Magnesium and Preeclampsia

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Abstract

Hypertensive disorders which include preeclampsia during pregnancy has been known to be a major contributor to maternal mortality. A systematic literature search was performed to examine the evidence for the use of intravenous magnesium sulfate (MgSO4) in the treatments and/or prevention of preeclampsia. Keywords included magnesium (Mg), prevention, and preeclampsia. Fifteen full text articles met inclusion criteria for final review. MgSO4 is currently the most widely used therapy form in eclamptic women used to prevent the most serious effects of eclampsia. Mg therapy reduces seizure frequency and also works as a vasodilator. However, the prevention of seizures may be independent of changes of alterations in angiogenic factor levels. A majority of the studies were performed on women that were already preeclamptic and were compared to pregnant women that had normative pregnancies. Dietary Mg was also tested as a preventative in the development of preeclampsia. MgSO4 has been accepted as standard treatment for preeclampsia and eclampsia however there may be inconsistent application or knowledge of the effectiveness of the therapy amongst healthcare professionals.

***Keywords*:** Magnesium, prevention, preeclampsia.

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Magnesium and Preeclampsia

Preeclampsia (PE) is a complication of pregnancy that presents in the second or third trimester and may range from mild to severe. Characteristics of such a condition include high blood pressure and proteinuria (Dhakal, Subedi, & Paudel, 2012). If PE is not properly managed, it may progress to severe preeclampsia (SPE), followed by complications with the function of the kidney, liver, and lungs. If left untreated, PE/SPE can advance to eclampsia. Eclampsia is the most severe form, potentially resulting in seizures, coma, and death. Preeclampsia has an effect on approximately 2% - 8% of pregnancies (Dhakal et al., 2012). Despite the various studies performed on preeclamptic women, preeclampsia is still responsible for a large amount of morbidity and mortality for mothers and their babies (Zhou et al., 2014). A literature review is necessary to determine whether MgSO4 has adequate evidence to be included in the standard treatment protocol for preeclampsia.

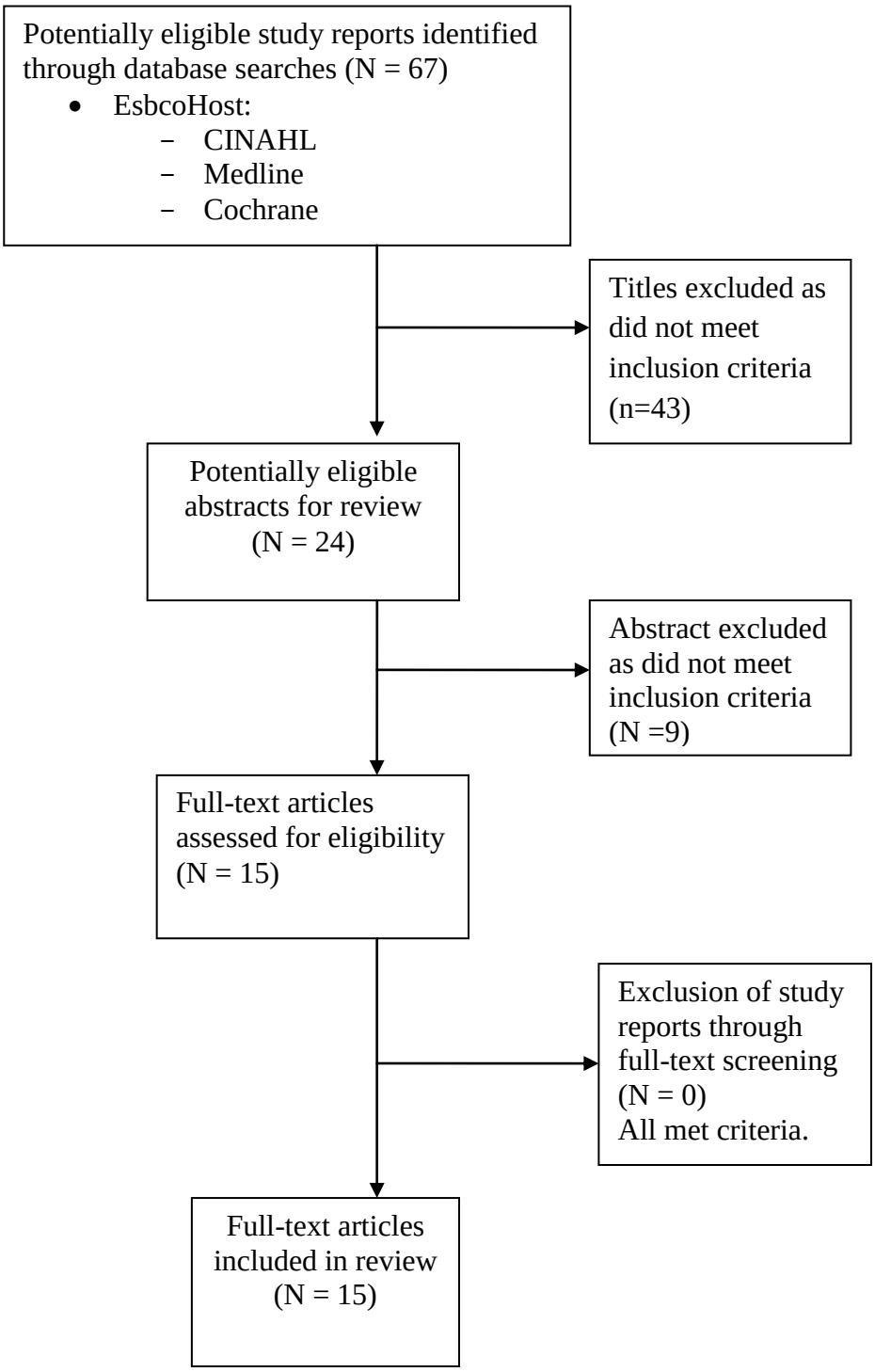
Methods

This was a systematic literature review which was completed in September of 2015. The databases used the EbscoHost platform, inclusive of CINAHL, Cochrane, and Medline. The keywords used for the search were magnesium, prevention, and preeclampsia. The inclusion criteria were human, pregnant female with preeclampsia, articles in English, and measured magnesium level. The exclusion criteria consisted of males and non-pregnant females, non-human subjects, lack of magnesium measurements, and did not have preeclampsia or eclampsia. The steps included were the title review, abstract review, and full text article review.

Results

Fifteen full text articles were identified as meeting all inclusion / exclusion criteria. See Figure 1 for more details on search process.

Figure 1.Search Results on Magnesium and Preeclampsia



Of the fifteen articles reviewed there were five cohort studies, three case-control, two cross-sectional, one random control trial (RCT), and four reviews, one of which included a meta-analysis. See Table 1 for more details on the studies reviewed.

The meta-analysis focused on links between dietary factors and gestational diabetes and preeclampsia. Schoenaker, Soedamah-Muthu, & Mishra, (2014) assessed 23 cohort and 15 case-control studies which included women of reproductive ages. A link between certain dietary factors/supplements to gestational hypertension and preeclampsia was observed. An insignificant association was noted for both magnesium ($p=0.41$) and calcium ($p=0.21$) intake. Dietary counseling showed a significant effect on maternal blood pressure (systolic, $p < 0.001$, diastolic, $p < 0.001$). Limitations to the meta-analysis included inconsistent findings and heterogeneous study designs (Schoenaker, Soedamah-Muthu, & Mishra, 2014).

A literature review focusing on RCT study designs identified six trials inclusive of 11,444 women that measured how effective, if at all, $MgSO_4$ was for women with preeclampsia and their babies. Their result was in favor of the $MgSO_4$, by reducing the incidences of eclampsia by about half. Flushing, the dilation of blood vessels under the skin in the face, was a side effect they found from $MgSO_4$. These side effects may be deemed acceptable for the immediate positive effect noted. However, the limitation of this study is that there are not any known side effects from long-term use of IV $MgSO_4$ during pregnancy (Duley, Gulmezoglu, & Henderson-Smart, 2003). In further research of the side effects of administration of $MgSO_4$ as an anticonvulsant, another cohort study with RCTs was done and included 24 studies and 34 subject groups. This particular study also noted flushing as a side effect of $MgSO_4$, along with vomiting, weakened muscles, nausea, and dizziness (Smith et al., 2013).

A randomized control study was conducted in West Bengal, India to see if prophylactic magnesium sulfate had an effect on mildly preeclamptic women and women with gestational hypertension. The group consisted of 48 women which were split up and randomly given either MgSO4 or a placebo. The intervention group had a lower sulfate umbilical artery index after MgSO4 was given, when compared to the placebo group. This study concluded a significance with a p value of <0.05 (Dasgupta et al., 2012).

A small prospective cohort study completed at Beth Israel Deaconess Medical Center in Boston, MA consisted of treating preeclamptic women with magnesium for seizure prophylaxis and was compared to untreated preeclamptic women. The angiogenic levels did not differ between the two groups of women (p = > 0.05). Magnesium was found likely to decrease the risk of seizures but does not alter the angiogenic factor levels (Vadnais et al., 2012).

A case-control study was performed involving 16 preeclamptic, 16 healthy pregnant, and 10 non-pregnant women on the amount of magnesium in serum and cerebral spinal fluid in each group that were given $MgSO_4$. After given an IV of MgSO4, preeclamptic women showed a 3-fold increase in serum magnesium, while the healthy pregnant group showed a 3.5 fold increase. Protein interactions with magnesium could be a factor of decreased ionized magnesium in the blood, but much more evidence is needed to deem its relationship to preeclamptic women (Apostol et al., 2010).

In a retrospective cohort study, two groups of women consisted of two different drug groups; the diazepam group contained 47 women and the MgSO4 group contained 30 women. At the University of Nigeria Teaching Hospital (UNTH) in Enugu, Nigeria, the study examined the maternal and perinatal outcome of SE after the use of MgSO4. The study compared new findings

with retrospective ones. The adults in the MgSO4 group did not have any bouts of seizures, while one woman from the diazepam group did. Apgar scores from babies were low but insignificant. In addition, hospital stays were shorter amongst the group that was receiving MgSO4. This study is limited by its backdated nature and reliance on the patients' records (Ugwu, Dim, Okonkwo, & Nwankwo, 2011).

The cross-sectional study by Adekanle et al., (2014) included 75 preeclamptic females and 75 normotensive pregnancies to have their serum Mg levels measured. The study showed that there was a lower level of magnesium in the preeclamptic females when compared to the females with normal pregnancies. The mean serum levels for the preeclamptic women were 0.58mmol/L. The mean serum levels for the normal pregnancies were 0.73mmol/L. The limitations to this study was the fact that all of the participants were black and had to already be a patient at the study location (Adekanle et al., 2014). Similarly, the cross-sectional study by Tavana & Hosseinmirzae (2013) examined maternal serum magnesium level in preeclamptic and normal pregnant females from the onset of pregnancy. The level of magnesium in the preeclamptic women was lower than the women with normal pregnancies since the beginning of pregnancy. It was suggested that the higher prevalence of PE in developing countries may be due in part because the dietary intake in pregnant females are not rich in magnesium (Tavana & Hosseinmirzae, 2013). To improve intervention by earlier risk identification, especially among populations experiencing health disparity, a prospective cohort study was done with 2,081 women, specifically focusing on 1,300 cases of preeclampsia. The newly developed miniPIERS risk prediction model was helpful to identify pregnant women in low or middle income countries that were at risk of hypertensive complications. This model showed a significance value of $p=<0.01$. Its limitations were the use of opposing maternal outcome and a retrograde elimination

for the final variable of choice, the use of fullPIERS dataset for outside justification, and finally, it was limited to a very broad selection of inclusion criteria (Payne et al., 2014).

Regimens for administration of MgSO4 has evolved over time but still has not been evaluated in a formal manner (Duley, Matar, Almerie, & Hall, 2010). The objective of their study was to compare the different regimens for administering magnesium sulfate in preeclamptic females. Although evidence has supported MgSO4 for the prevention of preeclampsia, these trials were too small to determine what regimen and what dosage is most beneficial.

Interestingly, an observational study consisted of five major public hospitals, including 44 nurses examined the current circumstances of the management and capabilities of administering MgSO4 to patients with severe preeclampsia/eclampsia (SE/E). To assess the extent of healthcare practitioner knowledge, the hospitals and participating nurses first took a pretest. The highest score was from Dang Sub Regional Hospital, with a 50%. The lowest score was a 0% from Guleria District Hospital. There were significant differences in posttests, with the lowest score of 0% reaching 56%, and the highest pretest score of 50% moving up to 89%. In most of the health care facilities, there were not any tests available to check for proteinuria. The limitation to this study was that records of preeclampsia were insufficiently filed, so there may be missing cases (Dhakal et al., 2012). The study reflected that initial knowledge of the use of MgSO4 for PE /SE was limited however improved with training.

Table 1. Comparison of Studies on Magnesium and Preeclampsia

Authors	Types of studies	# subjects
		N= ___
			Outcomes/Measures used	Findings	Limitations

Adekanle, Adeyemo, Adeniyi, Okere, Jimoh, Adebara, Bakare, Atiba, Adelekan, & Olofinbiyi.	Prospective case-control study.	N = 150 75 normotensive 75 preeclamptic	The study compared the serum magnesium between preeclamptic women and normal pregnancies over a six month period.	Magnesium in preeclamptic women were considerably lower than the women with normal pregnancies.	All subjects were black. Only pregnant women that received care at this specific location were included.
Apostol, A., Apostol, R., Ali, Choi, Ehsuni, Hu, Li, & Altura.	Case-control study.	N= 42 16 Preeclamptic 16 Non-preeclamptic 10 Non-pregnant	The magnesium in serum and cerebral spinal fluid in preeclamptic women was compared to healthy pregnant women that were given $MgSO_4$.	When given an IV of MgSO4: Preeclamptic women showed a 3- fold increase in serum magnesium. The healthy pregnant group showed a 3.5 fold increase in serum magnesium.	The protein interaction with magnesium and calcium in the blood of preeclamptic women needs much more evidence to deem the relationship.
Dasgupta, Ghosh, Seal, Kamilya, Karmakar, & Saha.	Randomized controlled study (RCT).	N = 48 24 Placebo 24 Intervention	The Mann-Whitney U-test and Wilcoxon's signed rank test was used for comparison between the two groups.	Magnesium sulfate significantly decreases fetal umbilical artery as well as the middle cerebral artery pulsatility index.	Women with multiple pregnancies, congenital fetal anomalies, irregular fetal heart rate, diabetes, and hypersensitivity to magnesium could not be included.

de Aquino, Leite, Cabral, & Brandao.	Cross-sectional analysis.	N = 73, with risk factors of developing PE.	ROC curves were used to define the individualities of the ophthalmic artery resistive index (OARI).	Doppler flowmetry of OARI did not present to be a reputable exam approach for predicting PE.	The ROC curve/ OARI values of pregnancy did not display good results for sensitivity and specificity.
Dhakal, Subedi, & Paudel.	Prospective cohort study.	N= 44 nurses N= 5 large public hospitals.	The objective was to explore the knowledge of severe preeclampsia/ eclampsia management using MgSO4 in the 5 largest hospitals of Mid-Western Development Region in Nepal.	Trained staff received low scores, the highest being 50%, during a pretest of their knowledge of administration of MgSO4. The difference between pretests and posttests was significantly greater ($p < 0.05$).	There was a high chance of missing cases due to files not being stored correctly.
Duley, Gulmezogu, & Henderson-Smart.	Literature review.	N= 11,444 women 6 trials.	Measured the effects of anticonvulsants for pre-eclampsia on women and their babies.	No p-values included. The risk of eclampsia was cut in half when treated with MgSO4.	The safety and lack of serious side effects with of higher dosages/longer duration of MgSO4 cannot be supported by the data.
Duley, Matar, Almerie, & Hall.	Literature review.	N= 866 451 eclamptic 415 preeclamptic.	Different regimens of administration were given to preeclamptic and eclamptic women.	The review established that there isn't enough validation to decide the best dose of MgSO4 for	The trials were too small for reliable conclusions.

				preeclamptic women.	
Ephraim, Osakunor, Denkyira, Eshun, Amoah, & Anto.	Case-control study.	N= 380 120 PIH 100 PE 160 healthy	Anthropometric measures, blood pressure, urinalysis, blood samples, and biochemical analysis were taken during these studies.	The Doppler flowmetry of ophthalmic artery was not a commendable technique in predicting PE.	The study was unable to use better methods of detecting proteinuria. The study findings are limited due to the sampling technique used.
Payne, Hutcheon, Ansermino, Hall, Bhutta, Z.A., Bhutta, S.Z., Biryabarema, Grobman, Haniff, Li, Magee, & Merialdi.	Prospective cohort study.	N= 2,081 women with hypertensive disorders N=1,300 women in the fullPIERS dataset.	miniPIERS risk study was to develop and validate a simple clinical prediction model in low and middle income countries for issues among women with hypertensive disorders of pregnancy, like preeclampsia.	miniPIERS model displayed a significant ability (p-value of <0.01) to identify women with increased adverse outcomes and risks during pregnancy, like preeclampsia.	The use of opposing maternal outcome, broad inclusion criteria, the use of retrograde elimination for final adjustable choice, and the use of fullPIERS dataset for confirmation.
Schoenaker, Soedamah-Muthu, & Mishra.	Meta-analyses.	N= 23 cohort studies. N= 15 case-control studies.	Evaluate reviews from observational studies in women of a reproduction-age group on the links between certain dietary factors/ supplements, and gestational	Insignificant magnesium (p=0.41) and calcium (p=0.21) intake was shown. A meta-analysis of dietary counseling shows a substantial effect on maternal	Unreliable findings have been conveyed and limited studies were found. This created substantial diversity between studies examining the calcium intake amongst women

			hypertension and preeclampsia.	blood pressure (systolic, p=<0.001, diastolic, p=<0.001).	with and without hypertensive disorders of pregnancy, like preeclampsia.
Smith, Lowe, Fullerton, Currie, Harris, & Felker-Kantor.	Literature review.	N= 24 studies N= 34 subject groups.	A review of the literature was performed to conduct clinical outcomes of women who use MgSO4 therapy for severe pre-eclampsia or eclampsia.	There was a small incidence of most severe side effects, and if contrary effects occurred, delaying therapy was sufficient to mitigate the effect.	There may be an underestimate of the actual incidence of specific side effects due to only reporting the subset of studies.
Tavana & Hosseinmirzei.	Cross-sectional study.	N = 78 26 PE 52 Normative.	The goal of this study was to measure magnesium levels in preeclamptic females and normal pregnancies from the beginning of pregnancy for comparison.	The initial level of magnesium in the women with preeclampsia was significantly lower than the levels of the women with normal pregnancies.	The role of magnesium supplements needs to be further investigated.
Ugwu, Dim, Okonkwo, & Nwankwo.	Cohort retrospective study.	N= 77; 2 cohorts of women. N= 47 (diazepam cohort) N= 30 (MgSO4 cohort).	This study aimed to assess the maternal and perinatal result of severe preeclampsia since the start of MgSO4 at the UNTH Enugu and compare the results with those of	Apgar scores from babies at 1 minute (p=0.70) and 4 minutes (p=.726) were insignificant. In adults, no patients in the MgSO4 group had seizures, while one	The study is limited by its reflective nature and dependency on patients' records. More participants could have created more precise study results.

			earlier years.	woman from the diazepam group had a bout of seizures.	
Vadnais, Rana, Quant, Salahuddin, Dodge, Lim, Karumanchi, & Hacker.	Prospective cohort study.	N = 116 37 PE treated with magnesium 45 PE not treated 34 preterm labor treated with magnesium.	Preeclamptic women were treated with MgSO4 and the other group was not treated in order to see if the angiogenic factors were altered.	There was no change in angiogenic factor levels after the administration of MgSO4. MgSO4 does not directly decrease seizures through angiogenic factors.	The small sample size limited the ability to have a small subgroup analysis.
Zhou, Jing, Yunfei, You, Yu, Jianhua, & Wen.	Cohort study.	N = 61.	Plasma samples, isolation of monocytes/T cells, cell cultures, flow cytometry, transcription factor array, and quantitative real-time transcriptase.	Transcriptional dysregulation in monocytes and T cells are contributors to the inflammatory response (factor of preeclampsia).	There were very few participants for subgroup analysis.

Discussion

The evidence gathered consistently identifies the benefits over burdens for the use of MgSO4 in the hospital for the treatment of preeclampsia. Mg levels of serum are significantly lower in women with PE. Serum magnesium levels are vital for metabolism to take place at the cellular level for proper muscle contractions, cell death, and neuronal activity (Ephraim et al., 2014). In addition to the use of MgSO4 to reduce PE and the progression of SE, it was interesting to note that serum Mg increased 3-fold after given intravenously to women with PE demonstrated strong potential for preventing the onset of eclampsia. Interestingly, knowledge assessment revealed that nursing staff of five major public hospitals were not knowledgeable regarding the administration MgSO4 (Dhakal et al., 2012). The study highlighted both the need and the effectiveness of training for hospitals and their staff to better manage preeclamptic patients in the future (Dhakal et al., 2012).

Reducing cases of eclampsia by half when the use of MgSO4 is present, shows that there should be a continuous use for it as new incidences of PE or SE develop. Furthermore, the benefit to the infants is also a significant incentive for mothers with preeclampsia to agree to use MgSO4, and this research has also shown a reduction of placental abruption (Duley et al., 2003). Flushing was a noteworthy side effect of the use of MgSO4, but this is clearly offset by the potential benefit of preventing convulsions, coma, and death from eclampsia (Duley et al., 2003).

Although PE is considered a second trimester disease, there is a need to detect the disease during the first trimester. A Doppler flowmetry of the OARI was performed on women at high risk for PE but did not prove to be a good predictor (de Aquino et al., 2014). There is evidence supporting a global application of this treatment modality. The miniPIERS risk model invention was a remarkable way to be able to recognize pregnant women at risk for preeclampsia in lower

income countries. The fact that it had a p-value of <0.01 showed its significance and there is no doubt that it will help the future of health amongst women at risk for preeclampsia (Payne et al., 2014).

More widespread use of the miniPIERS risk prediction model would be beneficial. Adding nutrition assessment and counseling to include assessment of dietary Mg is warranted. Insufficient magnesium and calcium intakes have been linked to hypertensive disorders of pregnancy (Schoenaker et al., 2014). Considering high blood pressure/hypertension are attributes to PE, a magnesium and calcium replete diet might serve as a preventative measure that needs more widespread access and application. Healthy systolic and diastolic blood pressures after dietary counseling have been clearly demonstrated (Schoenaker et al., 2014). Assessment of magnesium status during pregnancy and identification of a magnesium deficit might be correlated to the development of preeclampsia and may shed further light on the relationship of this mineral to a potentially deadly condition. There is a role for the Registered Dietitian Nutritionist in the prevention of PE / SE that has not been sufficiently developed.

In conclusion, there appears to be good evidence that $MgSO_4$ should be included in the standard treatment protocol for PE and SE. Additionally early risk assessment and appropriate dietary intervention was identified as warrented.

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