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MAGNESIUM SULFATE IN THE TREATMENT OF PRE-ECLAMPSIA AND ITS ADVERSE EFFECTS

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Abstract: Introduction: One of the most serious complications of pre-eclampsia is the occurrence of a seizure, called eclampsia. Magnesium sulfate is the first choice in the treatment of preeclampsia, despite the risk of toxicity and possible adverse effects. Objective: To analyze the evidence on the use of magnesium sulfate in preeclampsia and address its main adverse effects. Methodology: A bibliographic search was carried out in three databases from 2017 to 2022 using the descriptors: "pre-eclampsia", "magnesium sulfate", "preeclampsia", "magnesium sulfate". Outcome: Studies show that magnesium sulfate has proven to be a superior agent than other drugs in reducing the risk of eclampsia. The main regimens for using magnesium sulfate are Pritchard's and Zuspan's. Its use carries a small risk of magnesium intoxication. Side effects include: flushing, sweating, nausea, drowsiness, headache, blurred vision, loss of patellar reflex, respiratory paralysis and even cardiac arrest. Conclusion: Prophylaxis of eclamptic seizures with magnesium sulfate is a milestone in the clinical management of preeclampsia. When administered, careful monitoring for signs of intoxication is paramount.
Keywords: Gestational hypertension. Pre eclampsia. Eclampsia. Magnesium sulfate.

INTRODUCTION

Hypertensive disorders of pregnancy are a major cause of maternal and fetal morbidity and mortality. Hypertension in pregnant women can be divided into 4 categories: pre-eclampsia/eclampsia; chronic hypertension; pre-eclampsia superimposed on chronic hypertension; and gestational hypertension.

Preeclampsia (PE) is a multifactorial and multisystem disease, specific to pregnancy, considered as the clinical expression of a maternal endothelial disease, mediated by the placenta and resulting from insufficient trophoblastic invasion of the spiral arterioles of the uterus. Although the pathophysiology of PE is not fully understood, some hallmark features of the disease are: increased vascular resistance of the uterine artery, chronic immune activation, intrauterine growth restriction, elevation of inflammatory cytokines, maternal endothelial dysfunction, reduction of vasodilators, and other systemic imbalances (AMARAL et al., 2017).

Clinically, pre-eclampsia is defined by the presence of arterial hypertension (systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg) associated with proteinuria (≥ 300 mg/24 hours), which manifests itself in a previously normotensive pregnant woman, after twentieth week of pregnancy. Proteinuria can be replaced by the protein/creatinine ratio, which is considered altered when the value is at least 0.3 mg/dL.

Currently, pre-eclampsia is also considered when, in the absence of proteinuria, there is maternal target organ dysfunction. Then, systemic alterations such as thrombocytopenia, impaired liver function, renal failure, lung edema and brain or visual disturbances, in association with hypertension, can diagnose PE without the need for proteinuria, 2017).

In its severe forms, the seizure sets in and the disease formerly called pre-eclampsia is now called eclampsia. And Eclampsia refers to the occurrence of convulsive, generalized tonic-clonic or coma crises in pregnant women with pre-eclampsia, being one of the most serious complications of the disease (FERNANDES et al., 2019; PADDA et al., 2021; PASCOAL et al, 2019; PERAÇOLI et al., 2019). Eclamptic seizures are a medical emergency and can occur after 20 weeks of gestation, either before delivery, intrapartum or postpartum. They require urgent intervention to prevent the death of the mother and fetus.

The definitive treatment of pre-eclampsia is delivery, in order to avoid the development

of serious complications resulting from the progression of the disease. Before terminating the pregnancy, it is essential to stabilize the clinical picture.

In this context, magnesium sulfate (MgSO4) is recommended by all major guidelines as the first choice agent for the prevention and treatment of eclamptic seizures in women with pre-eclampsia and eclampsia and is used worldwide (AKBAR et al., 2020; COUTINHO et al., 2021; PADDA et al., 2021). Despite the risk of toxicity and possible adverse effects, many studies prove that MgSO4 is superior in the treatment of eclampsia compared to other drugs. The ideal magnesium sulfate regimen must be a dose that is sufficient to protect against eclampsia and has minimal side effects. Note that it is essential to be aware of the signs of intoxication in every administration of MgSO4.

In this review, we will address the use of magnesium sulfate in the treatment of pre-eclampsia and prevention of eclamptic seizures, identifying its main adverse effects and toxicity.

OBJECTIVE

General objective: To analyze the use of magnesium sulfate in the treatment of pre-eclampsia and prevention of eclampsia.

Specific objectives: To verify the efficacy and indications of treatment with magnesium sulfate in pregnant women. Describe recommendations for prescribing magnesium sulfate. Identify the adverse effects and possible complications of treatment with magnesium sulfate.

METHODOLOGY

This is a simple (or narrative) literature review. The present study carried out a bibliographic search in three electronic databases of scientific publications: PubMed (US National Library of Medicine), SciELO (Scientific Electronic Library Online) and BVS (Virtual Health Library). For the incorporation of articles in the review, the last six years of production were used as the search period, from January 2017 to September 2022.

We chose to use Health Sciences Descriptors (DeCS) from the Virtual Health Library, developed from the Medical Subject Headings (MeSH) of the US National Library of Medicine (NLM). A combination of the following descriptors in Portuguese and English was used: "pre-eclampsia", "magnesium sulfate", "preeclampsia", "magnesium sulfate".

Inclusion criteria were: articles in Portuguese and English, published in the period from 2017 to 2022, which addressed the proposed themes for this research, made available in full. Exclusion criteria were: duplicate articles in the databases, which did not use the terms "pre-eclampsia" or "magnesium sulfate" in the title or abstract, which did not directly address the studied proposal.

At the end of this process, 10 articles were selected to compose the present review, which were considered more relevant to the researched topic. In addition, reference books and journals on obstetrics were included as complementary elements of the bibliographic survey for a better understanding of the subject.

RESULT

The expressive number of publications on the use of magnesium sulfate (MgSO4) as an anticonvulsant, tocolytic and fetal neuroprotector portrays the relevance of the drug in the broad scenario of contemporary obstetric practice. MgSO4 reduces the incidence of eclampsia and maternal mortality, therefore, it must be considered in women with preeclampsia who are at risk of developing eclampsia or with severe target organ involvement or according to individual

protocol (PADDA et al, 2021; SCOTT et al., 2022).

Initially, it was believed that eclamptic seizures had a similar pathophysiology to other seizure disorders, however, the usual anticonvulsant drugs have not been shown to be as beneficial as MgSO4 in controlling eclamptic seizures. In this sense, studies show that magnesium sulfate proved to be a superior agent to benzodiazepines, phenytoin, lytic cocktail (chlorpromazine, promethazine and pethidine) and placebo in reducing the risk of eclampsia in women with PE (AKBAR et al., 2020; FERNANDES et al., 2019; PADDA et al., 2021; RAMOS et al., 2017). Its low cost, easy availability, relatively simple administration and monitoring procedure, and the fact that it does not cause sedation are positive points.

Magnesium (Mg2+) is the fourth most common ionized mineral in the human body and is distributed mainly in bones, muscles and soft tissues. Sulfate is the only magnesium preparation available for parenteral use (MgSO4.7H2O) and can be administered intramuscularly (IM) or intravenously (IV). As the intestinal absorption of magnesium is unstable, parenteral administration is preferred for the main obstetric indications (COUTINHO et al., 2019; COUTINHO et al., 2021).

There is no magnesium dosage regimen that is widely accepted as a standard of care. The main regimens for using magnesium sulfate are Pritchard's and Zuspan's, which must be used according to the experience of each service, since they are considered equally effective. Magnesium sulfate heptahydrate must be used and be aware of the available concentration of magnesium: MgSO4 50% (10 mL ampoule contains 5 g of magnesium); 20% MgSO4 (10 mL vial contains 2 g of magnesium); 10% MgSO4 (10 mL ampoule contains 1 g of magnesium) (FERNANDES et al., 2019; PERAÇOLI et al., 2019).

Pritchard's regimen involves administering two doses of MgSO4, consisting of a 4 g slow intravenous dose followed immediately by a 10 g intramuscular dose divided into 5 g into each buttock. Its maintenance dosage consists of 5 g intramuscularly every four hours. In the Zuspan regimen, there is a single slow intravenous dose of 4 g as a loading dose, followed by a maintenance infusion of 1 g per hour in a continuous infusion pump, as shown in Table 1.

MgSO4 scheme	**attack dose**	**maintenance dose**
Pritchard's Scheme	4 g intravenously (bolus), given slowly + 10 g intramuscularly (5 g in each buttock)	5 g deep intramuscularly every 4 hours
Zuspan's scheme	4 g intravenously (bolus), given slowly	1 g intravenously per hour in a continuous infusion pump (BIC)

Table 1– Magnesium sulfate regimens in the treatment of preeclampsia

Source: Adapted from Peraçoli et al. (2019).

As intramuscular administration results in greater fluctuation in magnesium levels and is associated with local effects, particularly pain and the risk of hematomas and abscesses, intravenous regimens have increasingly become recommended in various obstetric centers around the world.

The mechanism of action by which magnesium sulfate is effective in preventing eclampsia is unclear. MgSO4 is an anticonvulsant agent that appears to act on the central nervous system (CNS), vascular endothelium, and neuromuscular junction. In this perspective, magnesium acts as an antagonist of N-methyl-D-aspartate (NMDA) receptors, thus promoting blockade of these receptors and, consequently, generalized CNS depression and inhibition of excitability in the cerebral cortex (AKBAR et al, 2020; COUTINHO et al., 2019; DHARIWAL et

al., 2017; PADDA et al., 2021). Furthermore, it is suggested that it is a potent vasodilator by decreasing intracellular calcium and stimulating the synthesis of nitric oxide in endothelial cells, causing arterial vasodilation and reduction of vasospasm. It is also understood that the vasodilator effect on intracranial vessels enables the reduction of cerebral ischemia in women with PE. Furthermore, magnesium inhibits calcium metabolism and acetylcholine release at the neuromuscular junction.

Although MgSO4 has been shown to be effective in preventing eclampsia, its use carries a small risk of magnesium intoxication or hypermagnesemia. This problem occurs mainly in women with significant renal involvement or who have received high MgSO4 infusion rates. The most common symptoms of magnesium intoxication are due to its depressant effects on the CNS, blockade of neuromuscular transmission and peripheral depression that affects muscle contractility.

Maternal side effects depend on the adequacy of doses and infusion speed, and the most frequent ones are transient and less severe, such as flushing, sweating, nausea, drowsiness, headache and blurred vision. The first warning of maternal toxicity is loss of the patellar reflex, usually at magnesium concentrations between 3.5 and 5 mmol/L. More serious adverse effects such as respiratory paralysis and cardiac arrest may occur at supratherapeutic concentrations above 5 mmol/L. The main adverse effects of using magnesium sulfate are related to its serum concentration in Table 2.

Effects	**Serum magnesium levels**
physiological effects	1.8 to 2.5 mg/dL (0.7 to 1.05 mmol/L)
therapeutic effect	4.8 to 8.4 mg/dL (2 to 3.5 mmol/L)
Loss of deep reflexes	8.5 to 12 mg/dL (3.5 to 5 mmol/L)
respiratory paralysis	12 to 16 mg/dL (5 to 6 mmol/L)
Cardiac conduction changes	> 18 mg/dL (7.5 mmol/L)
cardiac arrest	30 mg/dL (12.5 mmol/L)

Table 2– Different serum magnesium concentrations and their main effects

Source: Adapted from Coutinho et al. (2021).

Sulfate therapy is contraindicated for women with myasthenia gravis, due to the risk of myasthenic crisis, defined by respiratory failure associated with severe muscle weakness. It must also be avoided in patients with myocardial impairment or cardiac conduction defects, due to its anti-inotropic effects. In addition, concomitant administration with calcium channel blockers can cause neuromuscular blockade and arterial hypotension, but the risks seem to be minimal in clinical practice.

As for possible fetal and neonatal complications, none seem to be increased with adequate antenatal exposure to MgSO4 (COUTINHO et al., 2019). Therefore, given the low risk of toxicity and since labor and delivery are the most likely times for seizures to occur, women with pre-eclampsia or eclampsia must receive parenteral MgSO4 during labor and up to 24 hours after birth or after the last puerperal seizure. Postpartum, sulfate therapy is recommended for new-onset preeclampsia with any associated neurological symptoms, such as headache or blurred vision (HAUSPURG et al., 2022). As high serum concentrations of MgSO4 can lead to respiratory and cardiac depression and death, careful administration and monitoring

for toxicity is critical.

DISCUSSION

Currently, magnesium sulfate therapy is recommended in the main guidelines around the world and has established itself as an important and effective treatment of pre-eclampsia and prevention of eclamptic seizures. It is a drug with anticonvulsant action that performs better compared to other drugs in relation to PE and that has adverse effects depending on the doses administered and the speed of infusion.

Magnesium sulfate, then, is not a risk-free drug, although maternal magnesium intoxication is rarer in the presence of normal glomerular filtration and the loading dose can be administered safely regardless of renal function. However, compliance with proper administration techniques and careful monitoring for signs of intoxication are mandatory. The obstetrician must not be apprehensive about the use of magnesium sulfate, as failing to administer it is more reckless than the occurrence of any risk. Only a few precautions are recommended, which must be followed.

In this sense, if there is a need to refer the pregnant woman to another service, the preferred scheme is intramuscular (Pritchard), as it provides greater safety for transport (PERAÇOLI et al., 2019). When administered intravenously, an infusion pump must be used with strict nursing control to avoid the risk of depression and respiratory arrest due to overdose (RAMOS et al., 2017).

Maintenance doses must be administered only after mandatory clinical assessment of MgSO4 toxicity, which must be performed every 1 or 2 hours and include the following conditions: presence of the patellar reflex, which is a deep reflex whose disappearance is the first manifestation hypermagnesemia clinic; respiratory rate greater than 12 breaths per minute; and urine output greater than 100 ml every 4 hours (≥ 25 ml/hour). Routine assessment of serum magnesium levels is not necessary, but is indicated every 6 hours when the clinic is suggestive of intoxication or if there is renal failure (COUTINHO et al., 2019). The main conditions that must be monitored during sulfate therapy are shown in Table 3.

duration of treatment	24 hours postpartum or after the last puerperal seizure
Clinical control of toxicity	Preserved deep reflexes
	Respiratory rate ≥ 12 bpm
	Diuresis ≥ 100 ml / 4 hours
Serum toxicity control	Indicated if creatinine ≥ 1 mg/dL
	Therapeutic level is between 2 and 3.5 mmol/L
Antidote	Calcium gluconate 10%, 10 ml (contains 1 g) IV

Table 3– Clinical guidelines related to the use of magnesium sulfate

Source: Adapted from Coutinho et al. (2021).

In the face of changes in these parameters, it is recommended to reduce or stop the intravenous infusion or not to perform the intramuscular dose. Then, MgSO4 levels and renal function are evaluated. When values are within normal limits, treatment must be restarted. In patients with renal insufficiency (creatinine ≥ 1.2 mg/dL), the maintenance dose must be half the recommended dose, and the infusion of magnesium sulfate must only be interrupted if diuresis is less than 25 ml. It is important to remember that the recommendation is to maintain magnesium sulfate for 24 hours after the resolution of the pregnancy or after the last seizure.

The antidote used in magnesium sulfate intoxication is calcium gluconate. This quickly reverts the adverse maternal effects of MgSO4 and, in cases considered less severe of intoxication, it is used at an initial dose of 10 ml at 10% (1 g intravenously administered

slowly). Higher doses such as 15 to 30 ml at 10% are indicated for patients with cardiac arrest or who show signs of severe cardiac toxicity associated with hypermagnesemia (COUTINHO et al., 2021; FERNANDES et al., 2019; PERAÇOLI et al., 2019;).

CONCLUSION

In view of the evidence, it is observed that pre-eclampsia is a very important disease specific to pregnancy, since it influences the outcomes related to the maternal-fetal binomial. Pregnant women with PE are susceptible to having convulsive crises, configuring the picture of eclampsia, which makes the scenario a medical emergency, as it puts the lives of both at risk.

Prophylaxis of eclamptic seizures with magnesium sulfate is a cornerstone of the clinical management of preeclampsia. When administered appropriately and at the right time, such a procedure is capable of reducing maternal and fetal mortality and morbidity (AMARAL et al., 2017). Despite the fear of adverse effects, it must be administered whenever indicated, with careful monitoring of signs of intoxication being essential.

In this sense, during the administration of MgSO4, a clinical evaluation of the presence of deep tendon reflexes, adequate respiratory rate and satisfactory urinary output must be performed. Otherwise, therapy must be discontinued and the use of calcium gluconate antidote must be considered. Therefore, the safe prescription of magnesium sulfate must follow the recommended doses and be associated with strict clinical monitoring.

After all, the prevalence of eclampsia has decreased due to improved prenatal care, judicious use of medical therapy, including prophylaxis of seizures with magnesium sulfate, and delivery at term by induction or caesarean section (PADDA et al., 2021). For this reason, the use of magnesium sulfate and the recognition of its adverse effects are essential in obstetrical medical practice to ensure the safety of patients with preeclampsia.

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