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Original Article

The impact of magnesium sulfate therapy on angiogenic factors in preeclampsia

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ABSTRACT

Objective: The objective was to evaluate whether intravenous magnesium sulfate (magnesium) alters levels of angiogenic factors in women with preeclampsia.
Study design: This was a prospective cohort study comparing women with preeclampsia treated with magnesium for seizure prophylaxis to those who were not. Serum levels of angiogenic factors, soluble fms-like tyrosine kinase 1, soluble endoglin and placental growth factor, were measured at the time of diagnosis and approximately 24 h later. Secondary analysis compared women receiving magnesium for preeclampsia to women receiving magnesium for preterm labor. Analysis of covariance was used to compare levels at 24 h, adjusting for levels at enrollment and potential confounders.
Results: Angiogenic factor levels did not differ between preeclampsia groups with and without magnesium or between preeclampsia and preterm labor groups treated with magnesium (all $P > 0.05$).
Conclusion: Magnesium likely decreases seizure risk in preeclampsia by a mechanism other than altering angiogenic factor levels.

Introduction

Magnesium sulfate (magnesium) is routinely used for seizure prophylaxis in patients with preeclampsia and eclampsia. Both observational studies and randomized controlled trials suggest that administration of magnesium reduces the risk of seizures and other complications in women with preeclampsia [1–7]. The mechanism of action of magnesium is not well understood [8,9]. Possible mechanisms that have been considered include enhanced vasodilation of cerebral vasculature, production of prostacyclin which decreases vasospasm secondary to endothelial dysfunction, reduction of endothelial injury from free radicals, prevention of calcium influx into ischemic cells, a direct anticonvulsant effect via antagonism of the glutamate N-methyl-D-aspartate receptor [10], inhibition of platelet aggregation, decrease in the release of acetylcholine at motor end plates [11], and reduction of placental TNF-alpha secretion [12]. Other effects that have been considered and dismissed include smooth muscle relaxation, inhibition of firing of cerebral cortical neurons and reduction in local ischemia [13].

The pathophysiology of preeclampsia is also poorly understood and may involve maternal, fetal and placental

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factors. An imbalance between anti-angiogenic factors, soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng), and pro-angiogenic factors, placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), likely contributes to the development of preeclampsia [14]. Compared to women with normal pregnancies, the levels of sFlt1 and sEng are elevated in serum of women with a clinical diagnosis of preeclampsia or eclampsia, while levels of PlGF and VEGF are low [14–17]. A disturbance in angiogenic profile prior to the onset of preeclampsia [15,18–20] and a correlation between levels of sFlt1 and the severity of preeclampsia have been demonstrated [15]. In addition, the over expression of sFlt1 in rats induces the preeclampsia phenotype [14,21,22], and the use of VEGF antagonists in patients with cancer results in symptoms consistent with preeclampsia [23,24].

A link between seizure prevention with magnesium and angiogenic factors was suggested by the report that promotion of angiogenesis by VEGF is dependent on extracellular magnesium levels [25]. We hypothesized that magnesium reduces the risk of seizure in patients with preeclampsia in part by altering serum levels of pro- and anti-angiogenic factors. Possible mechanisms for this action of magnesium include: binding of sFlt1 and sEng receptors resulting in the release of VEGF, binding of calcium channels resulting in decreased secretion of sFlt1, induction of vasodilation and decreasing placental ischemia resulting in decreased secretion of sFlt1, alteration of the translation process resulting in a decreased synthesis of sFlt1 and binding of sFlt1 resulting in decreased direct endothelial damage from sFlt1.

The objective of this study was to evaluate whether intravenous magnesium alters levels of angiogenic factors in women with preeclampsia. We measured sFlt1, sEng and PlGF at the time of diagnosis or before administration of magnesium and approximately 24 h later. We also calculated the sFlt/PlGF ratio, which has been used as a measure of circulating angiogenic imbalance in prior studies [18,26].

Materials and methods

This prospective cohort study was conducted at Beth Israel Deaconess Medical Center, Boston, MA from May 2009 through December 2010. Patients with a confirmed diagnosis of preeclampsia, as defined by American Congress of Obstetricians and Gynecologists (ACOG) criteria, and patients receiving magnesium tocolysis for preterm labor were eligible for the study [27]. Exclusion criteria included maternal age less than 18 years, gestational age less than 24 weeks and prior treatment with magnesium in the current pregnancy. The decision to treat with magnesium was made by the primary obstetrician and was not influenced by participation in this study. The protocol was approved by the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center.

The primary aim of the study was to compare the levels of angiogenic factors in women diagnosed with preeclampsia who received magnesium to the levels in women with preeclampsia who did not receive magnesium. In an attempt to isolate the potential effect of magnesium on angiogenic factors, we also compared the women diagnosed with preeclampsia and treated with magnesium to women in preterm labor who received magnesium for tocolysis. A therapeutic magnesium level was defined as $\geqslant$4.0 mg/dL.

Demographic information was collected from the participants at the time of consent. Serum samples were collected at the time of diagnosis or prior to initiating magnesium therapy (time 1) and approximately 24 h later (time 2). All samples were collected prior to delivery. After collection, samples were centrifuged at 3000 RPM for 10 min at 4 °C, aliquotted and stored at −80 °C until analysis. Serum sFlt1, sEng and PlGF were measured, as previously described [14], using commercial ELISA kits (R&D Systems, Minneapolis, MN). All samples were run in duplicate. If more than 20% variation existed between duplicates, the assay was repeated and values were averaged. In cases where an additional ELISA was needed for one angiogenic factor, often all three factors were rerun; in these cases, the values also were averaged. Samples were randomly ordered, and a single person who was blinded to the study group performed all ELISAs.

All analyses were performed using SAS 9.2 (SAS institute Inc., Cary, NC). All tests were two sided, and P values <0.05 were considered statistically significant. Data are presented as mean (±standard deviation), median (interquartile range) or proportion. The t, Wilcoxon, chi-square or Fisher's exact test was used for bivariate analyses based on data type and distribution.

In order to determine whether magnesium altered angiogenic factor levels in women with preeclampsia we compared levels at time 2 in the two groups while accounting for the level at time 1, as well as potential confounders. The angiogenic factor levels were not normally distributed; thus, the values were log transformed. Analysis of covariance was used to calculate the adjusted mean log level of each of the 4 angiogenic factor or ratio values at time 2, along with 95% confidence intervals. In each of the 4 models we included the factor level or ratio at time 1 as an independent variable, as well as baseline participant and pregnancy characteristics that were statistically significantly different between the groups and were believed to potentially affect the levels of angiogenic factors. Four additional models were created to compare women with preeclampsia treated with magnesium to women with preterm labor who were treated with magnesium.

The sample size assumptions were based on angiogenic factor data from previous research at our center [28]. We assumed a 20% decrease in sFlt1 among women with preeclampsia treated with magnesium compared with a 0% decrease in the group with preeclampsia without magnesium, a pooled standard deviation of 26, a two-tailed $\alpha = 0.05$ and 80% power. We also assumed a non-normal distribution; thus, the sample size was adjusted using an inflation factor of 1.15 [29]. The calculation yielded a minimum required sample size of 33 women per group.

Results

A total of 37 women with preeclampsia treated with magnesium, 45 women with preeclampsia not treated with magnesium and 34 women with preterm labor treated with magnesium were enrolled and included in