

19. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. Clinical pharmacokinetics. 2000;38(4):305-14.

20. Mihu D, Diculescu D, Costin N, Mihu CM, Blaga L, Ciortea R, *et al*. Applications of Doppler ultrasound during labor. 2011;13(2):141-9.

21. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, *et al*. Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. 2002;359(9321):1877-90.

22. Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and Safety of Magnesium Sulfate on Neuroprotection: A Meta-analysis Based on PRISMA Guidelines. Medicine. 2016;95(1):e2451.

23. Makrides M, Crosby DD, Bain E, Crowther CA. Magnesium supplementation in pregnancy. The Cochrane database of systematic reviews. 2014(4):Cd000937.

24. Rantonen T, Kääpä P, Grönlund J, Ekblad U, Helenius

H, *et al*. Maternal magnesium sulfate treatment is associated with reduced brain-blood flow perfusion in preterm infants. 2001;29(7):1460-5.

25. Belfort MA, Saade GR, Grunewald C, Dildy GA, Varner MA, Nisell HJAjoo, *et al*. Effects of blood pressure on orbital and middle cerebral artery resistances in healthy pregnant women and women with preeclampsia. 1999;180(3):601-7.
26. Morris RK, Malin G, Robson SC, Kleijnen J, Zamora J, Khan KS. Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2011;37(2):135-42.
27. Tarzamni M-K, Nezami N, Gatreh-Samani F, Vahedinia S, Tarzamni MJAIM. Doppler waveform indices of fetal middle cerebral artery in normal 20 to 40 weeks pregnancies. 2009;12(1):29-34.
28. Jamileh S, Masoumeh S, Nezamaddin E, Jalileh S, Reza GG, Sedigheh B, *et al*. Effect of magnesium sulfate on middle cerebral, umbilical artery and uterine arteries Doppler parameters in pregnancy up to 32 weeks. 2018;22(94):549-52.
29. Belfort MA, Saade GR, Suresh M, Johnson D, Vedernikov YPJAjoo, gynecology. Human umbilical vessels: responses to agents frequently used in obstetric patients. 1995;172(5):1395-403.
30. Houlihan DD, Dennedy MC, Ravikumar N, Morrison JJJJopm. Anti-hypertensive therapy and the feto-placental circulation: effects on umbilical artery resistance. 2004;32(4):315-9.
31. Berkley E, Chauhan SP, Abuhamad A. Doppler assessment of the fetus with intrauterine growth restriction. American journal of obstetrics and gynecology. 2012;206(4):300-8.
32. Keeley MM, Wade RV, Laurent SL, Hamann VDJO, gynecology. Alterations in maternal-fetal Doppler flow velocity waveforms in preterm labor patients undergoing magnesium sulfate tocolysis. 1993;81(2):191-4.
33. Kovac CM, Howard BC, Pierce BT, Hoeldtke NJ, Calhoun BC, Napolitano PGJAjoo, *et al*. Fetoplacental vascular tone is modified by magnesium sulfate in the preeclamptic ex vivo human placental cotyledon. 2003;189(3):839-42.
34. Prior T, Mullins E, Bennett P, Kumar SJAjoo, gynecology. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. 2013;208(2):124. e1-. e6.
35. Binder J, Monaghan C, Thilaganathan B, Morales-Rosello J, Khalil A. Reduced fetal movements and cerebroplacental ratio: evidence for worsening fetal hypoxemia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018;51(3):375-80.
36. Plasencia W, Maiz N, Poon L, Yu C, Nicolaides KJUiO, Obstetrics GTOJotISoUi, *et al*. Uterine artery Doppler at 11+ 0 to 13+ 6 weeks and 21+ 0 to 24+ 6 weeks in the prediction of pre-eclampsia. 2008;32(2):138-46.
37. Schauf B, Mannschreck B, Becker S, Dietz K, Wallwiener D, Aydeniz B. Evaluation of red blood cell deformability and uterine blood flow in pregnant women with preeclampsia or iugr and reduced uterine blood flow following the intravenous application of magnesium. Hypertension in pregnancy. 2004;23(3):331-43.
38. Rezavand N, Farshchian N, Gaviri A, Veisi F, Jalilian N. Evaluation the effect of magnesium sulfate on the parameters of doppler flow velocity of the uterine arteries and fatal outcomes in severe preeclampsia. 2016;32:1959-63.