Protocol Title

A Randomized Study of an Alternate Dosing Protocol for Magnesium Sulfate in Obese Preeclamptic Women

Objectives. In the current proposed study, we hope to identify pharmacokinetic (PK) drug effects (a therapeutic serum magnesium level) that an alternate magnesium sulfate dosing regimen will achieve in obese preeclamptic pregnant women.

Specific Aim 1: To determine if an alternate magnesium sulfate dosing regimen in preeclamptic pregnant women with BMI ≥ 35 kg/m^2 will result in a larger proportion of obese women who have therapeutic serum magnesium levels (≥ 4.8 mg/dL) for seizure prophylaxis after 4 hours of administration.

Aim 1a: To determine if an alternate magnesium sulfate dosing regimen in preeclamptic pregnant women with BMI ≥ 35 kg/m^2 will result in a larger proportion of obese women who have therapeutic serum magnesium levels (≥ 4.8 mg/dL) for seizure prophylaxis at the time of delivery compared to a current standard dosing protocol.

Specific Aim 2: To determine if, and which, maternal side effects are more common at 1 hour, 4 hours, and time of delivery with an alternate magnesium sulfate dosing protocol in obese women.

Hypotheses

We hypothesize that a randomized trial of alternate dosing of intravenous magnesium in obese women will allow us to:

1. Determine optimal antenatal magnesium dosing protocols to optimize therapeutic serum magnesium levels in obese preeclamptic women.
2. Determine significant covariates and correlations between maternal serum magnesium levels and maternal side effects and outcomes.
3. Determine the optimal antenatal magnesium dose to minimize adverse drug effects while maintaining a therapeutic serum magnesium level in the mother.

Background

Magnesium sulfate is one of the most commonly prescribed intravenous medications in contemporary obstetric practice.[1,2] Magnesium is the drug of choice for preventing seizures in women with preeclampsia, a leading cause of maternal morbidity and mortality.[3,4] More than 77% of expectant mothers experience side effects related to antenatal magnesium administration.[5] Magnesium may also negatively impact obstetric outcomes and lead to adverse neonatal effects.[1,3,6-8] Current intravenous magnesium treatment for various indications (preeclampsia, tocolysis, neuroprotection) follows standardized protocols (4-6 g loading dose followed by an infusion at 1-2 g/h) based on institution preference. These protocols proposed by Prichard in 1979 were derived clinically to provide estimated serum magnesium levels necessary to treat eclamptic seizures.[9] These standardized protocols are administered unaltered to all patients, without adjustment for maternal or fetal factors that may affect serum magnesium levels. The PI has previously constructed a detailed, robust pharmacokinetic (PK) model of intravenous magnesium sulfate administered antenatally to expectant mothers and exposed fetuses with the aim of optimizing maternal and fetal outcomes while preventing maternal and neonatal overdosing and morbidity associated with current magnesium treatment protocols.[10]

The PK data derived from this pilot study at another academic institution suggests obese pregnant women may require an increased dose of magnesium sulfate to maintain a therapeutic serum level for prevention of eclamptic seizures ($\geq$ 4.8 mg/dL). In that pilot study, statistical modeling suggested more obese preeclamptic women take approximately twice as long as non-obese preeclamptic women to achieve steady state levels of the drug.

Study Design

The proposed study would use 1:1 allocation to randomize women with a BMI $\geq$ 35 kg/m^2 treated with magnesium sulfate for preeclampsia to either standard dosing of the drug at OHSU (4g loading dose, followed by a 1 g/hr infusion) or to increased dosing (6g loading dose, followed by a 2 g/hr infusion). Maternal serum magnesium levels will be obtained at baseline, as well as after administration of magnesium sulfate at 1 hour, 4 hours, and at the time of delivery (within 20 minutes). We will exclude patients who are < 32 weeks gestation, as these women will automatically be administered a 6g loading dose, followed by 2g/hr infusion for fetal neuroprotection. The outcome will be a comparison of the proportion of preeclamptic women in each magnesium sulfate protocol group who have therapeutic serum levels 4 hours after administration, and at the time of delivery (serum magnesium level of $\geq$ 4.8 mg/dL). We hypothesize that a significantly higher proportion of women with a BMI $\geq$ 35 kg/m^2 will be subtherapeutic at 4 hours and at the time of delivery when administered standard dosing of magnesium sulfate. Findings from the proposed research can be used to tailor treatment for preeclampsia in obese pregnant patients.

Study Population

Pregnant women between 32-42 weeks' gestation who are prescribed magnesium sulfate for preeclampsia.

Number of Subjects

Based on a previous retrospective study conducted by Tudela et al[11] and our own pilot data[10], we estimate that 50% of obese women will be subtherapeutic for eclamptic seizure prophylaxis 4 hours after magnesium sulfate administration. Assuming 95% of normal weight women have therapeutic serum magnesium levels after 4 hours of administration, we anticipate that 18 patients (36 total) are needed in each dosing group to detect a 50% difference in the proportion of women with a BMI $\geq$ 35 kg/m^2 who have therapeutic magnesium levels 4 hours after magnesium sulfate administration. Based on current patient load, which includes treatment of approximately 40 preeclamptic patients per month, and the additional inclusion criteria of the disease severity requiring magnesium sulfate administration, as well as a maternal BMI $\geq$ 35 kg/m^2, and anticipated number of patients declining study participation, we anticipate potential enrollment of 1-2 women and their neonates per week.

a. Inclusion and Exclusion Criteria

Pregnant women with preeclampsia admitted to OHSU hospital will be screened for eligibility using the institution's electronic medical record – EPIC, on admission.

Inclusion criteria:
Pregnant women who are ages 15 - 45
32-42 weeks' pregnant
Prescribed magnesium sulfate for preeclampsia

BMI $\geq$ 35 kg/m^2

Exclusion criteria:
Pregnant women < 32 weeks' pregnant
Women who are on dialysis
Women with pre-existing renal disease

Data collected in the course of a screen failure will be destroyed immediately.

b. Vulnerable Populations

- Pregnant women will be included, as this is the primary study population. The pregnant women randomized in this study are already prescribed magnesium sulfate for preeclampsia and the dosing regimens proposed are doses that are already administered at hospitals in the United States, with every hospital utilizing its own specific dosing protocol.
- Neonates (up to 28 days post birth) of uncertain viability or nonviable neonates will be included only to the extent of recording their birth outcome and birthweight. As the different dosing regimens follow United States guidelines and are already administered at hospitals in the US, there is no additional risk to neonates in this study.

For both pregnant women and neonates, there is a small chance of loss of confidentiality that we take every precaution to avoid.

Children, decisionally impaired adults, and prisoners will not be specifically included in this study.

c. Setting

- The research will take place at the OHSU Labor and Delivery Unit and Antepartum Unit and the study procedures will be carried out by OHSU personnel.

d. Recruitment Methods

When pregnant women with preeclampsia are identified at presentation to OHSU hospital through review of the medical record, the PI and research staff will screen for participation based on maternal age, gestational age, and whether or not magnesium sulfate will be prescribed as part of usual care.

Assistance with the initial screening process will take place through resident education sessions, as well as posting of study inclusion/exclusion criteria in the resident workroom as a reminder. A study factsheet and recruitment flyer will be posted on Labor and Delivery, Antepartum, and in the resident workroom to facilitate enrollment. Recruitment outside of these areas is not anticipated due to the specific circumstances in which a potential research subject would qualify for enrollment (i.e. inpatient). Additionally, a recruitment Grand Rounds will be presented to the Department of OB/GYN to educate them regarding the study enrollment criteria.

There will be no payment for participation in the study, however, laboratory studies requested for subjects that would not have normally been requested as part of usual care (i.e. blood, urine, and cerebrospinal fluid magnesium levels), will not be charged to the subject.

e. Consent Process

Once a potential participant has been identified, the PI or appropriate research staff will approach potential participants for consent while standard laboratory workup ensues for preeclampsia. Written informed consent will be obtained after having the purpose and details of the study explained in person by the PI or other research personnel. Because study participation is limited to inpatients who are prescribed the study drug, no outside recruitment of subjects will take place.

After explaining the purpose of the study, the process of randomization, and obtaining informed consent, the PI /research personnel will use a random number generator from OpenEpi to assign the patient to one of two magnesium sulfate dosing regimens.
The PI/research personnel will review the list of daily obstetric service patients to identify possible participants for recruitment.
During the consent process, it will be emphasized to the potential research subject that the study drug is given in varying doses at different institutions and that if they choose not to participate, they will receive the dose that is standardly prescribed at OHSU for preeclampsia.

Non-English Speaking Subjects

- Subjects who do not identify themselves as English speaking are eligible for consent if they identify as Spanish speaking and an interpreter is available to assist with the consent process and ongoing study requirements in a timely fashion. The primary study coordinator is Spanish speaking and will most often consent non-English speaking subjects.The English Consent and Authorization form will be translated into Spanish and submitted for IRB approval prior to use. Only English and Spanish speaking patients will be eligible to participate. The initiation of magnesium sulfate for preeclampsia will not be delayed to wait for the primary study coordinator or an in-person interpreter, and if the drug is ready to be administered prior to obtaining consent, the potential subject will no longer be eligible.

2. Procedures Involved

After obtaining informed consent, the subject will by randomly assigned to one of two treatment groups: 1.) a starting dose of magnesium sulfate of 4g, followed by 1g every hour until 24 hours after delivery (the current standard regimen used at OHSU), or 2.) a starting dose of magnesium sulfate of 6g, followed by 2g every hour until 24 hours after delivery. There will not be a placebo arm of the study; only a smaller dose or larger dose of magnesium sulfate administered. Although the study dosing is randomized, it is not blinded and both the investigator and the research subject may know what dose of magnesium sulfate is being administered. If the subject is found to be symptomatic at any point in the study, the usual clinical care will be provided, which would include checking a serum magnesium level and decreasing the dose of magnesium sulfate, if needed. Study participation will continue; however, the timing and details of the dosing change will be recorded and used for research purposes.

If there is an indwelling intravenous catheter in place for surgery, we will attempt to use it to draw blood. We will draw a sample from a vein if we are not able to collect the samples from an existing intravenous catheter.

Specimens will be collected as follows:

- Serum magnesium before the administration of magnesium sulfate
- Serum magnesium at 1 hour, 4 hours, and delivery after the initial dose of magnesium sulfate
- Each sample will be 5-10 ml (approximately 1-2 teaspoon). The total drawn for all samples will likely not exceed 5 teaspoons.
- Urine samples will be obtained if possible at these same time points.
- If the patient requires spinal anesthesia for cesarean delivery, 0.5 ml (a few drops) of spinal fluid will be taken to check for magnesium levels at the same time the spinal anesthetic is being performed.

	Visit 1 Day 1	Visit 2 Day 1	Visit 3 Day 1	Visit 4 Day 1
Consent Discussion, Screening tests and medical history	X			
Blood draw (1 teaspoon)	X	X	X	X
Urine sample (2 teaspoons)	X	X	X	X
Time (after magnesium sulfate administration)	baseline	1 hour	4 hours	Time of delivery (within 20 mins)

Information that may be abstracted from the subject's chart includes maternal age, race, height, weight, renal function and creatinine clearance (if available), maternal heart rate variability, medical comorbidities, chorioamnionitis, labor duration, mode of delivery, gestational age, cord pH, and birthweight. These covariates may be considered in the pharmacokinetic model. These covariates demonstrate biological plausibility, and have physiologic potential to significantly impact the optimal dosing of magnesium. Additionally, maternal side effects (flushing, sedation, nausea, vomiting, respiratory rate, oxygen saturations, blood pressure, heart rate, and patella tendon reflex depression) will be assessed prospectively by a physician or research assistant at the same time-points as the PK sampling. Neonatal data will include NICU admission, need for respiratory support, need for blood pressure support, electrolyte abnormalities, feeding difficulties, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, respiratory distress syndrome, retinopathy, patent ductus arteriosus, fetal/infant death.

3. Data and Specimens

a. Handling of Data and Specimens

Blood, urine, and rarely cerebrospinal fluid specimens will be assigned a unique identifier that will be associated with the subject's name and medical record number for initial laboratory analysis. After the magnesium level is determined, only the unique identifier will be present in the research database. The specimens are generally stored in the laboratory for approximately 5 days and then stored in the MFM repository (eIRB#7285). They will be transported to the laboratory through the pneumatic tube system at OHSU Hospital. In the event a CSF sample is

obtained, this sample would be stored in laboratory space for the Department of Obstetrics & Gynecology – WHRU freezers. The PI and research staff are responsible for transport of all specimens.

b. Sharing of Results with Subjects

Laboratory results that are part of the usual care and clinical decision making process will be shared with the subjects and providers, however, overall study results will take a much longer time to generate and will not be shared at the individual level. The OHSU Hospital Laboratory responsible for testing the specimens is CLIA certified.

c. Data and Specimen Banking

Specific data that may be banked includes maternal serum samples, urine samples, and CSF samples. While specimens will not be used for genetic research, they may be stored longer than 5 days for the purpose of correlating tissue levels of magnesium with clinical events. In the event the specimens are sent to the MFM Repository eIRB#7285, they will retain their unique identifier. Only the PI will be able to access the specimens and they will be retained for an indefinite period of time.

4. Data Analysis

Univariate and multivariate mixed-effects modeling will be utilized to assess the impact of various covariates on the outcome of serum magnesium level at different time points after magnesium sulfate administration. As previously described, assuming 95% of normal weight women have therapeutic serum magnesium levels after 4 hours of administration, we anticipate that 18 patients (36 total) are needed in each dosing group to detect a 50% difference in the proportion of women with a BMI $\geq$ 35 kg/m^2 who have therapeutic magnesium levels 4 hours after magnesium sulfate administration. Based on current patient load, which includes treatment of approximately 40 preeclamptic patients per month, and the additional inclusion criteria of the disease severity requiring magnesium sulfate administration, as well as a maternal BMI $\geq$ 35 kg/m^2, and anticipated number of patients declining study participation, we anticipate potential enrollment of 1-2 patients per week.

5. Privacy, Confidentiality, and Data Security

All information collected as part of the study will be stored on an encrypted, password protected computer that will only be available to the PI and essential trained research personnel. Hard copy data collection forms will be stored in a locked cabinet in the PI's administrative office. Separation of identifiers from data and specimens will take place as soon as subjects' participation has ended and only the PI and research personnel will be able to relink the data in the future if needed.

Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network. Access to data/specimens is restricted to study personnel. Access to data requires OHSU password authentication. Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code.
Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN) The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder.

6. Provisions to Monitor the Data to Ensure the Safety of Subjects

The investigators and study staff are responsible for recording the data, and they will be verifying its accuracy throughout the process. The PI will be reviewing the data in-depth periodically throughout the study. The PI will also be overseeing that the study procedures are being carried out as per the approved protocol via close supervision of the study visit and procedures and through frequent communication with the other investigators and staff. Anytime that an AE, SAE, UP or protocol deviation is reported by an investigator or study staff, the PI will review and assess the data, and proceed as per OHSU reporting policy. Otherwise, the PI entity will be reviewing the records periodically throughout the study. All adverse events will be assessed and reportable UPs will be submitted to the IRB, if judged related to the study protocol. All data will be stored for future analysis and stored in the MFM Repository eIRB#7285

7. Risks and Benefits

a. Risks to Subjects.

The possible risks of obtaining blood samples from a vein in the arm are pain, bruising, fainting, and rarely, infection. This risk is extremely small as sterile supplies will be used, and all hospital protocols will be followed.

Magnesium sulfate is known to have associated side effects (i.e. nausea, flushing, palpitations, headache, malaise, sweating, pulmonary edema, and loss of reflexes.) There may be some side effects we do not expect because we are still learning about different dosing of the study drug. The study drug may be discontinued or the dosing changed if subjects experience serious side effects.

One risk to taking part in this study is that the study drug or the dose administered may not be effective in helping to treat preeclampsia. This is a risk for all patients who are administered magnesium sulfate.

There are several drugs (prescription and non-prescription) that may cause problems when taken with the study drug. The investigator will carefully review all of the drugs a potential subject is taking before administering the study drug.

Possible risks of the study include a low risk of breach of confidentiality.

b. Potential Benefits to Subjects

There are no benefits from participation in the study.

8. Drugs or Devices

Magnesium sulfate is approved by the FDA for treatment of preeclampsia. It is not investigational. All applicable Research Pharmacy policies and procedures will be followed for the study. The two possibilities for dosing of magnesium sulfate are already administered during pregnancy at OHSU for different indications and the study drug will be handled in the same way as would be usual clinical practice.

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