



Maternal and Fetal Response to Pre Anesthetic Magnesium Sulphate in Cesarean Section

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Magnesium, the fourth most common cation in the body, has an antagonistic effect at the N-methyl-D-aspartate (NMDA) receptor, as well as calcium-channel blocker properties. Antagonism at the NMDA receptor is thought to alter the mechanism of central hypersensitivity and to subsequently decrease analgesic requirements including opioid consumption. This study aimed to assess the effects of preoperative administration of intravenous magnesium sulphate on the intubation stress response as a primary outcome and uterine, fetal middle cerebral and umbilical arterial blood flow, Apgar score and postoperative analgesia as secondary outcomes in participants undergoing elective caesarian section under general anesthesia.

Methods: This prospective randomized controlled double blinded study was carried out on 65 pregnant females between 21-35 years old undergoing elective caesarian section under general anesthesia. who were randomly classified randomly into two groups: Magnesium sulphate (Mg) group: received 25 mg/kg magnesium sulphate in 100 ml isotonic saline over 10 minutes before induction of anesthesia. Control group (C): received the same volume of isotonic saline over the same period.

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Results: Heart rate and mean arterial blood pressure were decreased significantly at post induction to the end of surgery in mg sulphate compared to control group and was insignificantly different between the studied groups at T0 and T1. VAS was significantly lower in mg sulphate group compared to control group at 1, 2, 4, 8, 12 and 24 hours and was insignificantly different among the two groups at PACU admission and 30 min. preoperative administration of magnesium sulphate (25 mg/kg) was associated with lower postoperative pain scores, less post-operative analgesic consumption, better hemodynamic stability without significant difference in umbilical, middle cerebral and uterine arteries blood flow or Apgar score compared to control group in patients undergoing cesarean section under general anesthesia. There was no statistically significant difference in the incidence of sedation and hypotension. No cases showed respiratory depression in the two groups.

Conclusion: Preoperative administration of magnesium sulphate (25mg/kg) was associated with better hemodynamic stability, lower postoperative pain scores, less post-operative analgesic consumption without significant difference in umbilical, middle cerebral and uterine arteries blood flow or Apgar score with nil complications except for PONV compared to control group in patients undergoing cesarean section under general anesthesia.

Keywords: Magnesium sulphate; N-methyl-D-aspartate and visual analogue scale.

1. INTRODUCTION

Caesarean section is one of the most commonly performed surgical procedures [1]. The use of low concentrations of volatile anesthetics with avoidance of opioids until delivery may induce intraoperative awareness and adverse hemodynamic responses during Caesarean section [2,3]. Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation. It activates many of the enzyme systems involved in energy metabolism and acts as a natural calcium antagonist by regulating calcium access into the cell [4].

Magnesium sulphate has been investigated as an adjuvant for intraoperative analgesia and for reduction of anesthetic requirements. It improves postoperative analgesia by acting as an antagonist of N-methyl-D-aspartate (NMDA) receptors [5,6]. The importance of magnesium sulphate (Mg) in anesthetic practice has been highlighted. It decreases stress of intubation (which is associated with catecholamine release) through reducing its release by the adrenal medulla and adrenergic nerve endings [7]. Also it can be associated with less postoperative complications, such as nausea and vomiting [8]. Also, magnesium sulfate had been proven to be beneficial for neuro protection, as an antiepileptic and as a potent vasodilator [9]. Doppler sonography is an appropriate method to evaluate blood circulation, so it can provide valuable information about fetal condition and wellbeing [10].

This study was designed to assess the effects of preoperative administration of intravenous magnesium sulphate on the intubation stress response as a primary outcome and uterine, fetal middle cerebral and umbilical arterial blood flow, Apgar score and postoperative analgesia as secondary outcomes in participants undergoing elective caesarian section under general anesthesia.

2. PATIENTS AND METHODS

This prospective randomized controlled double blinded study was carried out in Tanta University Hospital in Obstetric and Gynecology Department starting at December 2019 till May 2021 after approval from Institutional Ethics Committee and an informed written consent from all patients. Patients were familiarized with the visual analog scale (VAS, starting from 0, no pain to 100, worst pain imaginable).

Pregnant females between 21-35 years old undergoing elective caesarian section under general anesthesia. The indications for caesarean section included breech presentation, cephalopelvic disproportion and previous caesarean delivery were included.

Patient refusal, hypermagnesemia, magnesium sulphate hypersensitivity, preeclampsia and eclampsia, preterm deliveries, intrauterine growth retardation, diabetes mellitus, hypertension, hepatic diseases, renal disease, any degree of heart block or drug addiction were excluded.

Patients were randomly classified using computer generated random numbers in sealed opaque envelopes into two groups: Magnesium sulphate (Mg) group: patients received 25 mg/kg magnesium sulphate in 100 ml isotonic saline over 10 minutes before induction of anesthesia, Control group (C): patients received the same volume of isotonic saline over the same period.

The study drug was prepared by a dedicated anesthesiologist who was aware of group allocation but had no further role in the study.

Pre-operatively, in the holding area a wide bore intravenous (IV) cannula was inserted. Patients were premedicated with cimetidine 10 mg IV. Standard monitors were applied to each patient including (pulse oximetry, electrocardiogram (ECG), automated non-invasive blood pressure (NIBP). All the baseline parameters were observed and recorded.

Doppler studies including resistance index (RI), pulsatility index (PI), and systolic/ diastolic (S/D) ratio of uterine artery, middle cerebral artery and umbilical artery were recorded by the same investigator with high experience in ultrasound.

Umbilical artery doppler was measured with all patients placed in a semi recumbent position with a left lateral tilt, and then the uterine content is scanned to select an area of amniotic cavity with several loops of cord. Then, using a pulsed wave doppler on a free loop of cord, the characteristic sound and shape of the umbilical artery were identified. When the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and umbilical artery doppler PI was estimated. A minimum of 3 separate readings was averaged before the final values were obtained. Umbilical artery doppler studies were avoided during fetal activity and fetal breathing because of the effect of fetal breathing movements on waveform variability; recording was performed during fetal apnea.

2.1 Sample Size Calculation

Size was calculated using G*Power (Kiel University, Kiel Germany) software version 3.1.9.2.

Based on the results of the previous study, 25 patients were needed in each group to detect a significant difference of 15 beat/minute in the post intubation HR at a study power of 90% and

α error of 0.05. 30 patients were included in each group to avoid dropout cases.

2.2 Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Parametric variables were expressed as mean and standard deviation (SD). Comparison between two variables within the same group was compared by paired T test. Non-parametric variables were expressed as median and interquartile range (IQR) and were analyzed using Kruskal-Wallis test; further analysis was performed by Mann-Whitney (U) test to compare each two groups. Comparison between two variables within the same group was compared by Wilcoxon test.

3. RESULTS

In this study, 74 patients were assessed for eligibility, 9 patients did not meet the inclusion criteria and 5 patients refused to participate in the study. The remaining 65 patients were randomly allocated into two groups (30 patients each). All 65 patients were followed-up and analyzed statistically.

All the demographic data and patients' characteristics including age, weight, BMI, ASA physical status, gravity and parity were comparable between both groups ($P = 0.658, 0.091, 0.683, 0.582, 0.663$ and 0.573 respectively) Table 1.

At T2 to T7, heart rate was decreased significantly in mg sulphate compared to control group ($P = 0.001, 0.001, <0.001, <0.001, <0.001, <0.001$ respectively) and was insignificantly different between the studied groups at T0 and T1 ($P = 0.875$ and 0.071 respectively) Fig. 1.

At T2 to T7, mean arterial blood pressure was decreased significantly in mg sulphate group as compared to control group ($P = 0.009, 0.031, 0.021, 0.0001, 0.0003, 0.0001$) and was insignificantly different between groups at T0 and T1 ($P = 0.869$ and 0.086 respectively) Fig. 2.

VAS was significantly lower in mg sulphate group compared to control group at 1, 2, 4, 8, 12 and 24 hours ($P = 0.015, 0.020, 0.032, 0.015, 0.009,$

0.010 respectively) and was insignificantly admission and 30 min (P = 0.055, 0.125 different among the two groups at PACU respectively) Table 2.

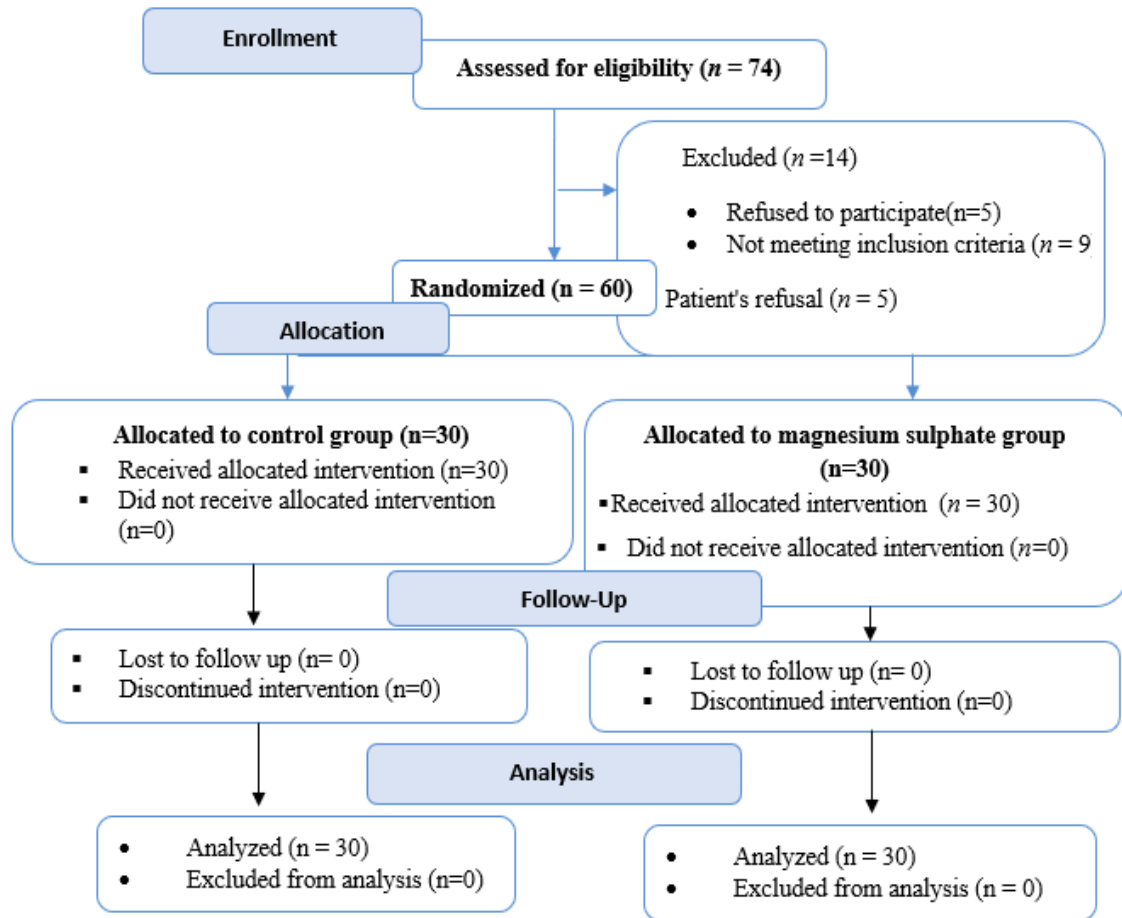


Fig. 1. CONSORT flow diagram of the participants through each stage of the randomized trial

Table 1. Demographic data and patients' characteristics in the studied groups

		Control group	Magnesium sulphate group	P value
Age (years)	Mean ± SD	28.89±4.88	28.27 ± 5.86	0.658
	Range	23-30	21-35	
Weight (kg)	Mean ± SD	72.40±6.65	75.20±5.93	0.091
	Range	64-93	68-90	
BMI (kg/m ²)	Mean ± SD	27.4 ± 3.16	27 ± 4.24	0.683
	Range	21.31-33.71	20.24-35	
ASA physical status	ASA I	22 (73.3%)	25 (83.3%)	0.582
	ASA II	8 (26.7%)	5 (16.7%)	
Gravidity	0 (%)	12 (40%)	12 (40%)	0.663
	1 (%)	8 (26.7%)	8 (26.7%)	
	2 (%)	4 (13.3%)	6 (20%)	
	3 (%)	4 (13.3%)	4 (13.3%)	
	4 (%)	2 (6.7%)	0 (0%)	
Parity	0 (%)	20 (66.7%)	22 (73.3%)	0.573
	1 (%)	10 (33.3%)	8 (26.7%)	

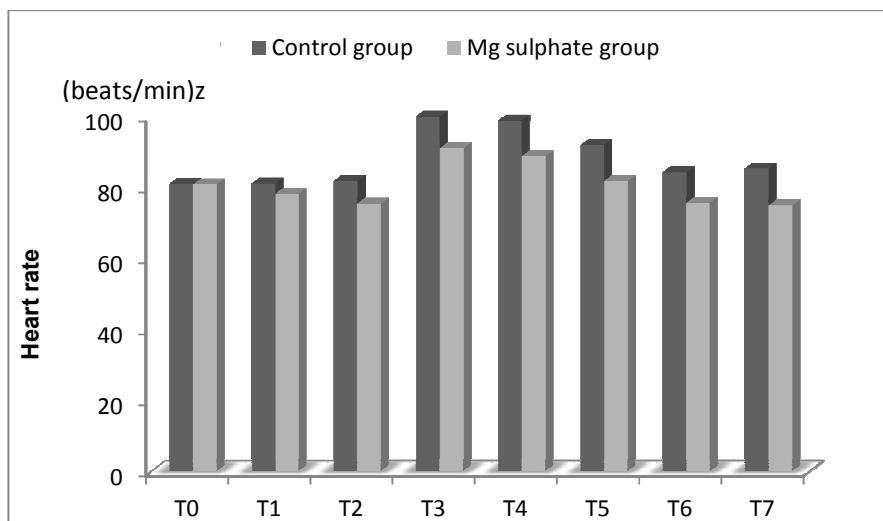


Fig. 2. Heart rate in the two studied groups

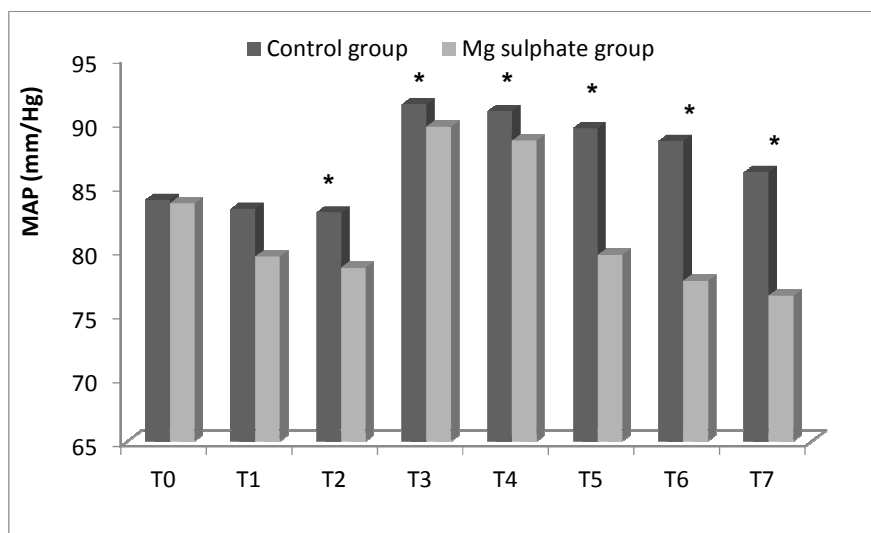


Fig. 3. Comparison of mean blood pressure between two groups

Nausea and vomiting were significantly different between both groups, sedation and hypertension were insignificantly different between both groups Fig. 3.

4. DISCUSSION

The standard general anesthesia for cesarean section does not include opioid until after delivery of the fetus; this may result in increased possibility of hyper sensitization, thereby increased post-operative acute pain and analgesia requirement [11]. Consequently, several analgesic modalities and adjuncts, of which magnesium may be included, have been

studied and reviewed for post caesarean analgesia [12].

The results of our study revealed that preoperative administration of magnesium sulphate (25 mg/kg) was associated with lower postoperative pain scores, less post-operative analgesic consumption, better haemodynamic stability without significant difference in umbilical, middle cerebral and uterine arteries blood flow or Apgar score compared to control group in patients undergoing cesarean section under general anesthesia. Magnesium is a physiologic calcium channel blocker and a non-competitive N-methyl-D-aspartate (NMDA) receptor

antagonist, and these properties appear to play an important role in the prevention and treatment of pre and postoperative pain. NMDA receptor antagonists are best administered before the generation of noxious stimuli in order to prevent central sensitization. On the other hand, magnesium acts on both adrenergic nerve terminals and the adrenal gland by blocking the release of catecholamines produces vasodilatation by acting directly on blood vessels

leading to decreased arterial blood pressure and heart rate. The vasodilator properties of Mg sulphate increase uterine artery blood flow and improve fetal circulation. Increase Mg sulphate increases the production of vasodilator prostaglandins, thereby affecting cerebral vasodilatation. It causes vasodilatation of smaller-diameter intracranial vessels, which account for its neuroprotective effect for the newborn.

Table 2. Comparison of visual analogue scale (VAS) in the studied groups

	Range	Mean ± S. D	95% CI		t. test	p. value
			Lower	Upper		
Pacu control	10 – 60	25.33 ± 14.56	-0.15 – 13.48		1.957	0.055
Pacu Mg sulphate	10 – 50	18.67 ± 11.67				
30 min. control	10 – 50	23.33 ± 10.93	-1.24 – 9.90		1.557	0.125
30 min. Mg sulphate	10 – 50	19.00 ± 10.62				
1 hr. control	10 – 40	28.00 ± 8.87	1.16 – 10.18		2.515	0.015*
1 hr. Mg sulphate	10 – 40	22.33 ± 8.58				
2 hr. control	20 – 60	35.67 ± 11.04	1.07 – 12.27		2.383	0.020*
2 hr. Mg sulphate	10 – 50	29.00 ± 10.62				
4 hr. control	10 – 70	44.67 ± 13.58	0.76 – 15.90		2.203	0.032*
4 hr. Mg sulphate	10 – 70	36.33 ± 15.64				
8 hr. control	20 – 70	39.67 ± 14.26	1.53 – 13.80		2.501	0.015*
8 hr. Mg sulphate	20 – 50	32.00 ± 8.87				
12 hr. control	20 – 60	44.67 ± 9.73	2.17 – 14.49		2.707	0.009*
12 hr. Mg sulphate	10 – 60	36.33 ± 13.77				
24 hr. control	30 – 60	45.00 ± 9.38	1.78 – 12.88		2.645	0.010*
24 hr. Mg sulphate	20 – 60	37.67 ± 11.94				

*: significant as p value < 0.05, VAS: visual analogue scale

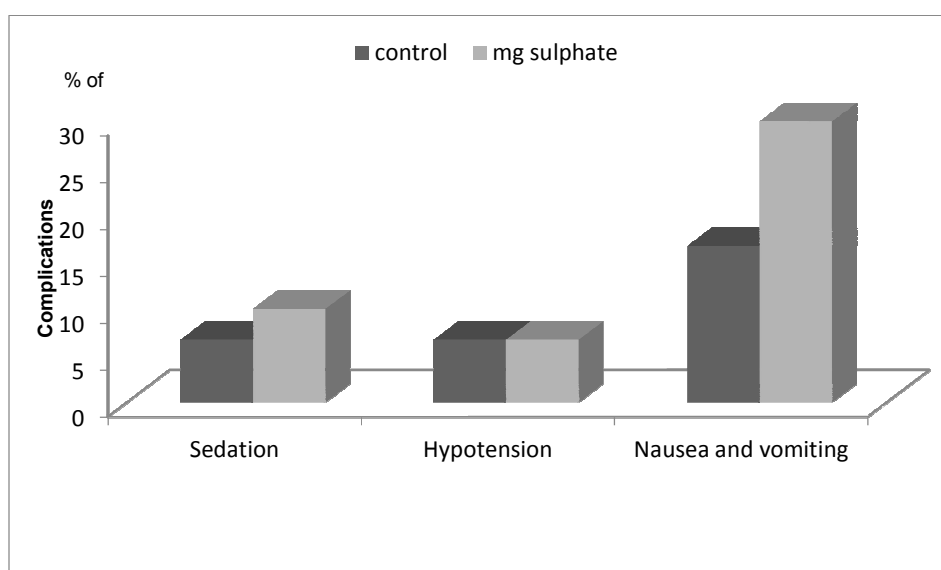


Fig. 4. Complications in the studied groups

Our results are in agreement with Ryu J-H et al. [13] who conducted a prospective study on 50 female patients undergoing gynecological surgery randomized into two groups the magnesium group received magnesium sulphate 50 mg/kg I.V. as a bolus and then 15 mg/kg/h I.V. by continuous infusion. The control group received the same amount of isotonic saline. After operation, patient-controlled analgesia with a solution of ketorolac and morphine was used and the consumption of this solution was recorded. Pain scores at rest and upon movement were evaluated 30 min, 4, 24, and 48 h after surgery. Postoperative pain scores and cumulative analgesic consumption were significantly lower in magnesium group. Mean arterial pressure just after intubation and during the immediate postoperative period was also significantly lower in magnesium group. Souza et al. [14] performed a prospective observational cohort analysis of 40 women with severe preeclampsia. Doppler ultrasonography scans were performed before and 20 minutes after intravenous administration of magnesium. There was a statistically significant increase in mean maternal heart rate and a statistically significant decrease in systolic, diastolic and mean maternal blood pressure before and after administration of magnesium sulphate.

On the other hand, Paech et al. [15], investigated women who underwent elective cesarean delivery randomized into high dose magnesium sulfate (50 mg/kg load and 2 g/h), low dose magnesium sulfate (25 mg/kg load and 1 g/h), or placebo. They found that magnesium sulfate does not reduce the severity of short-term or long-term (6 weeks) pain after cesarean delivery. Moreover, Elgebaly et al. [16] performed a double-blinded, prospective, randomized, controlled study designed to determine the analgesic efficacy and tolerability of intravenous magnesium sulfate versus intrathecal fentanyl. One hundred and five patients were randomly allocated to one of the three groups; the control group (B) received spinal anesthesia with 10 mg of 0.5% heavy bupivacaine, the test group (FB) received spinal anesthesia with 10 mg of 0.5% heavy bupivacaine plus 25 µg of preservative-free fentanyl and the test group (MB) received spinal anesthesia with 10 mg of 0.5% heavy bupivacaine along with intravenous magnesium sulfate (6 gm iv as a loading dose over 20-30 minutes, followed by infusion of magnesium sulfate 2 gm per hour for 24 hours). They measured VAS score only at the time of first analgesia requirement and did not reveal a

significant difference between intervention and control groups.

Magnesium Administration Protocols: All trials administered placebo control and intravenous magnesium interventions preoperatively as a bolus. However, three trials also administered an ongoing magnesium infusion for 24 hours postoperatively following the preoperative bolus [17]. The trial by Paech et al. [16] included two intervention arms (high dose and low dose), both with bolus infusion regimens. Dosage regimens: Doses ranged from 25 mg/kg to 50 mg/kg. One study used a standard dose of 6 grams as a bolus [18] which would likely be the highest dose-to-weight studied. 50 mg/kg was the most commonly studied bolus dose. Of those with postoperative infusion protocols, two groups received a standard 2 g/hr infusion.

Our study evaluated the efficacy of administration of intravenous mg sulphate on RI, PI and S/D ratio of uterine artery, umbilical artery and middle cerebral arteries. The umbilical artery represents the fetoplacental flow. Doppler parameters of the umbilical artery showed a statistically significant decrease in magnesium sulphate group after drug infusion compared to pre-infusion values with no significant difference between the studied groups. Also there was a statistically significant decrease in doppler parameters of both MCA and uterine artery in the Mg sulphate group after drug infusion as compared with the pre-infusion values without significant changes between both studied groups.

Our results also came in accordance with Sedek et al.[19] who evaluated the influence of antenatal administration of magnesium sulfate on the cerebral blood flow in a prospective observational interventional study on (40) patients. They showed that there was a significant difference between umbilical artery doppler parameters before and after administration of MgSo₄ in the studied patients. There was also a significant difference between MCA, uterine artery doppler parameters before and after administration of MgSo₄ in the studied patients.

Also, Souza et al. [15] revealed that RI decreased in the umbilical and middle cerebral artery and in both uterine arteries. Likewise, there was a significant reduction in the PI and S/D ratio in all the arteries assessed. There was no observed statistically significant difference

before and after use of MgSO₄ with regard to the umbilical/middle cerebral ratio. This can be explained because of a mathematical reason. When it decreases the numerator (umbilical artery) and the denominator (middle cerebral artery), the result remains unchanged.

Also, Arduini and Rizzo study in 1999 showed that there was a significant decrease in the fetal middle cerebral arteries PI after the use of MgSO₄ in women with severe preeclampsia [20,21].

Rantonen et al. found a significant decrease in the PI of the uterine artery after the use of MgSO₄ [22]. Similar results were shown by Hasanein and El-Shal [22]. Who showed that although the incidence of hypotension was not statistically significant in both groups, the incidence was higher in the magnesium group than in the saline group; this difference can be related to the effect of MgSO₄ or the effect of oxytocin boluses given to the magnesium group. Mireskandari et al. [18] and Elrahman and Youssry [19], however, recorded no significant difference in blood loss between patients receiving magnesium than control.

Maulik et al. reported an increased incidence of intraoperative hypotension in magnesium intervention patients than control, which was readily corrected with vasopressors [23].

There were some limitations in our study. In addition to the relatively small sample size, we didn't perform neuromuscular monitoring. Also, we didn't measure the maternal recovery time or maternal blood loss. In addition, we studied a relatively low dose of mg sulphate (25 mg/kg) as a bolus dose without infusion dose.

We recommended additional studies including a large number of patients using different doses and infusion regimens of magnesium sulphate for generalization of our results.

4. CONCLUSION

Preoperative administration of magnesium sulphate (25 mg/kg) was associated with better haemodynamic stability, lower postoperative pain scores, less post-operative analgesic consumption without significant difference in umbilical, middle cerebral and uterine arteries blood flow or Apgar score with nil complications except for PONV compared to

control group in patients undergoing cesarean section under general anesthesia.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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