Research Proposal
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Title

- Postpartum management of gestational hypertensive disorders using furosemide: A randomized controlled trial

Investigators

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Summary

- The main purpose of this study is to learn if incorporating a loop diuretic such as furosemide along with labetalol in the routine management of postpartum gestational hypertensive disorders could lower the need for additional anti-hypertensive agents to control blood pressures, improve blood pressures (as measured by systolic blood pressure, diastolic blood pressure and mean arterial blood pressures), shorten hospital stays and decrease readmissions for patients with gestational hypertensive disorders.
- Based on a study by Veena et al[1], there is reason to believe that the addition of furosemide to other anti-hypertensives may help decrease the need to add or increase the dose of medication to control blood pressures. There may be potential to shorten hospital stays and decrease readmissions, as well. Collecting data will be done using a prospective, randomized 1:1 controlled study assigning postpartum patients with a gestational hypertensive diagnosis to either labetalol alone or labetalol plus furosemide.
- Based on an estimated 8% need for increase in anti-hypertensive medication in the furosemide group and a 26% need in the standard treatment arm, to achieve 90% power

with a 2-sided alpha of 0.05, we calculate 96 patients per group. Analysis will be via Chi-square or Fisher's exact test for categorical variables. Student T-Test and Mann Whitney U tests will be utilized to compare continuous variables. Randomization will be performed using REDCap.

- The study will be performed in the postpartum wing of Miami Valley Hospital Main Campus and would recruit patients who have consented to participate in the study with enrollees coming from the OB Staff population.

Background and Literature Review

- We found four studies investigating loop diuretics in the management of postpartum hypertensive disorders- Matthews et al[2], Ascarelli et al[3], Amorim et al[4], and Veena et al. Of these studies, only Amorim and Veena were able to show statistical significance on any parameters. Amorim was able to show that there was an improvement of SBP, DBP and MAP, but their research was only presented as an abstract at a conference and not published, thereby making it impossible to draw any conclusions or practice guidelines. Veena demonstrated that by using furosemide and nifedipine in combination, the need for additional antihypertensive medication in severe pre-eclampsia in the postpartum period was reduced when compared to nifedipine alone.
- A systematic review[5] of postpartum hypertensive disorder management suggested that there was insufficient data to recommend any single pharmacological intervention at this time in the management of gestational hypertensive disorders. The review emphasized the need for further studies to be conducted to help guide management of patients affected by gestational hypertensive disorders in the future.

Objectives

- **Main Question**
  - Does the use of furosemide plus labetalol improve blood pressures in the postpartum period of patients with gestational hypertensive disorders versus labetalol alone?
  - **Primary**
    - Does the addition of a 5-day course of furosemide to labetalol avoid the escalation of anti-hypertensive therapy to control blood pressures.
  - **Secondary:**
    - Does the addition of furosemide to labetalol in postpartum hypertension:
      - Improve of systolic blood pressure, diastolic blood pressure and mean arterial pressure.
    - Shortened hospital stay
    - Affect breastfeeding status at 1 week postpartum visit in mothers planning to breastfeed.
    - Decrease readmission for postpartum hypertensive disorders.

Significance to patient, institution, and profession

- As a busy referral center with a level 3 NICU, Miami Valley care for a large number of patients with gestational hypertensive disorders
- The majority of the OB staff population being served at Miami Valley Hospital is African American. According to Myatt[6], the incidence of pre-eclampsia in the African American population is greater than double the Caucasian population (11% to 5%) thereby making this study very applicable to our patient population.
- With the construct of the study, we would be keeping costs low by utilizing already established resources and practices (blood pressure cuffs, nurses, routine one week blood pressure checks) while only adding on the unit cost of furosemide and basic metabolic panels.
- If treatment with labetalol and furosemide is found to be useful, it would be not only a very inexpensive, cost effective way of improving patient outcomes and possibly decreasing lengths of stay, but possibly improvement in global practice in places that are lacking in resources privy to first world countries.

Methods

- A prospective randomized 1:1 controlled trial including postpartum women with gestational hypertension or preeclampsia
    - Inclusion criteria: Age 18-45, Postpartum: 24-72 hours after delivery, no contraindications to the study medications
    - Exclusion criteria: chronic hypertension diagnosis, creatinine levels above 1.5 μm/L, unable to give consent
- One arm receiving 200mg labetalol BID alone on Day#1 or at least 24 hours after magnesium sulfate, if given
- One arm receiving 200mg labetalol BID and a five day course of furosemide 20mg QD on Day#1 or 24 hours after magnesium sulfate
    - The 20 mg dose is the standard dose for furosemide in this population.
- Tritrate labetalol to maintain blood pressures below 150 SBP and/or 100 DBP per ACOG recommendations.[7]
    - In the event of persistently elevated blood pressures, labetalol will be increased to 400mg BID and escalated to 600mg BID and finally 800mg BID as indicated
- Measurement of blood pressure every four hours until patient discharge
- Daily BMPs to assess for electrolyte abnormalities
- Measurement of urine output every 12 hours until discharge
- Demographics
    - Age (18-24, 25-34, 35-44, 45-51)
    - Nulliparous (yes, no)
    - BMI (underweight, normal, overweight, obese)

    - Race (Caucasian, African American, Asian, Hispanic, Other)
    - Diabetes (yes, no)
    - Multiple gestation (yes, no)
    - Preterm delivery (yes, no)
        - Gestational age at delivery
    - Cesarean delivery (yes, no)
    - IVF pregnancy (yes, no)
    - History of previous gestational hypertension/pre-eclampsia (yes, no)
    - Systemic lupus erythematosus (yes, no)
    - Renal disease (yes, no)
- Outcome variables
    - Need for additional antihypertensive medication (yes, no)
        - Labetalol 400mg BID
        - Labetalol 600mg BID
        - Labetalol 800mg BID
    - Highest systolic blood pressure (mmHg)
    - Highest diastolic blood pressure (mmHg)
    - Mean arterial blood pressure
    - Daily urine output (mL)
    - Length of postpartum stay (days)
    - Readmission for hypertension (yes, no)
    - Breastfeeding at 1 week postpartum (yes, no)
- The study duration is the length of the hospital stay plus 1 week postpartum blood pressure check.
- The research will be analyzed and interpreted by the research team conducting the study.
- Potential difficulties and limitations include compliance concerns of mandatory one week blood pressure follow up appointment.
- The unit cost of one tablet of labetalol 200mg and furosemide 40mg is currently $0.32 and $1.23, respectively. [8,9]
- The study would use already readily available automated blood pressure cuff machines on the postpartum wing.

Safety Monitoring

Monitoring of blood pressures will be performed every four hours while on the maternity postpartum floor. If the patient is found to be above 160 systolic or 110 diastolic, it will be rechecked in fifteen minutes. If still elevated, then escalation of blood pressure medicine will be done. The healthcare provider will ask the patient if they are exhibiting any signs of profound hypertension and/or hypokalemia including headache, vision changes, dizziness, lightheadedness, weakness, fatigue, muscle cramping, or heart palpitations. If any of these are identified, a physician will be notified and will assess the patient.

Patients will be instructed to let their doctor/nurses know if they are experiencing known side effects of Lasix that include new onset weakness, fatigue, muscle cramping, dizziness or

heart palpitations. If a patient has severe symptoms after discharge, they will be instructed to call the afterhours phone number on the consent form.

If a patient has signs of hypokalemia, we will test lab values for potassium (K+) levels (Complete metabolic panel). We will continue administering Lasix if the potassium result is between 3.0 and 3.4 μm/L and we will administer 20 mEq KDur BID. If it is less than 3.0 μm/L we will stop using Lasix.

References

1) **Veena, P., et al. "Furosemide in Postpartum Management of Severe Preeclampsia: A Randomized Controlled Trial." *Hypertension in Pregnancy*, vol. 36, no. 1, 2016, pp. 84–89., doi:10.1080/10641955.2016.1239735.**
2) **Matthews G, Gornall R, Saunders NJ. A randomised placebo controlled trial of loop diuretics in moderate/severe pre-eclampsia, following delivery. J Obstet Gynaecol 1997;17:30-2**
3) **Ascarelli MH, Johnson V, McCreary H, *et al.* Postpartum preeclampsia management with furosemide: a randomized clinical trial. *Obstet Gynecol* 2005;105:29-33**
4) **Amormim M, Katx L, Cursino T, *et al.* Postpartum furosemide for accelerating recovery in women with severe preeclampsia: A randomized clinical trial. *Int J Gynaecol Obstet* 2015;131:E195**
5) **Cairns AE, Pealing L, Duffy JMN, *et al.* Postpartum management of hypertensive disorders of pregnancy: a systematic reivew. *BMJ Open* 2017;7:e018696. doi:10.1136/bmjopen-2017-018696**
6) **Myatt L, Clifton RG, Roberts JM, et al: First-trimester prediction of preeclampsia in nulliparous women at low risk. Obstet Gynecol 119(6):2012a**
7) **ACOG Task Force on Hypertension in Pregnancy. *Hypertension in pregnancy: American college of obstetricians and gynecologists, 2013.***
8) **"Labetalol Prices, Coupons & Patient Assistance Programs." *Drugs.com*, www.drugs.com/price-guide/labetalol.**
9) **"Lasix Prices, Coupons & Patient Assistance Programs." *Drugs.com*, www.drugs.com/price-guide/lasix.**