USE OF CHEETAH® NON-INVASIVE CARDIAC MONITORING SYSTEM TO GUIDE DISCONTINUATION OF POSTPARTUM MAGNESIUM SULFATE IN WOMEN WITH SEVERE PREECLAMPSIA: A PILOT RANDOMIZED CONTROL TRIAL.

Investigator Initiated Study

Investigators: **OSU MFM and Anesthesia**

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1 STUDY SYNOPSIS

Title	Use of Cheetah® non-invasive cardiac monitoring system to guide discontinuation of postpartum magnesium sulfate in women with severe preeclampsia: A pilot randomized control trial.
Objective	Demonstrate the utility of using improvement in SVR via non-invasive cardiac monitor as an indicator for resolution of preeclampsia, and individualize the duration of magnesium in the postpartum period for women with preeclampsia with severe features.
Study Population	Pregnant women greater than 18 years of age and 24 0/7 weeks' gestational age admitted to L&D for delivery with preeclampsia with severe features and plan to receive magnesium sulfate.
Study Design	This is a single site pilot randomized, controlled, trial randomizing patients with PE with severe features to one of 2 groups: • 24 hours of postpartum magnesium sulfate (current arbitrary standard of care) • Using the Cheetah® device to aid in an individualized duration of magnesium sulfate based on reduction in SVR, up to a maximum of 24 hours postpartum.
Eligibility	Subjects enrolled in the RCT must meet all of the inclusion criteria listed below: **Inclusion Criteria** • PE with severe features, diagnosed using the ACOG standard criteria[4] requiring magnesium sulfate • Females older than 18 years of age • Singleton pregnancy • Gestational age greater than 24 0/7 weeks • The patient is physically and mentally able to understand the informed consent and is willing to participate in this study • Able to speak English or Spanish Subjects enrolled in the RCT must **not** have any of the exclusion criteria listed below: **Exclusion Criteria** • Multiple gestation • Prisoners • Patients with chronic renal insufficiency or epilepsy • Known cardiovascular disease • Patients with contraindications to magnesium sulfate use (e.g. myasthenia gravis)

	• Patients with eclampsia or HELLP syndrome • Contraindications for magnesium sulfate (In addition to subjects enrolled in the RCT, we propose an optional negative control cohort of 25 normotensive healthy women delivering > 37 weeks to compare hemodynamics)
Site	The Ohio State University Wexner Medical Center
Sample Size	60 patients with preeclampsia with severe features and plan to receive magnesium sulfate. (In addition to subjects enrolled in the RCT, we propose an optional negative control cohort of 25 normotensive healthy women delivering > 37 weeks to compare hemodynamics)
Study Duration	Estimated duration of study is approximately 1 year.

2 LIST OF ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynecologists
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
CO	Cardiac Output
CRF	Case Report Form
GCP	Good Clinical Practice
HELLP	Hemolysis, Elevated Liver Enzymes, Low Platelet Count
HIPAA	Health Information Portability and Accountability Act
HR	Heart Rate
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
IV	Intravenous
LMP	Last Menstrual Period
MAP	Mean Arterial Pressure
Mg2+	Magnesium Ion
MgSO4	Magnesium sulfate
NICU	Neonatal intensive care unit
PE	Preeclampsia
SAE	Serious Adverse Event
SD	Standard deviation
SVR	Systemic Vascular Resistance

3 BACKGROUND

3.1 Pregnancy hemodynamic changes

Pregnancy is a dynamic process associated with significant physiological changes in the cardiovascular system. These changes include an increase in cardiac output (CO), heart rate (HR), blood volume expansion, and a decrease in blood pressure (BP) and systemic vascular resistance (SVR) during pregnancy[1]. On the other hand, labor is associated with significant hemodynamic changes, including increased CO and BP, and other parameters which are altered after administration of neuraxial anesthesia[2,3]. Additionally, after the delivery of the placenta, there is a rapid return of CO and SVR to non-pregnant levels[2].

3.2 Preeclampsia

Preeclampsia (PE) is a multisystem disorder affecting up to 8% of pregnancies and is diagnosed using standard clinical and biochemical criteria (Box 1)[4]. PE with severe features is diagnosed with either systolic blood pressure of 160mm Hg or more, or diastolic blood pressure of 110mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time) and/or the presence of end organ injury such as thrombocytopenia, liver or renal injury, pulmonary edema, persistent symptoms (as defined in box 1) or eclampsia.

Box 1: Criteria for Diagnosis of PE

Systolic blood pressure of 140mm Hg or more, or diastolic blood pressure of 90mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)

AND one of

- Proteinuria (urine protein/creatinine ratio >0.3, 24-hour urine protein ≥300mg or ≥+2 proteinuria on urine dipstick)
- Thrombocytopenia (platelet count less that 100,000 x 10^9/L)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit of normal concentration), and severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

Globally, PE is a leading cause of morbidity and mortality for pregnant women. Pregnant women who develop PE are at risk of eclampsia, a serious complication defined as new onset seizures and/or unexplained coma in the setting of PE, stroke, placental abruption, coagulopathy, pulmonary edema, acute kidney injury, liver hematoma, intracranial bleeding, cardiopulmonary arrest, and death. Moreover, PE increases risk of future cardiovascular disease and represents a significant economic burden on healthcare systems[5]. Published literature has identified striking differences in the maternal hemodynamic profiles between normotensive pregnancies and those complicated by PE. **PE is associated with a significantly higher BP and SVR** with lower HR, stroke volume, and CO[6].

Women with PE also have higher levels of placental-derived anti-angiogenic proteins and significantly lower levels of pro-angiogenic proteins, when compared with healthy pregnant women[7]. The increased SVR noted in pregnancies complicated by PE have been associated with abnormal plasma levels of angiogenic proteins[7,8].

The cure for PE has remained the same for several decades: delivery of the fetus and placenta. Immediately after birth, there is resolution of many of the clinical symptoms of PE, including a decrease or normalization in BP, improvement in urine output, and improvement of symptoms of end organ damage, along with reduction in stroke volume, CO, mean arterial pressure (MAP), and SVR[6].

In the U.S., parenteral magnesium sulfate (MgSO4) is routinely given to pregnant women for the prevention of eclampsia in patients with PE, especially those with severe features, as multiple

studies and meta-analyses demonstrated its superiority compared with other agents[9]. However, despite the clear and therapeutic importance of MgSO4 in pregnancy, there are limited data on its optimal dosing. The MgSO4 dosing regimen currently used is based on a protocol developed more than 30 years ago and does not take into account patient characteristics. In addition, the "therapeutic dose" of MgSO4 has been determined empirically and is based upon historic dosages found to be typically tolerable and effective. In clinical practice, dosing is based on a standard protocol, irrespective of patient's characteristics. Typically, it is administered by an intravenous (IV) infusion with a loading dose of 4 to 6 grams over 15-30 minutes, followed by 2 g/h as a continuous IV infusion up to 24 hours postpartum[9]. The use of MgSO4 requires a higher level of care with frequent blood pressure monitoring, close urine output monitoring, and frequent examinations for signs of magnesium toxicity (such as loss of deep tendon reflexes and respiratory depression)[10]. It is estimated that women receiving MgSO4 are almost 5 times more likely to experience adverse events compared with those receiving no or other treatments. This is associated with significant healthcare costs[11] and patients dissatisfaction.

Moreover, there is no consensus in the published trials regarding the optimal dose to use (both loading and maintenance), or the duration of therapy (especially in the postpartum period) [4]. Multiple recent studies have questioned the utility of the use of magnesium sulfate for 24 hours postpartum and suggest no increased risk of eclampsia or maternal morbidity with use of shorter durations of use (such as 6 hours or 12 hours)[12–14]. However, most studies have no clear definition of a clinical parameter that defines the recovery phase from severe PE. One of several parameters that has been described as an indicator of clinical improvement from PE is the onset of diuresis[15]. This is believed to be a signal for reversal of increased SVR (vasoconstriction), and thus resolution of the disease. Historically, it was only possible to measure SVR with an invasive monitor such as a pulmonary artery catheter. The potential complications with these measurements outweighed the risk of benefit. Novel techniques including thoracic bioreactance, enable minimally invasive measurements of SVR and have been validated in the obstetric population.[16]

3.3 SVR as a measure of disease resolution

Although, the use of MgSO4 is to prevent eclamptic seizures, the rarity of these events in the U.S. severely diminishes the feasibility of any research study with seizure mitigation as a primary outcome. **Therefore, a hemodynamic surrogate end point (SVR), based on the key mechanism of action of MgSO4 as a vasodilator for eclampsia prevention, was selected**.

We are proposing to measure improvement in SVR using a novel, non-invasive, and well-validated hemodynamics monitoring system, as a criterion to discontinue MgSO4, in the postpartum period. Although the exact etiology of eclampsia is still unknown, it is believed that cerebral vasospasm plays an essential role. It is hypothesized that in the setting of PE, and as blood pressure increases out of the normal range, cerebral resistance increases to limit cerebral perfusion. Ultimately, with increasing blood pressure and cerebral perfusion pressure, autoregulation is lost, which in the setting of endothelial dysfunction leads to vasogenic edema, overperfusion injury, and eclampsia. Magnesium is a calcium antagonist and can act on many calcium channels in the vascular smooth muscle. This leads to decrease in intracellular [Mg2+], inactivation of calmodulin-dependent myosin light chain kinase activity and reduced vascular tone, which subsequently leads to vascular (arterial) relaxation, and dilatation. Since vascular resistance in inversely related to the 4^{th} power of blood vessel radius, effect of MgSO4 on vasodilation has the most significant impact on peripheral and cerebral vascular resistance. This vasodilatory effect of MgSO4, which we can detect peripherally, using Cheetah non-invasive cardiac monitoring, severs as a rationale for this study.

Therefore, **we sought to demonstrate the utility of using improvement in SVR via non-invasive cardiac monitor as an indicator for resolution of PE, and individualize the duration of magnesium in the postpartum period for women with PE with severe features**.

4 Hypothesis

We hypothesize that the use of the Cheetah® non-invasive cardiac monitor to individually determine the duration of magnesium sulfate postpartum (guided by timing of reduction in SVR) will result in shorter duration of MgSO4 infusion, compared with the traditional preset time point of 24hr postpartum, with no increase in maternal morbidity.

5 STUDY DESIGN

5.1 Type of Study

This is a single site pilot randomized, controlled, trial randomizing patients with PE with severe features to one of 2 groups:

- 24 hours of postpartum magnesium sulfate (current arbitrary standard of care)
- Using the Cheetah® device to aid in an individualized duration of magnesium sulfate based on reduction in SVR, up to a maximum of 24 hours postpartum.

A 30% reduction in SVR (maintained for 1 hour) from the time of delivery will be used as an indicator for resolution of PE and as the cutoff for discontinuation of magnesium sulfate. This SVR reduction is previously described in normal pregnancy within 1 hour postpartum[2] and similar reduction in SVR in pregnancies complicated by severe PE, from after delivery to 24-36hrs postpartum[6].

In addition to subjects enrolled in the RCT, we propose an optional negative control cohort of 25 normotensive healthy women delivering > 37 weeks to compare hemodynamics.

5.2 Study Population

Patients who meet all the inclusion and none of the exclusion criteria will be enrolled in the RCT part of the study.

Inclusion Criteria

- PE with severe features, diagnosed using the ACOG standard criteria[4] requiring magnesium sulfate
- Females older than 18 years of age
- Singleton pregnancy
- Gestational age greater than 24 0/7 weeks
- The patient is physically and mentally able to understand the informed consent and is willing to participate in this study
- Able to speak English or Spanish

Exclusion Criteria

- Multiple gestation
- Prisoners
- Patients with chronic renal insufficiency or epilepsy
- Known cardiovascular disease
- Patients with contraindications to magnesium sulfate use (e.g. myasthenia gravis)
- Patients with eclampsia or HELLP syndrome
- Contraindications for magnesium sulfate

5.3 Study Outcomes

Primary Outcome:

Duration of magnesium sulfate use in the postpartum period defined as the duration in hours between delivery and discontinuation of magnesium sulfate.

Secondary safety Outcome:

Composite of eclampsia, pulmonary edema, renal insufficiency/acute kidney injury, venous thromboembolism, peripartum cardiomyopathy, ICU admission, or maternal death.

Secondary Maternal clinical Outcomes

Maternal secondary outcomes

- Need for or up-titration of antihypertensive agents postpartum for severe hypertension
- Hospital readmission up to 4 weeks postpartum
- Changes in arterial blood pressure in the peripartumpartum period
- Changes in cardiac output during the peripartum period
- Changes in heart rate in the peripartum period
- Need to restart magnesium sulfate
- Urine output, and the onset of diuresis defined as UOP >0.5ml/hour for 2 consecutive hours
- Preeclampsia symptoms resolution
- Correlation between magnesium levels and changes patient hemodynamics
- Anesthetic type
- Length of stay in Labor and delivery
- Total hospital length of stay
- Hospital cost
- Patient satisfaction

- Time to start regular diet and ambulation
- Maternal non-invasive cardiac parameters pre- and post-neuraxial anesthesia, pre- and post starting magnesium sulfate, with pushing or during cesarean delivery, and after the use of different anti-hypertensives (e.g. labetalol, nifedipine, hydralazine) for emergent therapy for severe hypertension
- Postpartum hemorrhage or blood transfusion
- Postpartum resources utilization including ER/triage visits, scheduled or non-scheduled clinic visits

Neonatal secondary outcomes

- Fetal or neonatal death
- Intubation, continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) for ventilation or cardiopulmonary resuscitation within first 72 hours
- Composite of either neonatal encephalopathy as defined by the NICHD Neonatal Research Network criteria, seizures, or intracranial hemorrhage (intraventricular hemorrhage, subgaleal hematoma, subdural hematoma, or subarachnoid hematoma)
- Hyperbilirubinemia requiring phototherapy or exchange transfusion
- Hypoglycemia (glucose < 35 mg/dl) requiring IV therapy
- NICU admission and length of stay in NICU

5.4 Study Procedures

Patients with PE with severe features admitted for delivery, will be screened for eligibility. Those who meet all the inclusion criteria and none of the exclusion criteria will be approached for participation. Subjects shall sign an informed consent form (ICF) approved by our site's Institutional Review Board (IRB), which includes Health Information Portability and Accountability Act (HIPAA) authorization information. The informed consent process shall be completed by the PI or designee prior to initiation of the study procedures. The original signed and dated informed consent form is to remain in the subject's research records; one copy is provided to the subject; and per site requirements, once copy placed in the medical record.

If a patient expressed interest and signs the ICF, she would be enrolled in the study and randomized to one of the two arms. Randomization will occur as soon as decision to deliver is made, and before start of mgSO4. Those assigned to the Cheetah arm, will have the device placed ASAP after randomization and before start of magnesium sulfate, in order to obtain baseline hemodynamic parameters.

In addition to subjects enrolled in the RCT, we propose an optional negative control cohort of 25 normotensive healthy women delivering > 37 weeks to compare hemodynamics.

Once informed consent is obtained, baseline procedures including collection of demographic, medical and obstetric histories, vitals (weight, height, and blood pressure), concomitant medications (con meds), and other pertinent clinical information will be obtained. Intrapartum and postpartum outcomes, including receipt of anesthesia and anti-hypertensive medications will be collected. In addition to collecting non-invasive cardiac parameters, hourly urine output and serial magnesium sulfate levels will be measured. Delivery outcomes (maternal and neonatal clinical information) will be collected on all subjects enrolled in the study.

5.5 Data Collection

Case Report Forms (CRFs) will be completed by research staff through patient interview and medical chart abstraction. Clinical data, including subject demographics and information on the current and previous pregnancies, The PI or designated staff reviews CRFs and database entry for accuracy.

Information obtained directly (patient interview) or indirectly (chart abstraction) is specifically for research purposes and obtained by trained members of the site's research staff. No subject names or other identifiers will be recorded on CRFs. Paper CRFs will be utilized with data written legibly, using black pen. Source documents will be kept as originals in the site's specific research chart. All entries will be signed and dated. Corrections will be made by making a single strike through on the prior entry with correction to the side to include date and in the initials of the research staff. Research staff will undergo an initiation training session to learn standard procedures for data entry.

5.6 Subject's Study Duration

In addition to the immediate delivery and postpartum data collection, postpartum data including any readmissions, ER/triage visits, scheduled or non-scheduled clinic visits will be recorded up to 4 weeks postpartum. If patient did not present for follow up, a phone call will be made to collect these data. Therefore, participation in this study ends after the last contact with the patient with a maximum potential study duration would be 4 weeks.

5.7 Subject Withdrawal

Subjects may withdraw from the study at any time without penalty or repercussion and for any reason without prejudice to their future medical care.

5.8 Regulatory Compliance

This study will be conducted in accordance with this protocol and the applicable requirements outlined in ICH E6 Good Clinical Practices and Title 21 CFR. The study will also be conducted in conformance with the Declaration of Helsinki and local laws and regulations.

This study will be exempt from the IDE requirements under Section 812.2(c)(3) because the device is (i) noninvasive; (ii) does not require any invasive sampling procedures that present significant risk [per 21 CFR Part 812.3(k), blood sampling that involves simple venipuncture is considered noninvasive]; (iii) would not be used as a diagnostic procedure in our clinical study without confirmation of the diagnosis by another, medically established diagnostic procedure.

6 Data Safety Monitoring Plan

A Data Safety Monitoring Plan will be developed for this study.

7 DATA ANALYSIS

7.1 Data Management

7.1.1 Data Collection

The subjects' demographic and clinical data will be collected and documented on the case report form (CRF) specifically designed for this study. The data will be entered into a secure password protected clinical database.

7.2 Statistical Methods and Data Analysis for the RCT.

7.2.1 Endpoint

This study's primary outcome is duration of magnesium sulfate use in the postpartum period, expressed in hours. The decision to discontinue magnesium in the Cheetah arm will be based on demonstration of 30% reduction in SVR (maintained for 1 hour) from the time of delivery.

7.2.2 General statistical methods

All summaries and analyses will be presented in tabular or graphical form. Data will be reported as mean ± standard deviation (SD), median [interquartile range] for continuous variables or number and percentage of subjects in each level of a categorical measurement. All statistical tests will be 2-tailed and performed at the 5% significance level, unless stated otherwise.

7.2.3 Demographics and baseline clinical variables

Demographic and available baseline clinical variables will be summarized descriptively for each arm of the study. Differences in distributions of demographic and clinical variables between the two arms will be analyzed using either a 2-sample t-test or the Wilcoxon Rank Sum test, depending on the distribution of the data, for continuous variables, and the Chi-square or Fisher's Exact tests for categorical variables as appropriate.

7.2.4 Primary efficacy analysis

The primary outcome will be compared between the two study arms using either a 2-sample t-test or the Wilcoxon Rank Sum test, depending on the distribution of the data. Multivariate linear regression modeling adjusting for race, gestational weeks, body mass index (BMI, continuous), and other significant variables will provide the primary efficacy analysis for this study. All other analyses are considered exploratory.

7.2.5 Sample size assessment and feasibility

Assuming an average reduction in magnesium sulfate use of 4 hours in the Cheetah® device group, alpha error of 5% and power of 90%, the study requires 21 patients in each arm. Allowing for 15% drop out, we plan to enroll a total of 60 patients.

In addition to subjects enrolled in the RCT, we propose an optional negative control cohort of 25 normotensive healthy women delivering > 37 weeks to compare hemodynamics.

The OSUWMC is a tertiary care referral center for the central Ohio region, with a delivery volume more than 5200 patients per year. In addition, we receive close to 750 transfers per year for high risk conditions including preeclampsia. The total number of women admitted with preeclampsia yearly is more than 450 patients. Given the high prevalence of preeclampsia with severe featuresat our tertiary care center, we anticipate completion of enrollment within 1 year.

8 REFERENCES

1. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation. 2014;130(12):1003–8.
2. Tihtonen K, Kööbi T, Yli-Hankala A, Uotila J. Maternal hemodynamics during cesarean delivery assessed by whole-body impedance cardiography. Acta Obstet Gynecol Scand. 2005;84(4):355–61.
3. Milsom I, Forssman L, Biber B, Dottori O, Rydgren B, Sivertsson R. Maternal Haemodynamic Changes during Caesarean Section: A Comparison of Epidural and General Anaesthesia. Acta Anaesthesiol Scand. 1985;29(2):161–7.
4. Espinoza J, Vidaeff A, Pettker CM, Simhan H. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133(1):e1-25.
5. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. BMJ. 2007;335(7627):974.
6. Lavie A, Ram M, Lev S, Blecher Y, Amikam U, Shulman Y, et al. Maternal cardiovascular hemodynamics in normotensive versus preeclamptic pregnancies: A prospective longitudinal study using a noninvasive cardiac system (NICaS™). BMC Pregnancy Childbirth. 2018;18(1):1–11.
7. Roberts JM. Pathophysiology of ischemic placental disease. Semin Perinatol. 2014;38(3):139–45.
8. Herraiz I, Llurba E, Verlohren S, Galindo A, Bartha JL, De La Calle M, et al. Update on the Diagnosis and Prognosis of Preeclampsia with the Aid of the sFlt-1/PlGF Ratio in Singleton Pregnancies. Fetal Diagn Ther. 2018;43(2):81–9.
9. Pryde PG, Mittendorf R. Contemporary usage of obstetric magnesium sulfate: Indication, contraindication, and relevance of dose. Obstet Gynecol. 2009;114(3):669–73.
10. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: Pharmacokinetic principles. Clin Pharmacokinet. 2000;38(4):305–14.
11. Simon J, Gray A, Duley L. Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: Economic evaluation of the Magpie Trial. BJOG An Int J Obstet Gynaecol. 2006;113(2):144–51.
12. Maia SB, Katz L, Neto CN, Caiado BVR, Azevedo APRL, Amorim MMR. Abbreviated (12-hour) versus traditional (24-hour) postpartum magnesium sulfate therapy in severe pre-eclampsia. Int J Gynecol Obstet. 2014;126(3):260–4.
13. Vigil-De Gracia P, Ramirez R, Durán Y, Quintero A. Magnesium sulfate for 6 vs 24 hours post delivery in patients who received magnesium sulfate for less than 8 hours before birth: A randomized clinical trial. BMC Pregnancy Childbirth. 2017;17(1):241.
14. Anjum S, Goel N, Sharma R, Mohsin Z, Garg N. Maternal outcomes after 12 hours and 24 hours of magnesium sulfate therapy for eclampsia. Int J Gynecol Obstet. 2016;132(1):68–71.
15. Miles JF, Martin JN, Blake PG, Perry KG, Martin RW, Meeks GR. Postpartum eclampsia: A recurring perinatal dilemma. Obstet Gynecol. 1990;76(3 Pt 1):328.

16. Vinayagam D, Bowe S, Sheehan E, et al. Non-invasive haemodynamic monitoring in pregnancy: a comparative study using ultrasdound and bioreactance. Fetl Diagn Ther 2017;41:272-282.