

Using of Magnesium Sulphate for Fetal Neuroprotection in Patients Presenting by Intrapartum Fetal Distress at Term: A Randomized Controlled Trial

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ABSTRACT

Background: labour is a stressful event for the fetus but is well tolerated by most fetuses. However, in some infants stress of labour in terms of metabolic acidosis can lead to Hypoxic Ischemic Encephalopathy (HIE). HIE around term remains a major cause of neonatal mortality and morbidity with lifelong chronic disabilities. Such insults are not limited to high risk pregnancies but can also occur in about 50% of low risk pregnancies. On current evidence, it is estimated that in about 10 of brain damaged infants, the cause is hypoxia during labour. There has been considerable interest in magnesium sulfate ($MgSO_4$) because magnesium alleviates excitotoxic damage by binding to the magnesium site on the NMDA (N-methyl-D-aspartate) glutamate channel.

Aim of the Work: magnesium sulphate ($MgSO_4$) for fetal neuroprotection in patients presenting by intrapartum fetal distress at term.

Patient and Methods: this is a randomized controlled trial (RCT). The current study was conducted to single term pregnant women who developed intrapartum fetal distress (as defined later) and need emergency CS (cesarean section) according to Ain Shams protocol. This study was carried on 200 pregnant females, recruited from observation and labour wards of Ain Shams University Maternity Hospital. The current study was conducted to single term 200 pregnant women who developed intrapartum fetal distress and needs emergency CS (cesarean section) according to Ain Shams protocol to examine the effects of administered magnesium sulphate. Patient were invited to participate in the study after providing clear explanation of the study and its expected values.

Result: patients were invited to participate in this study after providing clear explanation of the study and its expected values. The demographic data of included women showed no significant difference between groups in the age and gestational age. There was a significant difference in Apgar score at 5 min between $MgSO_4$ and placebo. $MgSO_4$ had significantly lower the risk of decrease Apgar score < 7 at 5 min ($p: 0.029$). $MgSO_4$ also had significantly lower seizure attacks ($p: 0.002$) and had highly significantly reduce NICU admission rate ($MgSO_4$ group 20(20%) and placebo group 43(43%) ($p: 0.001$)). In $MgSO_4$ group, 23 women reported adverse reactions associated with procedure. Among them, 16 (16%) reported only flushing and 7 (7%) reported only nausea. In placebo group, were 8 (8%) reported flushing and 2 (2%) reported nausea.

Conclusion and Recommendation: magnesium sulfate is effective in reducing risk of Apgar score < 7 at 5 min. Magnesium sulfate appear to be effective in reducing seizure and NICU admission. Magnesium sulphate is associated with maternal morbidity rather than non exposure in the form of nausea and flushing. The improvement in short-term outcomes without significant increase in side effects indicate the need for further trials to determine if there are long-term benefits of magnesium and to confirm its safety.

Keywords. Magnesium Sulphate, Fetal Neuroprotection, Intrapartum Fetal Distress, cesarean section.

INTRODUCTION

Labour is a stressful event for the fetus but is well tolerated by most fetuses. However, in some infants stress of labour in terms of metabolic acidosis can lead to Hypoxic Ischemic Encephalopathy (HIE)^(1,2,3). HIE around term remains a major cause of neonatal mortality and morbidity with lifelong chronic disabilities⁽⁴⁾.

Such insults are not limited to high risk pregnancies but can also occur in about 50% of low risk pregnancies. On current evidence, it is

estimated that in about 10 of brain damaged infants, the cause is hypoxia during labour⁽⁵⁾.

Neonatal HIE is an acute, non-static encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia. Persistent hypoxia implies 'asphyxia', usually associated with hypercarbia and causing metabolic acidosis⁽⁶⁾. The latter – in effect, a cumulative oxygen debt – is quantified in blood by the base deficit value and the risk of damage. Ischemia (insufficient blood to supply needs) of the 'nonessential' organs

occurs in early hypoxia; with prolongation, the essential organs (brain, heart and adrenal glands) also become ischemic⁽⁷⁾. The challenge to obstetricians remains how best to recognize those babies at risk of this intrapartum insult both before and during labor. Many associations and risk factors are unavoidable or unrecognizable, and others are fairly common and associated with poor predictive value⁽⁴⁾.

Such defects include mental retardation, seizure and particularly a virility of motor abnormalities often grouped as cerebral palsy. The fetus depends on the mother for placental exchange of oxygen and carbon dioxide. This in turn relies on adequate maternal blood gas concentrations, uterine blood supply, placental transfer and fetal gas transport. Disruption of any of these can cause fetal hypoxia. The causes of acute fetal hypoxia and subsequent acidosis include reduced utero-placental blood flow, placental abruption or fetal cord compression. The consequences of acidosis depend on its severity and duration and also the condition of the fetus before the insult⁽⁸⁾. Thus an intrapartum monitoring tool with high accuracy is required to ensure fetal wellbeing and prediction and diagnosis fetal hypoxia and metabolic acidosis with subsequent neurological damage during labour⁽⁹⁾. Labor admission test refers to an electronic FHR monitoring tracing performed for 20 to 30 minutes upon admission to the labor and delivery unit⁽¹⁰⁾. Admission test helps to identify cases already hypoxic or those likely to be at risk later in labour.

Pre-terminal CTG patterns such as prolonged bradycardia complicated by variable or late decelerations for a period > 30 min and loss of beat to beat variability > 90 min inspite of doing conservative management, warrant immediate delivery without FBS⁽¹¹⁾. Apgar score of less than 5 at 5 minutes and 10 minutes increased relative risk of cerebral palsy⁽¹²⁾. The Apgar score is affected by many factors, including gestational age, maternal medications, resuscitation, and cardiorespiratory and neurologic conditions. If the Apgar score at 5 minutes is 7 or greater, it is unlikely that peripartum hypoxia-ischemia caused neonatal encephalopathy⁽¹³⁾.

Asphyxia leads to two types of cerebral insults: the primary neuronal injury that occurs at the time of the hypoxic-ischemic insult and the secondary neuronal injury that occurs over hours to even days following the accumulation of excessive intra-neuronal calcium as a result of excitatory amino acid stimulation of the N-methyl-D-aspartate

(NMDA) cell receptors, formation of free oxygen radicals and gene induction⁽¹⁴⁾.

There has been considerable interest in magnesium sulfate ($MgSO_4$) because magnesium alleviates excitotoxicity damage by binding to the magnesium site on the NMDA (N-methyl-D-aspartate) glutamate channel⁽¹⁾. There is an evidence that it may also reduce secondary inflammation and associated injury⁽¹⁵⁾. Stabilized cell membranes inhibits free radical production and improves cardiovascular stability⁽¹⁶⁾.

Aim of the Work: this study aimed to detect using of magnesium sulphate ($MgSO_4$) for fetal neuroprotection in patients presenting by intrapartum fetal distress at term.

PATIENT AND METHODS

Study design:

A Randomized controlled trial (RCT). The current study was conducted to single term pregnant women who develop intrapartum fetal distress (as defined later) and needs emergency CS (cesarean section) according to Ain Shams protocol.

Study setting:

This study was carried out on 200 pregnant females, recruited from observation and labour wards of Ain Shams University Maternity Hospital.

Recruitment and initial assessment:

Suitable women were invited to participate in the study then an informed and signed consent was obtained from them. When the patient consent is obtained, they were included into the study according to exclusion and inclusion criteria.

Inclusion Criteria

Intrapartum fetal distress with on duty consultant-based decision to preform emergency CS(caesarian section) in patients age 20-40 years old pregnant at gestational age 37 week or later.

Exclusion Criteria

Cases in which use of $MgSO_4$ was contraindicated were: myasthenia gravis or renal impairment or cases where $MgSO_4$ was taken as a therapeutic measures such as: severe PET (pre-eclampsia) or where other confounders were presented such as: small for gestational date (SGA), multiple gestation are considered as exclusion criteria for this study. This study was approved by the Ethics Board of Ain Shams University.

The study was done after approval of ethical board of Ain Shams university.

Statistical Methods

Sample Size Justification

The required sample size has been calculated using the IBM© Sample Power© Software (IBM© Corp., Armonk, NY, USA).

The primary outcome measure is the proportion of patients with low Apgar scores (less than seven) at five minutes.

In a previous Cochrane review, **Nguyen *et al.***⁽¹⁷⁾ found a single RCT on the role of MgSO₄ for neuroprotection of the neonate the incidence of Apgar score <7 at 5 minutes was 1.49% versus 2.9% in women receiving MgSO₄ or placebo, respectively. The estimated relative risk was 0.51 with a 95%CI ranging from 0.05 to 5.46. Because of the limited evidence regarding the role of MgSO₄ for the outcome measure, the present study would target an effect size that may be clinically relevant.

Accordingly, it was estimated that a sample size of 100 patients in each study group (total 200 patients) would achieve a power of 80% (type II error, 0.2) to detect a statistically significant difference between the two groups for a small-to-medium effect size (**w**) of 0.198 using a two-sided chi-squared test with a confidence level of 95 % (type I error, 0.05).

The effect size (**w**) is calculated as follows:

$$w = \sqrt{\chi^2 / N}$$

Where χ^2 is the Chi-squared statistic and **N** is the total sample size⁽¹⁸⁾

Statistical Methods:

Data were analyzed using Stata® version 14.2 (StataCorp LLC, College Station, TX, USA).

Numerical data distribution was examined using the Shapiro-Wilk test. Normally distributed numerical data were presented as mean and SD. Categorical data were presented as number and percentage.

The following tests were done:

- Unpaired sample t- test of significance was used when compare between intergroup differences sample

- Chi-square test of significance was used in order to compare proportions between two different categorical data,
- Probability (P-value):
- P-value <0.05 was considered statistically significant.
- P-value <0.001 was considered as highly significant
- P-value >0.05 was considered insignificant

PATIENTS AND METHODS

The study comprised 200 pregnant women. They were divided into two groups:

- Group A: pregnant women diagnosed to have intrapartum fetal distress who will receive MgSO₄ (number 100).
- **Group B:** pregnant women diagnosed to have intrapartum fetal distress who will receive placebo (number 100).

Randomization and allocation

Randomization (balanced randomization of 1:1) was performed by computer generated sequence using MS Excel. The allocated groups was concealed in serially-numbered sealed opaque envelops that was only opened just after recruitment. Women in any of the groups were received the allocated treatment at least 20 minute before the procedure (emergency CS).

Study treatment and dosages:

- Test drug (MgSO₄): group A received a single bolus dose of 4g MgSO₄ slowly intravenous over 10 minutes.
- Placebo drug: group B was given an equal volume of isotonic 0.9% saline over 10 minutes.

Supplies and accountability:

The treatment was provided by on duty consultant-based decision

Data collection and schedule:

All patients eligible for the study underwent complete clinical examination , detailed medical history, "labor admission test" refers to an electronic FHR monitoring tracing performed for 20 to 30 minutes upon admission to the labor and delivery unit .Admission test help to identify cases already hypoxic or those likely to be at risk later in labour.

Each patient had a Case Record Form (CRF NO.1) in which the following data were recorded:

- Patient number.
- Age.
- Past medical and surgical history.

- Menstrual history and contraceptive history: especially emphasis on LMP to determine the exact gestational age.
- **Clinical examination of the patients:**
- General examination vital data (blood pressure, pulse, temperature, respiratory rate).
- Abdominal , and pelvic examination.
- Fundal level will be done.
- Fundal grip and pelvic grip will be done.
- Intrapartum fetal heart rate (FHR) to detect viability and any abnormalities.

Examination of the fetus:

Fetal wellbeing was assessed in each case. The objective of monitoring the fetus in labor was to detect fetal abnormalities at a stage where they were reversible. The current modalities for the monitoring of the fetus were intermittent auscultation or CTG (cardiotocography).

Full laboratory investigations.

Adverse effects.

The patient satisfaction.

Failed of procedure.

Procedure [CRF NO.2]:

A sampling frame was drawn of all patients coming with the above-mentioned criteria.

- **Group A:** Magnesium sulphate (MgSO₄).
- **Group B:** Placebo (saline solution).

The procedure:

Pregnant women diagnosed to have intrapartum fetal distress in any of the groups received the allocated treatment at least 20 minute before the procedure (emergency CS). Patients in the active arm given MgSO₄ and those in control arm was given the placebo according to randomization allocation.

Intrapartum fetal distress in the form of: persistent fetal bradycardia > 7 min, complicated variable or late decelerations for a period > 30 min and loss of beat to beat variability > 90 min inspite of doing conservative management.

- Other measures to reduce the effect of hypoxia were applied to all participate through:
- The position of the mother was changed to left lateral position (allow increased blood supply)
 - I.V. fluid bolus (to avoid maternal dehydration)

- Oxytocin or cervical ripening agent were discontinued.
- Fetal heart rate monitoring with cardiotocography was attempted.
- If umbilical cord prolapse was noted, elevate the presenting fetal part until preparing for emergency operative delivery
- After birth, Apgar score was used to identify distress newborn who need resuscitation.

Ethical and legal aspects

Good Clinical Practice (GCP):

The procedures that were set out in the study protocol, pertaining to the conduct, evaluation and documentation of this study were designed to ensure that the investigator abided by the principles of good clinical practice and ethical principles laid down in the current revision of the Declaration of Helsinki. The protocol and all corresponding document were approved by ethical and research Committee of the Council of OB\GYN Department, Ain Shams University.

Delegation of investigator responsibilities:

The investigator ensured that all persons assisting with the trial were adequately informed about the protocol, any amendments to the protocol, the study treatment and them trial-related duties and functions.

Patient information and informed consent:

Patient consented to participate after explaining the nature, scope and possible consequences of the clinical study in an understandable form to her.

An informed consent document, in Arabic language, contains all locally required elements and specifies who informed the patient. After reading the informed consent document, the patients gave consent in writing by personally dated signature.

If the patient was unable to read, oral presentation and explanation of the written informed consent form and information supplied to patients was taken place in the presence of an impartial witness. Consent was confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (e.g., the patient's thumbprint or mark).

RESULTS

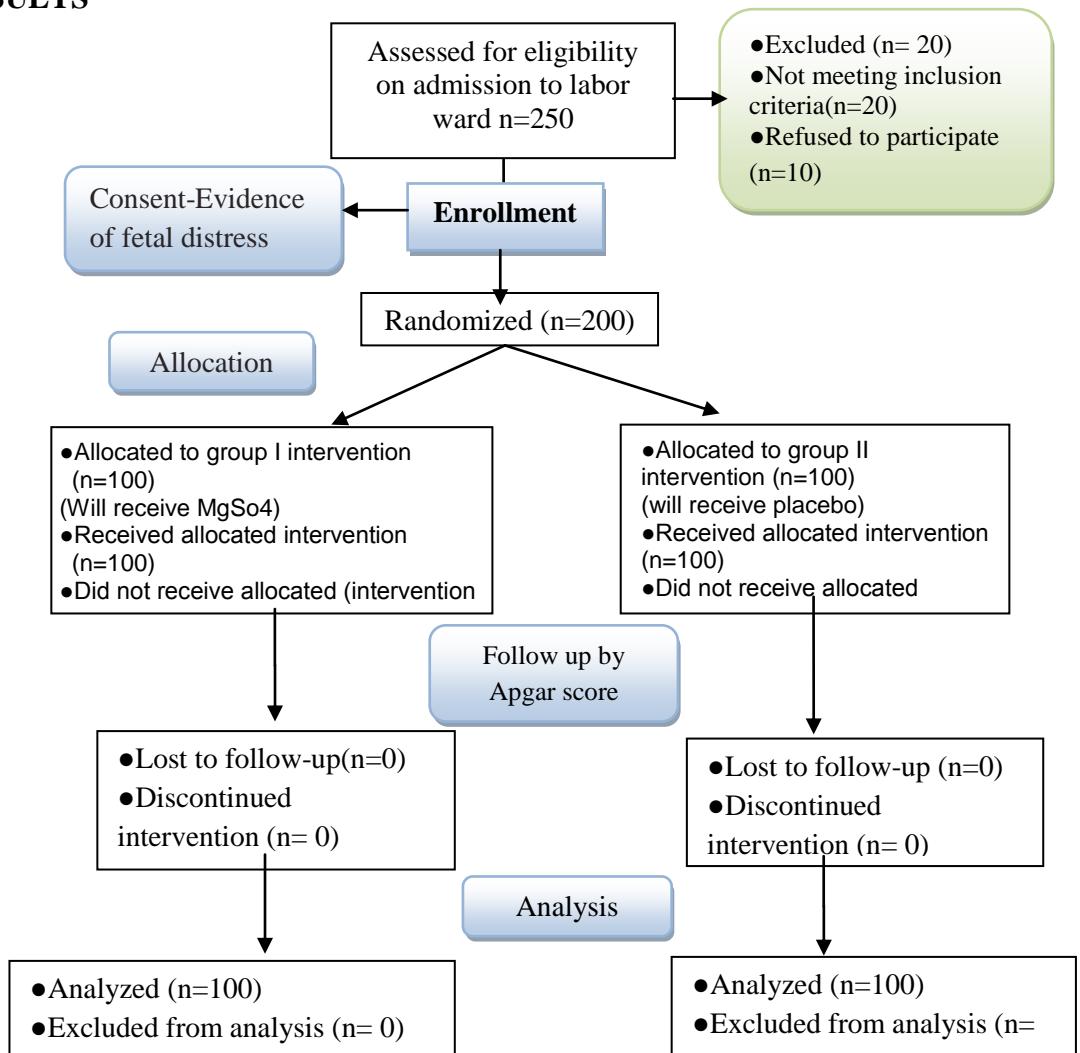


Figure 1: flow chart of recruitment of patients.

We approached 200 single term pregnant women conducted at Ain-Shams University Maternity Hospital who develop intrapartum fetal distress and needs emergency CS (cesarean section) according to Ain Shams protocol, to examine the effects of administered magnesium

sulphate, patients were invited to participate in the study after providing clear explanation of the study and its expected values.

The demographic data of included women showed no significant difference between groups in the age and gestational age as shown in table 1.

Table 1: demographic Characteristics and gestational age of patients in both study groups

Variable	Magnesium sulphate (n=100)	Placebo (n=100)	p-value¶
Age (years)	29.1 ± 6.5	29.1 ± 6.6	.932
Gestational age(weeks)	38.33 ± 1.22	38.29 ± 1.20	.815

Data are median (interquartile range), ¶Unpaired t test.

There was a significant difference in Apgar score at 5 min between MgSO4 and placebo as shown in table 2.

Table 2: Apgar score at 1 minute and 5 minutes in both study groups

Variable	Magnesium sulphate (n=100)	Placebo (n=100)	p-value¶
Apgar score at 1 min	5.7 ± 1.6	4.9 ± 1.0	.003
Apgar score at 5 min	7.7 ± 1.5	7.0 ± 1.8	.010

Data are mean ± SD, ¶Unpaired t test.

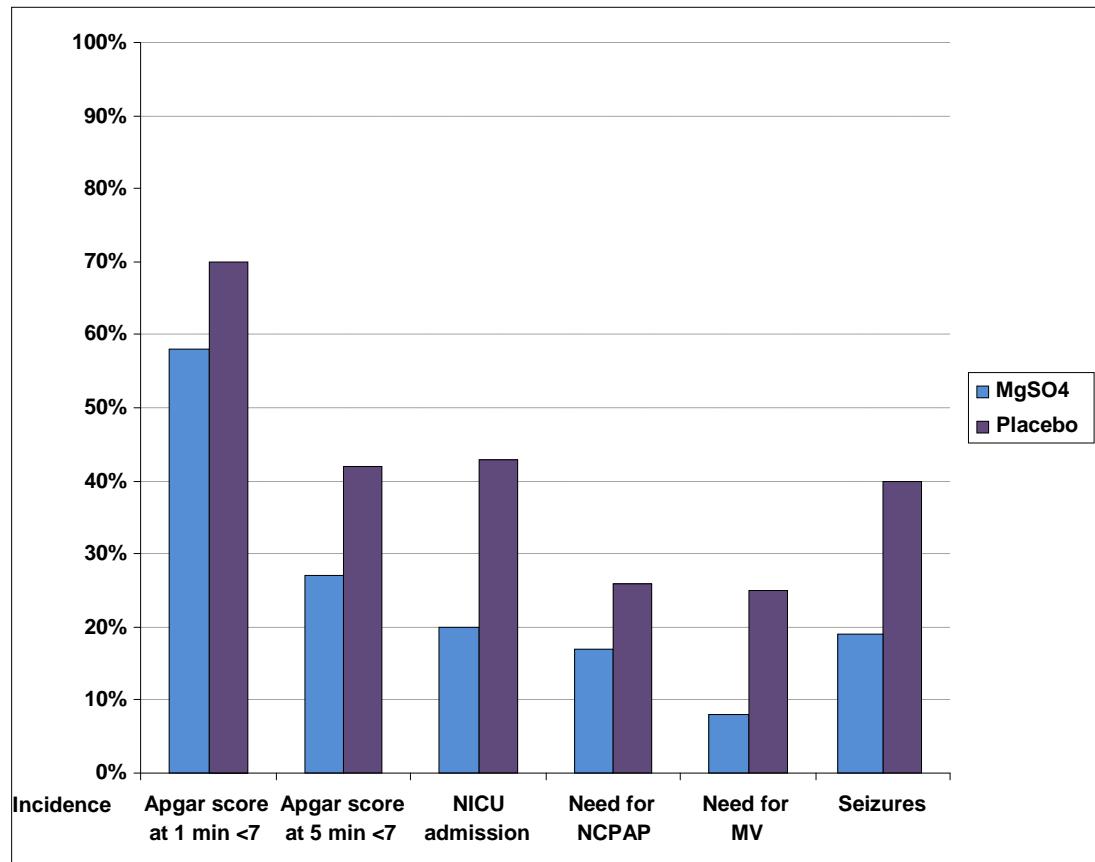
MgSo4 had significantly lower the risk of decrease Apgar score < 7 at 5min. Mgso4 also had significantly lower seizure attacks and had highly significantly reduce NICU admission rate as shown in table 3.

Table 3: comparison between groups according to incidence of neonatal adverse outcomes

Neonatal adverse outcome	Apgar score at 1 min <7	Apgar score at 5 min <7	NICU admission	Need for NCPAP	Need for MV	Seizures
MgSO₄ (n=100)	58 (58%)	27 (27%)	20 (20%)	17 (17%)	8 (8%)	19 (19%)
Placebo (n=100)	70 (70%)	42 (42%)	43 (43%)	26 (26%)	25 (25%)	40 (40%)
p-value	0.08	0.029	0.001	0.126	0.003	0.002

Data are number (%).

Chi-square test was used.

**Figure 2:** incidence of neonatal adverse outcomes in both study groups

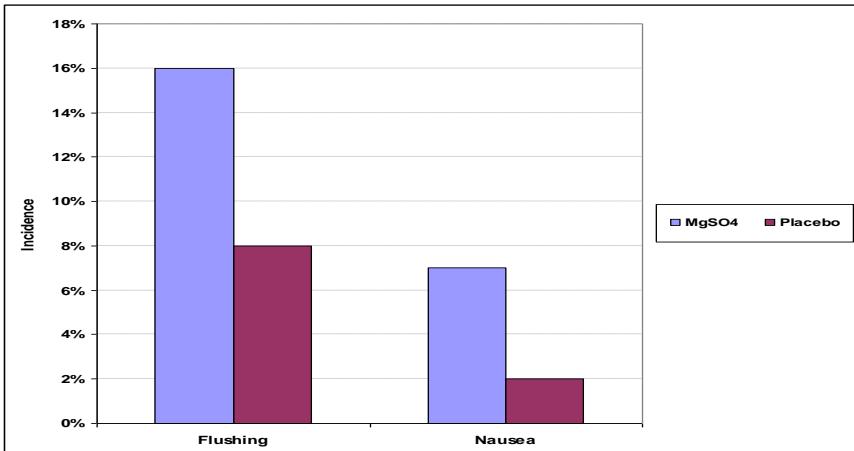
In MgSo4 group, 23 women reported adverse reactions associated with procedure. Among them, 16 (16%) reported only flushing and 7 (7%) reported only nausea. In placebo group, were 8 (8%) reported flushing and 2 (2%) reported nausea. None of women in both groups reported any other complication (as: vomiting, hypotension, respiratory depression) as shown in table 4 and figure 3.

Table 4: Comparison between groups according to incidence of maternal adverse outcomes

<i>Maternal adverse outcome</i>	<i>Flushing</i>	<i>Nausea</i>	<i>others</i>
MgSO₄ (n=100)	16 (16%)	7 (7%)	0(0.0%)
Placebo (n=100)	8 (8%)	2 (2%)	0(0.0%)
p-value	0.09		0.112

Data are number (%).

¶Z-test

**Figure 3:** comparison between groups according to incidence of maternal adverse outcomes

DISCUSSION

To the best of our knowledge, this is the first trial to study MgSo4 to produce neuroprotection to full term fetus. The finding of our study demonstrated that use of MgSo4 to reduced the risk of low Apgar score at 5 min < 7 is superior to placebo. Also, our results showed that MgSo4 significantly reduced the attacks of seizures when compared to placebo. There was a significant difference in the need for NICU admission in MgSo4 group 20(20%) and placebo group 43(43%) but no significant difference in need for NCPAP in MgSo4 and placebo. Our study is in agreement with results of results of Nguyen et al.⁽¹⁷⁾ who found a single RCT on the role of MgSO4 for neuroprotection of the full term neonate. Also, Nguyen et al.⁽¹⁷⁾ stated that 135 women at least 37 weeks' gestation with blood pressure \geq 140 mmHg systolic, \geq 90 mmHg diastolic were randomized into MgSo4 group ($n = 67$) vs placebo group ($n = 68$), women were given a loading infusion of 6 g MgSo4 over 15–20 minutes followed by a maintenance infusion of 2 g per hour continued until 12 hours postpartum and an equal volume of a saline solution by infusion to placebo group. The incidence of Apgar score <7 at 5 minutes was 1.49% versus 2.9% in

women receiving MgSO4 or placebo, respectively. The estimated relative risk was 0.51 with a 95%CI ranging from 0.05 to 5.46⁽¹⁹⁾. Crowther et al.⁽²⁰⁾ reported that mothers at risk of delivering before 30 weeks of gestation were given MgSo4 and neurodevelopmental benefits examined at 2-years-of-age, substantial gross motor dysfunction (3.4% vs 6.6%; RR, 0.51; 95% CI, 0.29–0.91) were significantly reduced in the MgSo4 group. Rouse et al.⁽²¹⁾ performed a major randomized trial demonstrated that administration of a 6 g bolus over 20–30 minutes followed by 2 g/hr (discontinued if not delivered by 12 hours), to 2241 women in gestational week (24 – 32), significantly reduced the incidence of cerebral palsy, assessed at or beyond 2 years of age (RR 0.45; 95% CI 0.23–0.87). Crowther et al.⁽²⁰⁾ performed a randomized trial demonstrated that administration of (16mmol MgSO4 followed by 4 mmol/h for 24 hours) to 1062 women in gestational week (30 or less) vs placebo, with birth planned within 24 hours, showed a 32% relative reduction of cerebral palsy (RR 0.55; 95% CI 0.35–0.88), gross motor dysfunction also significant reduction: RR: 0.61 (95% CI: 0.44–0.85). Magee et al.⁽²²⁾ performed a major randomized trial demonstrated that antenatal

administration of MgSo4 to women in gestational age \leq 31+6 weeks with imminent preterm birth, reduces the risk of CP (RR 0.71; 95% CI 0.55 to 0.91; 4, trials, 4446 infants), and “substantial gross motor dysfunction” (inability to walk without assistance) (RR 0.60; 95% CI 0.43 to 0.83; 3 trials, 4287 women) at 2 years of age.

Tagin et al. ⁽²³⁾ demonstrated that 6 randomized controlled trials and 5 cohort studies, that involved 18,655 preterm infants, and they showed that the ability of MgSo4 to reduce the risk and achieve statistically significant difference in the rate of moderate to severe CP (odd ratio [OR] 0.61, 95% confidence interval [CI] 0.42–0.89, P 0.01). In our study, time of administration of MgSo4 was intrapartum. **Tagin et al.** ⁽²⁴⁾ demonstrated that administration of MgSO4 (250 mg/kg 30 min after birth and 125 mg/kg after 24 and 48 hours vs. placebo) to 40 full-term neonates with asphyxia. EEG abnormalities (slowing of electrical seizure activity and discontinuous pattern) occurred in 43.75% of the cases in the placebo group compared with 31.25% in the MgSo4 group, CT scan abnormalities (focal, multifocal or diffuse hypodensities) occurred in 62.5% of the placebo group compared with 37.5% of the cases in the MgSo4 group. **Tagin et al.** ⁽²³⁾ demonstrated that administration of MgSo4 within the first 24h after birth for newborns >35 weeks gestation with HIE, there were significant reduction in the unfavorable short-term composite outcome (as: death, HIE, seizure) (RR 0.48, 95% CI 0.30 to 0.77) between MgSo4 and the control groups.

On the other hand, **Girsen et al.** ⁽²⁵⁾ studied the effect of maternal MgSO4 exposure for eclampsia prophylaxis on the neonates. Newborns exposed to MgSO4 were more likely to have Apgar scores <7 at 1 and 5 min (15% vs 11% unexposed, P=0.01 and 3% vs 0.7% unexposed, P=0.008). **Marret et al.** ⁽²⁶⁾ performed a randomized trial demonstrated that administration of MgSO4 (4 g) single-dose over 30 minutes to 573 women in gestational weeks (33 or less) with birth planned within 24 hours, non-significantly reduced neonatal white matter injury (OR 0.78; 95% CI 0.47–1.31). In our study, seizure attack was 19(19%) in MgSo4 group and

40(40%) in placebo this is both significant clinically and statistically (p=0.002).

Our results are supported by those of **Tagin et al.** ⁽²³⁾ demonstrated that administration MgSo4 within the first 24h after birth newborns >35 weeks gestation with HIE, there was significantly reduced incidence of seizures (RR 0.84, 95% CI 0.59 to 1.19) between the MgSo4 groups and the control groups.

In our study, the number of NICU admission was 20 (20%) in mgso4 group and 43 (43%) in placebo group this difference was also highly significant clinically and statistically (P=0.001). Our results is not supported by **Girsen et al.** ⁽²⁵⁾ who performed a randomized trial among 2166 term pregnancies with preeclampsia, 1747 (81%) received MgSO4 for eclampsia prophylaxis and 419 (19%) did not. NICU admission rates were higher among newborns exposed to MgSO4 vs unexposed (adjusted odds ratio 1.9, 95% confidence interval 1.3 to 2.6, P<0.001).

The results of this study had significant clinical implications as to improve Apgar score at 5 min in MgSo4 group and minimizing the rate of seizure and NICU admission. MgSo4 has most of the ideal neuroprotective agent in developing countries. The cost of a treatment course is acceptable per patient even for heights dose and long duration used in NICU. MgSo4 levels in serum and CSF are well controllable because they are easy to measure and follow compared to other calcium antagonists. The main limitation of the study is that range of results and other comparison studies, suggested that its effect depends on the timing of treatment, route of administration, different dose regimens and co-medication.

Conclusion and Recommendation:

Magnesium sulfate is effective in reducing risk of Apgar score <7 at 5min.

Magnesium sulfate appear to be effective in reducing seizure and NICU admission. Magnesium sulphate is associated with maternal morbidity rather than non exposure in the form of nausea and flushing. The improvement in short-term outcomes without significant increase in side effects indicate the need for further trials to determine if there are long-term benefits of magnesium and to confirm its safety.

REFERENCES

1. Westermaier T, Stetter C, Kunze E, Willner N, Raslan F, Vince GH and Ernestus RI(2013): Magnesium treatment for neuroprotection in ischemic diseases of the brain. *Exp. Transl. Stroke Med.*, 5:6-12.
2. Chisty Al, Iqbal A, Anjum A and Maqbool S(2001): Spectrum of multiorgan systemic involvement in birth asphyxia. *Pak. J. Pathol.*, 12:81-92.
3. Miller D, Lockwood C and Barss V (2017): Intrapartum fetal heart rate assessment. *Uptodate*, 25:3 - 19.
4. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, Strohm B, Thoresen M, Whitelaw A and Azzopardi D(2010): Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ*., 5:340:363.
5. Yazawa K(2005): Neonatal encephalopathy and cerebral palsy. *J. Nippon. Med. Sch.*, 6: 85-93.
6. Clerici G , Luzietti R and Di Renzo G (2001):Monitoring of antepartum and intapartum fetal hypoxemia : pathophysiological basis and available techniques. *Biol. Neonate* , 7:246-253.
7. Kumar S and Paterson-Brown S (2010): Obstetric aspects of hypoxic ischemic encephalopathy. *Early Hum. Dev.*, 86: 339-344
8. Bobrow C, and Soothill P (1999): Causes and consequences of fetal acidosis. *BMJ*., 2: 246-249.
9. Agrawal SK, Doucette F, Gratton R, et al. Intrapartum computerized fetal heart rate parameters and metabolic acidosis at birth. *Obstet Gynecol* 2003; 102:731.
10. Blix E, Brurberg KG, Reirer E *et al.* (2016): ST waveform analysis versus cardiotocography alone for intrapartum fetal monitoring: a systematic review and meta-analysis of randomized trials. *Acta Obstet. Gynecol. Scand.*, 95:16-25.
11. Baskett T, Calder A, Arulkumaran S(2007): Fetal surveillance in labour. In: Munro Kerr's Operative Obstetrics .11th ed. Elsevier Publishing.London.pp:38-39.
12. Li F, Wu T, Lei X, Zhang H, Mao M and Zhang J (2013): The Apgar score and infant mortality. *PLoS One*, 8:69072-69085.
13. American Academy of Pediatrics Committee on Fetus and Newborn(2015): The Apgar Score. *Pediatrics*, 136:819-825.
14. Gathwala G, Khera A, Singh J and Balhara B(2010): Magnesium for neuroprotection in birth asphyxia. *J. Pediatr. Neurosci.*, 5:102–104.
15. Sugimoto J, Romani AM, Valentin-Torres AM, Luciano AA, Ramirez Kitchen CM, Funderburg N and Mesiano S (2012): Bernstein HB: Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. *J. Immunol.*, 188:6338-6346.
16. Shokry M, Elsedfy GO, Bassiouny MM, Anmin M and Abozid H(2010): Effects of antenatal magnesium sulfate therapy on cerebral and systemic hemodynamics in preterm newborns. *Acta Obstet. Gynecol. Scand.*, 89:801-806.
17. Nguyen TMN, Crowther CA, Wilkinson D and Bain E(2013): Magnesium sulphate for women at term for neuroprotection of the fetus. *Cochrane Database of Systematic Reviews*, 2: 9395-9405.
18. Chow S-C, Shao J and Wang H (2003): Sample Size Calculation in Clinical Research. First Edition. Marcel Dekker . New York.
19. Witlin AG, Friedman SA and Sibai BM(1997): The effect of magnesium sulfate therapy on the duration of labour in women with mild preeclampsia at term: A randomised, double-blind, placebo controlled trial. *American journal of obstetrics and gynecology*, 176(3):623-627.
20. Crowther CA, Hiller JE, Doyle LWand Haslam RR(2003): Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA*., 290(20):2669–2676
21. Rouse DJ, Hirtz DG, Thom E *et al.*(2008): A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N. Engl. J. Med.*, 359:895-905.
22. Magee LA, Sawchuck D, Synnes A, von Dadelszen (2011): Magnesium sulphate for fetal neuroprotection consensus committee; SOGC maternal fetal Medicine Committee. SOGC Clinical Practice Guideline. Magnesium sulphate for fetal neuroprotection. *J. Obstet. Gynaecol.*, 33(5):516–529
23. Tagin, M, Shah PS and Lee KS (2013): Magnesium for newborns with hypoxic-ischemic encephalopathy: a systematic review and meta-analysis. *J. Perinatol.*,33: 663–669
24. Tagin M, Abdel-Hady H, Rahman S, Azzopardi D and Gunn A (2015): Neuroprotection for perinatal hypoxic ischemic encephalopathy in low- and middle-income countries. *J. Peds.* 2:56-62.
25. Girsen AI, Greenberg MB, El-Sayed YY, Lee H, Carvalho B and Lyell DJ (2015): Magnesium sulfate exposure and neonatal intensive care unit admission at term. *J. Perinatol.*., 35 (3):181-186.
26. Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Leveque C, Hellot MF and Benichou J (2007):Magnesium sulphate given before very-preterm birth to protect infant brain. *B. J. OG.*, 114(3):310–318.