Websites:
http://www.sciencepub.net
http://www.cancerbio.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

Cancer Biology

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Using of Mg Sulphate for Fetal Neuroprotection in women Presenting by Fetal Distress during labour at Term: A Randomized Controlled Trial.

Rehab Abdelhamid Aboshama and Laila Ezzat

Department of Obstetrics and Gynecology, Faculty of Medicine – Fayoum University, Fayoum, Egypt
E-mail: lailaezzat972000@gmail.com

Abstract MgSo4 protect the fetal from in-utero hypoxia by preventing large blood pressure fluctuations, increase cerebral blow flow and decrease pro-inflammatory cytokines. MgSO4 also blocks excess release of glutamate in the calcium channel, protecting the susceptible fetal and newborn brains from glutamate-induced damage and antioxidant effects. This study aims to determine the potential efficacy of MgSO4 as a neuroprotective agent for the term fetus given to women presented by intrapartum fetal distress. The study was done in Fayoum university Hospital from 2018 to 2019 and was approved by institute ethics committee. 200 single term pregnant women who develop intrapartum fetal distress according to Fayoum university hospital protocol participated in this study. The cases were randomly assigned to two groups (100 patients each). **Results** Risk of Apgar score less than 7 at 5 min was not significantly reduced in the MgSO4 group than that in placebo group. The number of NICU admission was 4 in MgSO4 group and 5 in placebo group and no cases show any neonatal complication. There is statistically significant difference between cases and controls as regards maternal outcomes and complications; with higher percentage of maternal complication were noted among cases who take MgSO4, but on the other hand there is no statistically significant difference regards type of maternal complications. **In Conclusion** Administration of MgSO4 was safe but did not offer significant cerebral protection from asphyxia in term fetus.
[Rehab Abdelhamid Aboshama and Laila Ezzat. **Using of Mg Sulphate for Fetal Neuroprotection in women Presenting by Fetal Distress during labour at Term: A Randomized Controlled Trial.** *Cancer Biology* 2020;10(4):1-6]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). http://www.cancerbio.net. 1. doi:10.7537/marscbj100420.01.

Key Words Mgsulphate, fetal distress, labour, NICU, maternal complications

1. Introduction

Labour is a stressful event for the fetus but it is well tolerated by most fetuses. However, in some infants stress of labour can lead to Hypoxic Ischemic Encephalopathy (HIE) due to metabolic acidosis. HIE 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. (1)

Neonatal Hypoxic Ischemic Encephalopathy is an acute encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia and characterized by clinical and laboratory evidence of acute or subacute brain injury. Persistent hypoxia implies asphyxia, usually associated with hypercarbia and causing metabolic acidosis. The clinical signs of HIE include low Apgar scores, low cord pH, neonatal seizures, and encephalopathy. (2)

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 uteroplacental 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. (2)

Intrapartum CTG patterns such as prolonged bradycardia complicated by variable or late decelerations for a period > 30 minutes and loss of beat to beat variability > 90 minutes, recurrent late deceleration, recurrent variable decelerations and sinusoidal pattern, in spite of doing conservative management, warrant immediate delivery without fetal blood sampling. Apgar score of less than 5 at 5 minutes and 10 minutes increases relative risk of cerebral palsy. (3)

The Apgar score is affected by many factors, including maternal medications, gestational age, congenital malformations, cardiorespiratory and neurologic conditions and resuscitation. If the Apgar score at 5 min is 7 or more, it is unlikely that peripartum hypoxia–ischemia caused neonatal encephalopathy. (4)

Asphyxia leads to two phases of cerebral insults: the primary neuronal injury (energetic failure) that occurs at the time of the hypoxic–ischemic insult, where the oxidative energy metabolism of cells decreases, 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. (5)

There has been considerable interest in magnesium sulfate (MgSO4) because magnesium alleviates excitotoxic damage by binding to the magnesium site on the NMDA glutamate channel. There is evidence that it may also reduce secondary inflammation. Stabilized cell membranes inhibit free radical production and improve cardiovascular stability. (6)

Aim of the study

The aim of this study is to assess the effectiveness of Magnesium Sulphate given to single term pregnant women who developed intrapartum fetal distress as a neuroprotective agent for the fetus.

2. Patients and methods

A Randomized controlled trial (RCT). The current study will be conducted to a single term pregnant women who developed intrapartum fetal distress to examine the effects of antenatal administered Magnesium Sulphate (MgSO4) on various maternal and infant outcomes compared with controls (100 patients each) according to Fayoum university protocol

The current study will be conducted to single term pregnant women who develop intrapartum fetal distress according to Fayoum university protocol.

Suitable women were invited to participate in the study, and then an informed and written consent were obtained from them.

Inclusion Criteria:

• Pregnant women at least 37 week of gestation.

• Not more than 35 years old.

• Fetal distress (perinatal asphyxia) diagnosed by CTG changes (Non reassuring or pathological changes according to NICE guidelines 2017).

• Clinical chorioamnionitis.

Prolonged rupture of membranes.

Exclusion Criteria.

• Medical disorders such as chronic hypertension, preeclampsia, eclampsia, DM, pulmonary hypertension, hepatic coma with risk of renal failure, and any renal, cardiac or pulmonary disease.

• Rh

• Preterm labor.

• Fetal malpresentation.

• Contraindications to the use of Magnesium Sulphate.

• Any indication for magnesium Sulphate therapy (seizure prophylaxis or tocolysis).

• Myasthenia gravis.

• Congenital fetal anomalies

• Fetal growth restriction (birth weight < 10th Percentile for gestational age).

• Advanced cervical dilation (8cm).

Grouping: The study comprised 200 pregnant women. They were divided into two groups each are 100: • Group A: pregnant women diagnosed to have intrapartum fetal distress who will receive MgSO4. • Group B: pregnant women diagnosed to have intrapartum fetal distress who will receive placebo.

Test drug (MgSO4): group A will be received a single bolus dose of 4g MgSO4 slowly intravenous over 15-20 minutes without maintenance dose. • Placebo drug: group B will be received an equal volume of isotonic 0.9% saline over 15-20 minutes.

All patients eligible for the study will undergo detailed medical history, ultrasound, Doppler, complete clinical examination, CTG performed for 20 to 30 minutes upon admission to the labor and delivery unit. Each patient will have the following data: • Patient number, name. • 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.

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

CBC, PT, PTT, RBS, ALT, AST, Searum creatine…. etc) was done.

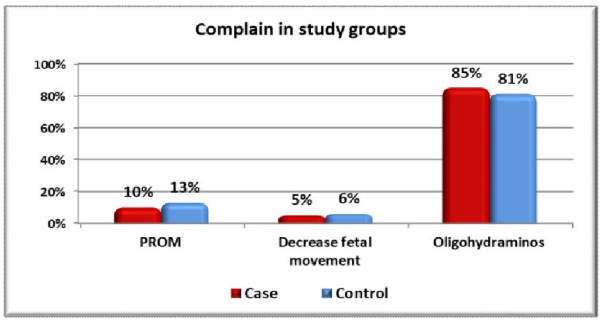
Pregnant women diagnosed to have intrapartum fetal distress (Non reassuring or pathological changes according to NICE guidelines 2017) in any of the groups will receive the allocated treatment at least 20 minute before the procedure (emergency CS). Patient in the active arm given MgSO4, and those in control arm was given the placebo according to randomization allocation. Intrapartum fetal distress in the form of: persistent fetal bradycardia more than 7 min, complicated variable or late decelerations for a period more than 30 min and loss of beat to beat variability more than 90 min inspite of doing conservative management. Other measures to reduce the effect of hypoxia will be applied to all participate through: •

The position of the mother will be changed to left lateral position (allow increased blood supply). • I.V. fluid bolus (to avoid maternal dehydration). • Oxytocin or cervical ripening agent will be discontinued. • Fetal heart rate monitoring with cardiotocography will be attempted. • If umbilical cord prolapse is noted, elevate the presenting fetal part until preparing for emergency operative delivery. After birth, Apgar score will be used to identify distress newborns that need resuscitation.

Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using Statistical Package of Social Science (SPSS) software version 18 in windows 7. • Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data. • Quantitative data included in the study was first tested for normality by One-Sample Kolmogorov-Smirnov test in each study group then inferential statistic tests were selected.

The procedures that were set out in the study protocol; pertaining to the conduct, evaluation and documentation of this study. The protocol and all corresponding document were approved by ethical and research Committee of the Council of OB\GYN Department, Fayoum university.

3. Results



There is no statistically significant difference with p-value >0.05 between cases and controls as regards patient complain; which indicated proper matching between study groups as most of cases presented by oligohydraminos.

Table (1) Comparisons of demographic characters in different study groups

Variables	Cases (n=100)		Placebo (n=100)		p-value	Sig.
Age (years)						
Mean /SD	29.9	4.7	29.7	4.9	0.8	NS
Residence						
Urban	35	35%	40	40%	0.6	NS
Rural	65	65%	60	60%		

Table (2): Comparisons of gravidity in different study groups

Variables	Cases (n=100)		Placebo (n=100)		p-value	Sig.
	Mean	SD	Mean	SD		
Gravidity	4	1	4	1	0.8	NS

Table (3): Comparisons of complains in different study groups

Complain	Cases (n=100)		Placebo (n=100)		p-value	Sig.
	No.	%	No.	%		
PROM	10	10%	13	13%	0.7	NS
Decrease fetal movement	5	5%	6	6%		
Oligohydraminos	85	85%	81	81%		

Table (4): Comparisons of Apgar score in different study groups

Variables	Cases (n=100)		Placebo (n=100)		p-value	Sig.
	Mean	SD	Mean	SD		
Apgar 1 min	8.09	1.3	8.03	1.4	0.8	NS
Apgar 5 min	9.8	0.85	9.8	0.9	0.7	NS

Table (5): Comparisons of different neonatal outcomes in different study groups

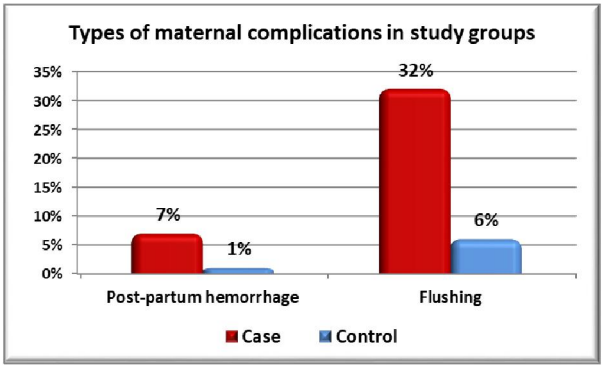
Variables	Cases (n=100)		Placebo (n=100)		p-value	Sig.
	No.	%	No.	%		
NICU admission						
No	96	96%	95	95%	0.9	NS
Yes	4	4%	5	5%		
Neonatal complication						
No	100	100%	100	100%	------	-----
Yes	0	0%	0	0%		

(Chi test)

Table (6): Comparisons of different maternal outcomes in different study groups

Variables	Cases (n=100)		Placebo (n=100)		p-value	Sig.
	No.	%	No.	%		
Maternal complications						
No	62	62%	93	93%	**<0.001**	**HS**
Yes	**38**	**38%**	7	7%		
Type of maternal complications						
Post-partum hemorrhage	7	7%	1	1%	0.6	NS
Flushing	31	32%	6	6%		

(Chi test)



That there is statistically significant difference with p-value <0.05 between cases and controls as regards maternal flushing and post partum hemorrhage; with higher percentage of maternal flushing is noted among cases who take magnesium sulfate 32% versus 6% among control group, but on the other hand there is no statistically significant difference with p-value >0.05 as regards post partum hemorrhage.

4. Discussion

Magnesium sulfate is one of the most commonly prescribed intravenous medications in obstetric practice. Magnesium has long been considered the drug of choice for preventing seizures in women with preeclampsia, a leading cause of maternal morbidity and mortality. Several retrospective studies of magnesium use in preeclamptic women and women in preterm labor also suggest that magnesium has a beneficial effect for fetal neuroprotection when very preterm delivery is imminent **(7)**.

Our study is in agreement with the Cochrane review of Nguyen TMN who found a single Randomized controlled trial on the role of MgSO4 for neuroprotection of the full term neonate. Cochrane review of Nguyen TMN included one trial (involving 135 women with mild pre-eclampsia at term). The included trial compared Magnesium Sulphate (n=67) with a placebo (n=68). (8)

Cochrane review of **Nguyen** was included, for example: neuroprotection of the fetus, growth restriction, chorioamnionitis, prelabour rupture of the membranes, antenatal fetal distress, intrapartum fetal distress, pre-eclampsia, labour. (8)

Our study is in agreement with Cochrane review of **Nguyen TMN** as there was no significant difference between $MgSO_4$ and placebo in Apgar score less than 7 at 5 min in **Nguyen TMN** Cochrane review as 1 patient only in $MgSO_4$ group had Apgar score less than 7 at 5 min and 2 patients had Apgar score less than 7 at 5 min (8)

There was no significant difference seen between groups in the rates of postpartum haemorrhage as in **Nguyen TMN** Cochrane review results as in our study 7% patient experienced postpartum haemorrage in $MgSO_4$ group while 1% patient only experienced postpartum haemorrhage in placepo group.

Our study is in agreement with **Nguyen TMN** as there is significant difference between groups in the rates of flushing in both studies. Regarding the maternal adverse reactions in our study, 32% patient experienced flushes in $MgSO_4$ group while 6% experienced flushing in placebo group. (8)

In **Girsen AL** study NICU admission remained significantly associated with antenatal $MgSO_4$ exposure as Antenatal maternal MgSO4 treatment was associated with increased NICU admission rates among exposed term newborns of mothers with preeclampsia, on other hand in our study there was no significant reduction in the need for NICU admission in the $MgSO_4$ group 4(4%) and placebo group 5(5%). (9)

Greenberg MB compared NICU admission rates between term neonates exposed to antenatal MgSO4 and those unexposed. The primary outcome was NICU admission. In all, 28 out of 190 MgSO4 exposed neonate's ≥ 37 weeks were admitted to the NICU, compared with 4 of 74 non-exposed neonates. NICU admission was associated in a dose-dependent relationship with total hours and mean dose of MgSO4 exposure. Number needed to harm with MgSO4 was 11 per NICU admission (10)

de Haan HH is in agreement with our study as it concluded that administration of MgSO4 was safe but did not offer significant cerebral protection from asphyxia in the near-term fetus.

de Haan HH studied the safety of fetal MgSO4 treatment and possible beneficial effect on the brain during perinatal asphyxia. Occlusions induced asphyxia, associated with mortality; 4 of 11 fetuses in the control group versus 1 of 9 in the magnesium-treated group died (not significant). (11)

Conclusion and Recommendation

Magnesium sulfate is not effective in reducing risk of Apgar score of less than 7 at 5minutes. It appears to be effective in reducing NICU admission. The associated side effect of the use of magnesium sulphate is essentially in the form of flushing. There is no improvement in short-term outcomes without significant - increase in side effects indicates the need for further trials to determine if there are benefits of magnesium and to confirm its safety. So we aren't recommending giving MgSo4 for neuroprotection at term.

Acknowledgments

Authors would like to acknowledge to all doctors and staff of Department of Obstetrics and Gynecology, Fayoum University Hospital for their sincere support and help.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

References

1. Westermaier T, Stetter C, Kunze E et al., (2013): Magnesium treatment for neuroprotection in ischemic diseases of the brain. Experimental and Translation.
2. Amr Abdel-Aziz Mahmoud, Ahmad ElSayed Hassan, Reda Mokhtar Kamal et al., (2017): Using of Magnesium Sulphate for Fetal Neuroprotection in Patients Presenting by Intrapartum Fetal Distress at Term: A Randomized Controlled Trial. The Egyptian Journal of Hospital Medicine; 69 (2), 1794-1802.
3. Li F, Wu T, Lei X., (2013): The Apgar score and infant mortality. PLoS One., 8:69072-69085.
4. American College of Obstetricians and Gynecologists., (2015): The Apgar score. Obstetrics Gynecology; 126(4), e52–5.
5. Gathwala G, Khera A, Singh J et al., (2010): Magnesium for neuroprotection in birth asphyxia. Journal of Pediatric Neuroscience; 5(2):102–104.
6. Sugimoto J, Romani AM, Valentin-Torres AM et al., (2012): Bernstein HB: Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. Journal of Immunology; 188(12):6338-6346.
7. Kathleen F. Brookfield and Abigail Vinson., (2019): Magnesium sulfate use for fetal neuroprotection. Current Opinion of Obstetrics and Gynecology; 31(2):110–115.
8. Nguyen TMN, Crowther CA, Wilkinson D et al., (2013): Magnesium sulphate for women at term for neuroprotection of the fetus. Cochrane Database of Systematic Reviews; (2): CD009395, 1- 10.
9. Girsen AL, Greenberg MB, El-Sayed YY et al., (2015): Magnesium sulfate exposure and neonatal intensive care unit admission at term, Journal of Perinatology, 35(3), 181 – 185.
10. Greenberg MB, Penn AA, Whitaker KR et al., (2013): Magnesium sulfate exposure in term neonates. Journal of Perinatology; 33(3), 188–193.

11. De Haan H H, Gunn A J, Williams CE et al., 1997: Magnesium sulfate therapy during asphyxia in near-term fetal lambs does not compromise the fetus but does not reduce cerebral injury. American Journal of Obstetrics and Gynecology; 176(1 part1):18-27.

10/17/2020