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Hypomagnesemia at admission in ICU associated with complications in preeclampsia with severity criteria

Summary

Background: Severe preeclampsia is a multifocal syndrome recognized by hypertension and proteinuria of recent onset after the 20 WG. It is defined as blood pressure levels greater than 160/110 mmHg associated with hypertensive encephalopathy, creatinine greater than 1.1 mg/dl, AST or ALT greater than 70 mg/dl or twice its previous value, LDH > 600 mg/dl, total bilirubin greater than 1.2 mg/dl at the expense of indirect bilirubin. Affecting between 3 and 10% of pregnancies, it is one of the leading causes of maternal death in the world.

Objective: To estimate the association of magnesium levels as a factor for the development of complications in patients with severe preeclampsia.

Methods: Observational, prospective, longitudinal, and analytical study. A total of 56 patients from a second-level hospital with severe preeclampsia criteria were included, and serum magnesium measurements were taken at admission, 12 hours and 24 hours. Descriptive and analytical statistics were obtained using measures of association with 95% CI, Cox proportional hazards.

Results: Patients admitted to the ICU had greater neurological symptoms with low magnesium levels, in addition to complications such as HELLP syndrome in 25% and eclampsia in 7.1%, which did not show significant differences. **Conclusion:** The application of magnesium sulfate causes changes in the delay and decrease of signs and symptoms. The effects on clinical variables, history, and complications with hypomagnesemia justify the administration of magnesium sulfate as the ideal treatment for neurological involvement in preeclampsia.

Keywords: Hypomagnesemia, HELLP syndrome, Eclampsia

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Introduction

Worldwide, a woman dies every 3 minutes from preeclampsia, approximately 50,000 women die annually. Since magnesium sulfate emerged as a therapeutic agent proposed by Lazard, in the late 1925s and early 1930s, who published the first cases treated intravenously, the reduction in complications has been remarkable, especially in the development of seizures in patients with severe preeclampsia and eclampsia.[1] Several studies have compared anticonvulsants of various kinds against magnesium sulfate, and the results have always been favorable to magnesium sulfate. However, its mechanisms and effects on the brain of pregnant women with preeclampsia are poorly understood.[2]

The MAGPIE trial was a randomized, multicenter study conducted between 1998 and 2001 that sought to determine whether magnesium sulfate therapy was beneficial in women with preeclampsia, where no significant differences were found in severe maternal morbidity, toxicity, complications of labor, or neonatal morbidity. However, adverse effects were lower in women receiving intravenous maintenance doses. It was concluded that magnesium sulfate reduced the risk of eclampsia, and therefore maternal death, and is currently used as primary and secondary prophylaxis.[3]

Magnesium is the fourth most abundant ionized mineral in the human body, and the second most abundant cation within cells. Magnesium acts as a natural antagonist of calcium (Ca2+), a key element in smooth muscle contraction; it reduces the release of acetylcholine at the neuromuscular junction, which inhibits the transmission of nerve impulses, thus causing muscle relaxation. At the level of the central nervous system, it blocks the receptors of the enzyme N-Methyl-aspartate (NMDA), causing the receptors of the enzyme amino-hydroxy-methyl-isoxazolepropionate (AMPA), a postsynaptic neuron, to be activated and the excitatory response to be reduced, reducing hypoxic cellular damage; It also contributes to the release of neuropeptides such as calcitonin gene-related peptide (CGRP), which has a vasodilator effect and reduces the release of substance P, generating a negative effect on the secretion of inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin.[4]

The therapeutic range ranges from 4 to 7 meq/L (4.8 to 8.4 mg/dL) in women with adequate renal function. Toxicity is directly related to these levels. There is loss of deep tendon reflexes with values between 7 and 10 mEq/L (8.5 to 12 mg/dL), respiratory paralysis between 10 and 13 mEq/L (12 to 16 mg/dL), arrhythmias with values greater than 15 mEq/L (greater than 18 mg/dL), and cardiac arrest with values greater than 25 mEq/L (greater than 30 mg/dL). If there are clinical signs of toxicity, the maintenance dose should be discontinued, and with values greater than 8 mEq/L (9.6 mg/dL), determination of serum magnesium every two hours. The infusion can be restarted when the dose is less than 7 mEq/L (8.4 mg/dL).[5] The maintenance dose should be adjusted in women with renal impairment. It should be maintained at 1 g/hour if serum creatinine is greater than 1.2 and less than 2.5 mg/dL and the maintenance dose should not be administered if serum creatinine is equal to or greater than 2.5 mg/dL. If recurrent seizures

occur despite the use of magnesium sulfate, an additional bolus of 2 g should be given in 20 minutes and an increase in the maintenance infusion to 2 g or 3 g/hour.[6]

The different treatment regimens are:

a) Zuspan: Loading dose of 4 g for 20 minutes followed by a maintenance regimen of 1 g per hour for 24 hours.

b) Zuspan Modified: Loading dose 4 g IV diluted in 250 mL 5% glucose solution for 20 minutes followed by 1-2 g IV per hour (900 mL glucose 5% + 10 ampules) to deliver 100 to 200 mL/h.

c) Pritchard includes a loading dose of 4 g intravenously combined with 10 g intramuscularly (divided and administered into 2 separate injections, one into each buttock), followed by a maintenance regimen of 5 g intramuscularly every 4 hours for 5 doses.

d) Sibai: Loading dose of 6 g intravenously in 10 minutes followed by 2-3 g per hour.

e) Dhaka: Loading dose of 10 mg, followed by 2.5 mg administered over four hours.[7]

In a group of 710 patients, Arcos HH et al. found the relationship between serum magnesium levels as a risk factor for the development of preeclampsia and severity criteria, establishing that suboptimal levels are related to at least 74%.[8]

The purpose of this study is to estimate the association of low magnesium levels with complications in patients with severe preeclampsia.

Materials and methods

An observational, longitudinal, prospective, and analytical study was carried out in a second-level care hospital in the State of Mexico. The sample size was calculated using the Epi Info calculator; with a 95% CI, with a power of 80%, with a percentage in an unexposed group of 24% and a percentage of the exposed group of 74%, with a total of 53 patients, with quota sampling. Patients with severe preeclampsia criteria were included with blood pressure values of 160/110 mmHg after 20 WGs, in addition to magnesium measurement from hospital admission and during admission to the Intensive Care Unit. Those with chronic kidney disease and severe malnutrition were excluded. Patients who left the ICU before 24 hours of stay were excluded. To carry out the research, it was submitted to an opinion of the health ethics committee and research committee with registration number R-2022-1401-077.

Statistical analysis

Descriptive statistics were used using measures of central tendency according to their normality, as well as frequencies and percentages. Differences were made between magnesium levels, with a cut-off point for hypomagnesemia < 1.6mg/dl with clinical data and complications during their stay in the ICU using a chi-square test. With a significant $p < 0.05$. To determine the Hazzard Ratios, proportional risks of COX were used.

Results

The total number of women in ICU was 56, with a mean age of 27.9 + 6.53. The most frequent comorbidities were gestational hypertension (21.4%) and chronic hypertension. 91.1% reported having had prenatal care; the most frequent clinical signs on admission to the ICU were hyperreflexia (98.2%), while the most frequent symptom reported by patients was headache (64.3%). The initial treatment of patients in the ICU was nifedipine and metoprolol, while the most frequent complications were HELLP syndrome (25%) and postpartum hemorrhage (16.1%) followed by acute kidney injury (14.3%). The length of hospital stay was on average 2 days and the mortality rate was 1.8% (Table 1).

Table 1 Demographic, Clinical and Outcome Characteristics of Patients with Severe Preeclampsia in the Intensive Care Unit (ICU)

VARIABLES	N=56	%
	Stocking	+DS
	Median	RIQ
Age	27.9	6.53%
Chronic High Blood Pressure	8	14.30%
Number of Gesta	2	(1-3)
Body Mass Index	30	(28-33.2)
Shock Index	0.59	(0.52-0.67)
Labs & Symptoms		
Total bilirubin (mg/dL)	0.9	(0.2-0.52)
Indirect Bilirubin (mg/dL)	0.2	(0.1-0.5)
ALT (U/L)	31.5	(16-98)
AST (U/L)	36	(23.7-132.2)
Ingress Magnesium (mg/dl)	1.8	(1.6-2.0)
12-hour magnesium (mg/dL)	2.4	(1.8-3.3)
Magnesium at 24 hours (mg/dL)	2	(1.7-2.4)
Uric Acid (mg/dl)	5.5	(4.5-7.3)
INR	0.86	(0.84-0.91)
Fibrinogen (mg/dL)	610	(531-726)
Creatinine (mg/dL)	0.6	(0.5-0.7)
Urinary Index	1.5	(1.14-2.27)
Epigastralgia	20	35.70%
Nausea	21	37.50%
Vomit	19	33.90%
Headache	36	64.30%
Visual disturbances	20	35.70%
Tinnitus	19	33.90%
Hyperreflexia	55	98.20%
Medications during ICU		
Nifedipine	54	96.40%
Prazosin	11	19.60%
Losartan	11	19.60%
Metoprolol	42	75%
Hydrochlorothiazide	6	10.70%
Use of Magnesium Sulfate	37	66%
Complications		
Postpartum Hemorrhage	9	16.10%
Hypovolemic Shock	3	5.40%
Acute pulmonary edema	4	7.10%
HELLP Syndrome	14	25%
Eclampsia	4	7.10%
Disseminated Intravascular Coagulation	3	5.40%
Cerebral Vascular Disease	3	5.40%
Acute Kidney Injury	8	14.30%
Pulmonary thromboembolism	3	5.40%
Death	1	1.80%
Length of Stay in ICU	2	(1.0-2.0)

The associations of magnesium less than 1.6mg/dl with respect to history, clinical symptoms and outcomes were obtained with a significant difference in the first hours of admission to the ICU. The patients who had the highest serum magnesium level were the multi-pregnant, while the patients who had levels below 1.6 mg/dl at admission presented headache, epigastric pain, nausea, vomiting, visual disturbances, and among the first complications that occurred in the first hours of admission were HELLP syndrome followed by Eclampsia. AKI was more prevalent among women with magnesium levels greater than 1.6 mg/dl (Table 2). On the other hand, serum magnesium levels in the following 12 and 24 hours were not significant for the continuation of clinical studies or patient outcomes.

Table 2 Comparison of clinical variables, background, and complications according to magnesium levels at admission

Variable	n	Mg<1.6 N(45)	Mg>1.6 N(11)	p
Age > 34	11	7 (15.6%)	4 (36.4%)	0.198
Multi-Task	14	11 (24.4%)	3 (27.3%)	1
Gestational SAH	12	9 (20%)	3 (27.3%)	0.68
Epigastric pain	20	13(28.9%)	7 (63.6%)	0.04
Nausea	21	15 (39.1%)	6 (54.5%)	0.3
Vomiting	19	14 (31.1%)	5 (45.5%)	0.48
Headache	36	29 (64.4%)	7 (63.3%)	0.01
Visual disturbances	20	13 (28.9%)	7 (63.6%)	0.041
Tinnitus	19	12 (26.7%)	7 (63.6%)	0.032
Hyperreflexia	30	23 (51.1%)	7 (70%)	0.318
Postpartum hemorrhage	9	3 (27.3%)	6 (13.3%)	0.358
Hypovolemic Shock	3	0 (0%)	3 (6.7)%)	0.761
Acute pulmonary edema	4	1 (9.1%)	3 (6.7%)	1
HELLP Syndrome	14	12 (26.7%)	2 (18.2%)	0.007
Eclampsia	4	3 (6.7%)	1 (9.1%)	0.78
CID	3	2 (4.4%)	1 (9.1%)	0.48
EVC	3	2 (4.4%)	1 (9.1%)	0.48
LRA	8	1 (9.1%).	7 (15.6%)	0.58
PET scan	3	2 (4.4%)	1 (9.1%)	0.488

The chi-square test was used with a significance level p < 0.005.

In a Cox proportional hazards analysis for the development of HELLP Syndrome, hypomagnesemia on ICU admission had an HR of 1.21 95% CI (0.26-5.53) with a p of 0.79, magnesium < 1.6mg/dl at 12 hours had an HR of 1.65 95% CI (0.20-13.26) with a *p* of 0.63 and a lower magnesium figure at 24 hours had an HR of 24.97 95% CI (0.06-178.6) with a p of 0.45. The other outcome was eclampsia; however, as there was a smaller sample of this sample, the Cox proportional hazards analysis with a magnesium < 1.6 at admission presented an HR of 1.40 95% CI (0.14-13.55) with a *p* of 0.76. At 12 hours an HR of 1.23 95% CI (0.34-10.67) and at 24 hours an HR of 1.18 95% CI (0.12-17.83). In a Kapplan-Meier analysis, it was observed that the lower the magnesium levels at ICU admission, the greater the development of complications such as HELLP Syndrome and therefore survival may decrease (Figure 1).

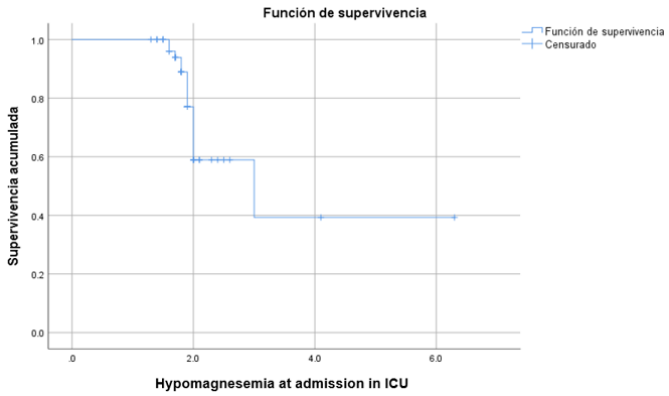

Figure 1 What is commented about kaplan-meier's analysis.

Discussion

Magnesium sulfate as a drug in the prevention and treatment of eclampsia has been widely used, resulting in a decrease in neurological manifestations caused by preeclampsia related to reversible posterior leukoencephalopathy. Since the publication of the MAGPIE study, the use of magnesium sulfate in preeclampsia has been questioned. It has been written against and in favor, however, the results worldwide show that magnesium sulfate is paramount in the prevention and control of neurological symptomatology. This is corroborated by our study, taking into account that if a patient has low magnesium levels, they can have complications, this being eclampsia and in our study the HELLP syndrome. Several studies have evaluated anticonvulsants of various kinds against magnesium sulfate with favorable results to magnesium sulfate,[9,10] and the eligibility of its application is increased because it is a safe treatment, with tolerable adverse effects, without having relevant repercussions on the health of the mother and the product of gestation.[11-13] The results of the present research are consistent with the findings of the MAGPIE trial, which showed that magnesium sulfate is essential in the prevention and control of neurological symptoms, as it was in our study.[14]

The levels found in women at admission were 1.9, which differs from the findings of Loustaunau who found that the mean magnesium content in hypertensive women was 1.7. While the lower limit in this sample was 1.7, the mean of the total was slightly higher, which may be due to differences in measurement technique.

The results support the theory of Euser et al.[14] that magnesium sulfate can act as a vasodilator, to decrease peripheral vascular resistance or relieve vasoconstriction, as well as favors the protection

of the blood-brain barrier and limits the formation of cerebral edema, in addition to the fact that it can act as a central anticonvulsant for eclampsia; however, in this research it had a large part of the HELLP syndrome, Although it is not related to magnesium, it is related to the severity of preeclampsia and therefore greater complications. Based on what was described by Padda[15] it is necessary to consider the mother's body weight and serum creatinine concentration in 24 hours to provide a dose with greater benefits. Since what was observed in this study is that patients who have a low magnesium level at admission to hospitalization or ICU, these factors must be considered in order to improve the therapeutic doses and avoid complications, since it is observed that hypomagnesemia on admission presents greater neurological symptoms than the following hours. Therefore, an adequate regimen must be followed, as well as serum magnesium monitoring, to avoid overdose and put the patient's life at risk due to cardiopulmonary compromise or organic functions such as renal. This research was conducted with a small number of the population, so the sample size will need to be increased to give an accurate risk of hypomagnesemia with the complications of preeclampsia, so more research studies are needed.

Conclusion

Although the results are not conclusive to define hypomagnesemia as an agent associated with HELLP syndrome and eclampsia, it is possible to affirm that the application of magnesium sulfate generates changes in survival and in the reduction of signs and symptoms, therefore, the effects on the clinical variables, history and complications with hypomagnesemia justify its administration as the perfect treatment for neurological compromise in preeclampsia.

Acknowledgments

None.

Conflicts of interest

None.

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