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Modulatory effect of two regimens of magnesium sulfate on the systemic inflammatory response in pregnant women with imminent eclampsia

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Abstract

Objective

This study compared the modulatory effect of two intravenous magnesium sulfate ($MgSO_4$) regimens on the systemic inflammatory response in pregnant women diagnosed with imminent eclampsia.

Study design

In a single-blind cross-sectional study, 33 women were allocated according to the Zuspan (n = 16) and Sibai (n = 17) $MgSO_4$ regimens, and treated for 24 h. Blood samples were collected pre-administration of the loading dose, at 24 h of the maintenance dose of $MgSO_4$, and at 48 h, when patients were without treatment. Plasma was used to determine interleukin (IL)-1 beta (IL-1β), IL-6, IL-10, tumor necrosis factor-alpha (TNF-α), heat shock protein (Hsp70), and heme oxygenase-1 (HO-1) by ELISA.

Results

The treatment with the Zuspan's regimen didn't change plasma concentrations of TNF-α, IL-10, and Hsp70 in the three-time points studied. However, it decreased IL-1β at 24 h and 48 h and IL-6 at 48 h, and increased HO-1 concentration at 48 h. On the other hand, compared to the pre-treatment period, Sibai's regimen induced a significant decrease in TNF-α, IL-1β, IL-6, and Hsp70, while increased HO-1 levels both at 24 h and 48 h and, IL-10 concentration at 48 h.

Conclusions

Sibai's regimen determined an early and efficient immunoregulatory effect on systemic inflammatory response in preeclampsia, suggesting that the maintenance dose of two grams of $MgSO_4$ was better than one gram in the treatment of imminent eclampsia.

Introduction

Preeclampsia is a pregnancy-specific multisystemic disease that affects 2–10% of human pregnancies and is the main cause of maternal mortality [1]. Although the pathophysiology of preeclampsia is not fully understood, the most accepted hypothesis in the literature emphasizes the maladaptive immune response and the inappropriate invasion of spiral arterioles by the trophoblast, which result in tissue damage caused by ischemia/hypoxia [2], [3]. All normal pregnancies are associated with a systemic inflammatory reaction; however, the tissue damage in preeclampsia determines a systemic inflammatory response with greater intensity [4]. Thus, this immune disorder appears to have its origin in the placenta and contributes to the pathogenesis of the disease [5], [6].

The exacerbated systemic inflammatory reaction that occurs in preeclampsia is characterized by the excessive production of pro-inflammatory cytokines, such as interleukin-1 [IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α), increased levels of superoxide anion and hydrogen peroxide, and shows a higher plasma concentration of heat shock protein 70 (Hsp70) [7], [8], [9], [10], [11]. On the other hand, women with preeclampsia are deficient in the mechanisms that control inflammation, showing a reduction in the levels of the anti-inflammatory cytokine IL-10 [12], and in the concentration of endogenous inhibitors such as haptoglobin, hemopexin, and heme oxygenase-1 enzyme [13], [14].

Clinically, preeclampsia is characterized by the association of arterial hypertension and proteinuria occurring after the 20th week of gestation, or in the absence of proteinuria, by the manifestation of maternal dysfunctions such as renal failure, liver involvement, neurological or hematological complications, uteroplacental dysfunction, and fetal growth restriction [1], [15]. In this context, preeclampsia can evolve into critical situations, directly related to the high rates of maternal and perinatal morbidity and mortality, which are hypertensive crisis, HELLP syndrome, and eclampsia [16].

Eclampsia is considered one of the serious complications of preeclampsia and is defined by the manifestation of one or more generalized tonic-clonic seizures and/or coma, in a pregnant woman with preeclampsia, in the absence of neurological diseases [17], [18]. Most patients have premonitory signs/symptoms in the hours before the initial seizure as headaches, such as persistent frontal or occipital headaches or thunderclap headaches, visual disturbances (scotomata, loss of vision as cortical blindness, blurred vision, diplopia, photophobia), and right upper quadrant or epigastric pain [19].

Despite advances in the understanding of preeclampsia, the pathogenesis of eclampsia seizures is not well established [18]. It is proposed to be due to increased permeability of the blood-brain barrier, which causes alteration in cerebral blood flow attributed to decreased of its autoregulation that is mediated and modulated through myogenic, neurogenic, metabolic, or endothelial control [20], [21], [22].

The manifestation of a seizure in pregnant women with preeclampsia is a medical emergency and requires immediate treatment to prevent maternal and perinatal mortality. A historic milestone for both the prevention and treatment of eclampsia seizures was the use of magnesium sulfate ($MgSO_4$), considered the medication of choice [23], [24], [25]. The two currently recommended regimens (Zuspan and Pritchard) are internationally accepted as standard regimens, for their clinical efficacy demonstrated in the two largest clinical trials of $MgSO_4$ [26], [27] and recommended by the World Organization of Health [28]. Therefore, there is consensus in the literature that patients with severe preeclampsia should prophylactically receive $MgSO_4$ to prevent eclamptic seizures [29].

According to Sibai et al. [30], [31], the maintenance dose of 1 g/hour of $MgSO_4$ in the Zuspan regimen [32] is not sufficient to achieve and maintain therapeutic concentrations and propose increasing the maintenance

concentration to 2 g/hour, in a continuous infusion, to achieve the same serum concentrations of the intramuscular treatment proposed by Pritchard. Thus, Sibai's regimen [31] suggests the use of an initial dose of 6 g of $MgSO_4$, followed by a maintenance dose of 2 g/hour, both administered intravenously [33].

The mechanism of action of $MgSO_4$ in the prophylaxis and treatment of eclampsia remains poorly understood. Some authors believe that this action is mainly peripheral at the neuromuscular junction with minimal or no central effect, while others believe that the main action is central with minimal effect on the neuromuscular blockade. Thus, magnesium would act as a peripheral vasodilator, reducing systemic blood pressure protecting the blood–brain barrier and limiting cerebral edema, increasing the seizure threshold through its interaction with the cell membrane [34], [35].

Magnesium sulfate use as prophylaxis for eclamptic seizures in clinical settings is supported by studies with experimental models of preeclampsia and eclampsia, which show satisfactory results from the use of this agent [36], [37], [38]. In addition to the effects on the central nervous system, $MgSO_4$ has anti-inflammatory effects, by reducing the synthesis of pro-inflammatory cytokines in eclampsia-induced in pregnant rats [37], [39], [40]. In vitro studies showed that $MgSO_4$ treatment of monocytes from umbilical cord stimulated with inflammatory agents significantly led to a decrease in the production of TNF-α and IL-6 [41]. These studies suggest that the reduction of neuroinflammation may be a mechanism by which magnesium prevents the eclampsia symptoms during severe preeclampsia.

While in vitro studies of the modulating effect of $MgSO_4$ on cytokine production are well characterized, reports in the literature regarding its therapeutic effect in vivo on the serum concentration of inflammatory cytokines in pregnant women with preeclampsia are scarce. Chen et al. [42] demonstrated that the treatment of preeclamptic women with $MgSO_4$ associated with nifedipine, a calcium channel blocker, reduces the circulating concentration of IL-6.

So far, there are no studies demonstrating the activity of $MgSO_4$ treatment on the modulation of the systemic inflammatory response, observing its effect on the production of anti-inflammatory molecules such as the cytokine IL-10 and the antioxidant enzyme heme oxygenase-1, which are decreased in preeclampsia [12], [14]. Furthermore, in the literature, there are no reports of the effect of $MgSO_4$ on the release of Hsp70 protein, which is increased in severe preeclampsia [7]. Considering the importance of immunomodulatory substances in the pathophysiology of preeclampsia and the recognized therapeutic effect of $MgSO_4$ in the prevention and treatment of eclampsia, this project was designed to evaluate the modulatory effect of two regimens of intravenous $MgSO_4$ treatment on pro- and anti-inflammatory mediators in pregnant women diagnosed with imminent eclampsia.

Section snippets

Study design and sample size

The single-blind cross-sectional study included 33 pregnant women with imminent eclampsia diagnosis, as defined by The American College of Obstetricians and Gynecologists [1], and received clinical assistance at the Obstetric Unit of Botucatu Medical School, São Paulo State University, UNESP, Brazil. The pregnant women were allocated according to the $MgSO_4$ regimen, in two groups: Zuspan's regimen (n = 16) and Sibai's regimen (n = 17). The sample size was calculated considering the difference in …

Background characteristics

Table 1 shows the clinical, demographics, and laboratory characteristics of preeclamptic women, with the diagnosis of imminent eclampsia, before treatment with Zuspan's or Sibai's regimens of $MgSO_4$. Both groups were homogeneous, and no statistical differences were detected between the two groups regarding the parameters of maternal age, gestational age at the moment of imminent eclampsia diagnosis, body mass index, ethnicity, parity, systolic and diastolic blood pressure, proteinuria, uric…

Discussion

The present study comparatively evaluated the immunomodulatory effect of magnesium sulfate on the systemic inflammatory response in pregnant women with imminent eclampsia undergoing treatment with two $MgSO_4$ regimens (Zuspan's regimen and Sibai's regimen). The results showed that preeclamptic women treated with Sibai's regimen had significantly higher serum concentrations of the magnesium ion when compared with the Zuspan's regimen group.

It is known that the serum concentration of magnesium ion…

Author contributions

MRV, JCP, and MTSP conceived the ideas, designed the experiments, analyzed the data, and prepared the manuscript. MRV, PBS, and FRGB performed the experiments. JCP, VTMB, HMN, RAAC, and JFA selected preeclamptic women for the study and treated the patients with magnesium sulfate. All authors reviewed the manuscript and approved the final version for publication.…

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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