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Furosemide for postpartum blood pressure control in patients with hypertensive disorders

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ABSTRACT

Objective: diuretics have the potential to reduce intravascular volume, decrease blood pressure The aim of our study is to evaluate the effectiveness of furosemide in postpartum patients with pre-eclampsia and chronic hypertension with superimposed pre-eclampsia.

Methods: This is a retrospective cohort study. Data was extracted from the record of patients who delivered between 2017 and 2020 and had chronic hypertension or, chronic hypertension with superimposed pre-eclampsia, gestational hypertension, or pre-eclampsia. Patients who received intravenous furosemide in the postpartum period were compared to those who did not. The groups were also analyzed for fetal growth restriction, and pregnancy outcomes comparing those who did receive furosemide and those who did not.

Results: The furosemide group had a statistically significant longer postpartum length of stay ($p < 0.0001$), required more antihypertensive medications ($p < 0.0001$), medication increases ($p < 0.0001$), and emergent blood pressure treatment ($p < 0.0001$), than the group who did not. There was no difference between groups in hospital readmission, or fetal growth restriction.

Conclusion: The postpartum length of stay and rates of readmission were not decreased in the group treated with intravenous furosemide. Future prospective studies that control for pregnancy comorbidities and severity of preeclampsia are needed to determine furosemide's effect on the volume status of the postpartum pre-eclamptic patient and determine its role in the treatment of these women.

Introduction

Hypertension affects approximately 10 % of pregnancies and causes a significant proportion of maternal morbidity and mortality [1,2]. Hypertension in the postpartum period requiring hospital readmission comprises a considerable number of obstetrical readmissions and overall hospital readmission rates [3,4]. Hypertension and hypertensive urgency can increase in the postpartum period due to postpartum fluid dynamics and changes in sodium balance in the setting of pre-eclampsia. Following delivery, an influx of volume into the intravascular space occurs as the pathophysiology of pre-eclampsia reverses [5,6]. These changes in fluid dynamics can take days to weeks to completely resolve.

In the postpartum period, blood pressure may improve in the first few days only to increase sometime later in the first postpartum week [7]. This shift can affect blood pressure and hinder successful and efficient blood pressure control during postpartum. Furosemide, a loop diuretic, may be a potential therapy to reduce intravascular volume in the postpartum period and assist with blood pressure control and readmission rates [8,9]. A randomized control trial from 2005 found benefits in patients with pre-eclampsia with severe features who received 5 days of furosemide postpartum, but no studies specifically evaluated both superimposed pre-eclampsia and pre-eclampsia with or without severe features [8–10].

The aim of our study is to determine the effectiveness of furosemide in postpartum patients with pre-eclampsia and chronic hypertension with superimposed pre-eclampsia. We hypothesized that treatment with furosemide would reduce oral antihypertensive medications, reduce length of postpartum admission, and readmission rates.

Methods

The study design was a retrospective cohort study approved by

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institutional IRB. Data was extracted from our university Epic electronic medical record database. Inclusion criteria was delivery at our university hospital from 2017 to 2020, with any of the following diagnoses: chronic hypertension on medication during pregnancy, chronic hypertension with superimposed pre-eclampsia, and pre-eclampsia. Patients who received at least one dose of intravenous furosemide in the postpartum period were compared to those who did not.

The primary outcomes were postpartum length of hospital stay (LOS), total number of oral antihypertensive medications administered, number of times the dose of an oral antihypertensive medication had to be increased, number of postpartum treatments with IV antihypertensive, and rates of postpartum readmission.

Statistical analysis

All statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc. Cary, NC, USA). Descriptive statistics for continuous variables were expressed as means and standard deviations (SD) or median and percentiles (25th, 75th), where appropriate. For categorical measures we presented frequencies and percentages. Initially, bivariate comparisons of key maternal and infant characteristics and study outcomes were analyzed using two-sample t-test, Wilcoxon rank-sum test, chi-square test, or Fisher's exact test. To examine the association between postpartum LOS and treatment group (no furosemide vs. furosemide), Poisson regression for count data was used to estimate the difference in postpartum LOS, contrasting between patients receiving furosemide and those not receiving furosemide while adjusting for various maternal and infant characteristics. We report both the predicted length of hospital stay and 95 % confidence interval (CI) for each group. For binary outcomes such as postpartum readmission, received oral antihypertensive BP treatment, and received emergent BP treatment multivariable logistic regression models were used while adjusting for maternal and infant characteristics. For each analysis, we report both the adjusted odds ratio (OR) along with their respective 95 % CI. All analyzes were based on a two-sided test with significance level of 0.05.

Results

There were 1938 women identified (221 in the furosemide group and 1717 in the non-furosemide group). The average maternal age across both groups was approximately 29 years old (see Table 1). The proportion of Black women that received furosemide in the postpartum period was higher than the proportion who did not received furosemide (56.6 % vs. 48.3 %; $p < 0.001$). Additionally, women in the furosemide group had higher BMI (45.5 vs. 38.0), more likely to have presentational diabetes (15.8 % vs. 11.0 %) and gestational diabetes (16.7 % vs. 7.6 %), higher rates of chronic hypertension (61.5 % vs. 54.4 %), preeclampsia (77.4 % vs. 67.4 %), and post-partum hemorrhage (15.8 % vs. 9.1 %). The furosemide group had lower rates of vaginal delivery compared to the non-furosemide group (31.2 % vs. 46.0 %, $p \leq 0.0001$). There was no difference in parity and mean gestational age. Mean birthweight was slightly higher for the furosemide group (2757.7 g vs. 2607.3 g, $p = 0.027$).

The median postpartum LOS in the furosemide group was 2.5 [2.0, 3.5] and 2.0 [1.7, 3.0] in the non-furosemide group ($p < 0.0001$). In a multivariable Poisson regression model adjusting for maternal and infant characteristics, the expected duration of postpartum LOS across the groups was not statistically significant at the 0.05 level (Table 2). More specifically, the incident rate ratios (IRR) is given by exponentiating the regression coefficient. Thus, the incident rate for those patients not receiving furosemide was 0.92 (95 % CI: 0.84, 1.0; $p = 0.051$) times the incident rate of those women receiving furosemide, holding the other variables constant. The predicted number of postpartum LOS for the no furosemide group was 2.3 days (95 % CI: [2.1, 2.5]) while the predicted number of postpartum LOS for the furosemide group was 2.5 days (95 % CI: 2.2, 2.7]). Women treated with furosemide had a higher number of antihypertensive medications received, higher emergent BP treatment, and higher medication treatment increased compared to those that did not received furosemide ($p < 0.0001$) in the multivariable Poisson regression analysis. The differences in number of antihypertensive medications received remained statistically significant after adjusting for maternal demographics with predicted number of 0.35 (95 % Cl: 0.26, 0.45) for the furosemide group and 0.17 (95 % CI: 0.13, 0.21) for the non-furosemide group.

Given the overwhelming number of mothers who did not require antihypertensive medication or received emergent BP treatment, we created two binary (yes/no) indicators. The results of the multivariable logistic regression analyses are presented in Table 3. The adjusted odds of receiving antihypertensive medication for a mother treated with furosemide is 3.69 (95 % CI: 2.69, 5.07) times the odds of a mother who was not treated with furosemide. Likewise, the adjusted odds of emergent BP treatment for a mother treated with furosemide is 6.52 (95 % CI: 4.16, 10.19) times the odds of a mother who was not treated with furosemide. There were no differences between the groups in terms of hospital readmission (OR = 1.45; 95 % CI: 0.90, 2.34; $p = 0.129$) after accounting for maternal and infant characteristics. Finally, we note that the adjusted odds of fetal growth restriction among mothers treated and not treated with furosemide were not statistically significant (OR = 1.21; 95 % CI: 0.59, 2.49; $p = 0.60$).

Table 1
Descriptive summary and bivariate analyses.

Maternal measures	No furosemide (N = 1717)	Furosemide (N = 221)	p-value
Age, mean (SD)	29.0 (6.4)	29.8 (6.0)	0.089[a]
Race, N (%)			0.010
White	684 (39.8 %)	83 (37.6 %)	
Black	830 (48.3 %)	125 (56.6 %)	
Other	203 (11.8 %)	13 (5.9 %)	
Parity, N (%)			0.089
0	589 (34.3 %)	61 (27.6 %)	
1	459 (26.7 %)	59 (26.7 %)	
≥ 2	669 (39.0 %)	101 (45.7 %)	
BMI, mean (SD)	38.0 (9.8)	45.5 (14.2)	< 0.0001[a]
Vaginal delivery, N (%)	790 (46.0 %)	69 (31.2 %)	< 0.0001
Diabetes, N (%)	189 (11.0 %)	35 (15.8 %)	0.035
GDM, N (%)	131 (7.6 %)	37 (16.7 %)	< 0.0001
CHTN, N (%)	934 (54.4 %)	136 (61.5 %)	0.045
Preeclampsia, N (%)	1157 (67.4 %)	171 (77.4 %)	0.003
PPH, N (%)	157 (9.1 %)	35 (15.8 %)	0.002
Infant Measures			
Gestational age, mean (SD)	35.6 (4.1)	35.7 (3.4)	0.810[a]
Birthweight, mean (SD)	2607.3 (943.5)	2757.7 (983.5)	0.027[a]
Outcomes			
Postpartum LOS, median [Q1, Q3]	2.0 [1.7, 3.0]	2.5 [2.0, 3.5]	< 0.0001[b]
Readmission, N (%)	121 (7.1 %)	26 (11.8 %)	0.013
Oral antihypertensive medication, N (%)	427 (24.9 %)	129 (58.4 %)	< 0.0001
Number of antihypertensive medication, median [Q1, Q3]	0 [0,0]	1 [0,1]	< 0.0001[b]
Emergent BP treatment, N (%)	65 (3.8 %)	45 (20.4 %)	< 0.0001
Number of emergent BP treatment, median [Q1, Q3]	0 [0,0]	0 [0,0]	< 0.0001[b]
Number of medication increase, median [Q1, Q3]	0 [0,0]	0 [0,1]	< 0.0001[b]
FGR, N (%)	521 (30.3 %)	56 (25.3 %)	0.126

[a] Significant level based on two-sample t-test.
[b] Significant level based on Wilcoxon rank-sum test; Q1 & Q3 (25th and 75th percentiles); BMI (body mass index); GDM (gestational diabetes mellitus); CHTN (chronic hypertension); PPH (post-partum hemorrhage; FGR (fetal growth restriction).

Table 2
Multivariable Poisson regression results for postpartum LOS.

	Beta	SE	p-value
Furosemide (no/yes)	-0.087	0.0445	0.051
Race			
White	0.018	0.0508	0.724
Black	0.0634	0.0503	0.207
Other	**Ref**		
Parity			
0	0.0779	0.0377	0.039
1	-0.0044	0.0381	0.908
≥ 2	**Ref**		
Delivery (vaginal cesarean)	-0.329	0.0319	< 0.0001
Diabetes (no/yes)	-0.0434	0.0469	0.355
GDM (no/yes)	0.008	0.0546	0.887
CHTN (no/yes)	-0.007	0.0367	0.856
Preeclampsia (no/yes)	-0.0319	0.0412	< 0.0001
PPH (no/yes)	-0.0929	0.0464	0.046
Age (5 years interval)	0.0028	0.0130	0.833
BMI (2 unit interval)	0.0007	0.0030	0.821
Gestational age (2 weeks interval)	-0.0255	0.0138	0.065
Birthweight (100 g interval)	-0.0054	0.0031	0.079

Note: The table provides Poisson regression coefficients and standard errors for each variable. For indicator variable such as Furosemide, the coefficient represents the expected difference in log count between no Furosemide and reference group Furosemide. Thus, the difference in the logs of expected LOS is expected to be 0.087 days lower for the no Furosemide group compared to the Furosemide group, while holding the other variables in the model constant. BMI (body mass index); GDM (gestational diabetes mellitus); CHTN (chronic hypertension); PPH (post-partum hemorrhage; FGR (fetal growth restriction).

Discussion

In our cohort, postpartum furosemide did not decrease the postpartum length of stay nor the rate of readmission in the postpartum period. This study brings up several questions. One of the most likely explanations that women who were treated with furosemide were hospitalized longer and their readmission rate was higher is that furosemide was preferentially administered to patients who were thought to have more severe hypertensive disease (i.e., higher rates and severity of hypertensive urgency, presence of lab abnormalities, etc.). Although in this study, the length of stay was not substantially longer for the treatment group, the question arises: would the length of stay have been even longer for these patients (presumably with a more severe disease process) if they had not received furosemide? The length of stay could also have been impacted by receiving or not receiving furosemide since the expected length of stay is usually 2–3 days postpartum except in extenuating circumstances.

This study design does not delineate patients who had chronic hypertension with superimposed pre-eclampsia from those who had pre-eclampsia with no prior diagnosis of hypertension in each of the cohort groups. There is a need for further studies to determine if furosemide has a role and what is that role in different subtypes of postpartum hypertension.

A recent study published in the American Journal of Obstetrics and Gynecology postulated that there are two different phenotypes of pre-eclampsia, one associated with fetal growth restriction and the other with normal weight fetuses [11]. In cases of pre-eclampsia without fetal growth restriction, patients may in fact have a high blood volume, high cardiac output, and low vascular resistance. We suspected that treatment with furosemide may be more beneficial in patients without fetal growth restriction and less beneficial in pre-eclampsia complicated by fetal growth restriction because of the already depleted intravascular volume [11]. Nevertheless, among the pregnancies complicated by fetal growth restriction in our population, we observed no significant difference between those who received furosemide and those who did not.

Table 3
Multivariable logistic regression results for readmission, BP medication, and receive emergent BP treatment.

	Readmission		BP medication		Emergent BP treatment	
Variables	OR	95 % CI	OR	95 % CI	OR	95 % CI
Furosemide (ref: no)	1.45	0.898, 2.342	3.694	2.692, 5.068	6.515	4.164, 10.193
Race (ref: other)						
White	1.361	0.703, 2.634	1.046	0.718, 1.522	2.34	0.799, 6.851
Black	1.904	0.998, 3.631	1.619	1.122, 2.338	3.852	1.346, 11.026
Parity (ref: ≥ 2)						
0	0.727	0.463, 1.142	0.941	0.712, 1.244	0.693	0.405, 1.183
1	0.772	0.498, 1.197	0.986	0.751, 1.295	0.763	0.455, 1.281
Delivery (ref: cesarean)	0.99	0.686, 1.429	1.628	1.297, 2.044	1.175	0.763, 1.808
Diabetes (ref: no)	1.015	0.578, 1.782	0.903	0.634, 1.287	0.766	0.368, 1.595
GDM (ref: no)	1.245	0.705, 2.198	0.765	0.515, 1.136	1.021	0.49, 2.128
CHTN (ref: no)	0.973	0.64, 1.48	1.329	1.023, 1.727	0.724	0.468, 1.121
Preeclampsia (ref: no)	2.157	1.318, 3.532	3.936	2.913, 5.318		
PPH (ref: no)	1.084	0.623, 1.887	0.601	0.403, 0.897	0.74	0.356, 1.538
Age (5 year interval)	1.156	0.991, 1.349	1.305	1.185, 1.438	1.273	1.06, 1.529
BMI (2 unit interval)	0.998	0.964, 1.034	1.045	1.022, 1.068	1.032	0.993, 1.071
Gestational age (2 week interval)	0.991	0.836, 1.175	0.955	0.862, 1.059	1.01	0.845, 1.207
Birthweight (100 g interval)	1.015	0.98, 1.051	1.011	0.989, 1.034	0.944	0.902, 0.987

Note: In the multivariable logit analysis for emergent BP treatment, pre-eclampsia was removed for the model due to quasi-separation of data. BMI (body mass index); GDM (gestational diabetes mellitus); CHTN (chronic hypertension); PPH (post-partum hemorrhage; FGR (fetal growth restriction).

Conclusion

Furosemide administration in the postpartum period for patients with a spectrum of pregnancy-associated hypertensive disorders has shown some benefits [12,13]. In our analysis, we observed no statistically significant difference in postpartum length of stay between the treatment and non-treatment groups. Patients who received furosemide were more likely to receive IV push antihypertensive medications and to be sent home on oral antihypertensives. Additionally, rates of readmission were not statistically significant between the two groups. Without randomization, there is the likelihood of selection bias by providers to administer furosemide to women who were thought to have a more severe disease process. More research, specifically in the form of randomized control trials with standardization of furosemide dosing and frequency, is needed on targeted furosemide therapy to determine if and for which patients its use has a role in the treatment of postpartum hypertension.

Ethics

The UAMS Institutional Review Board approved study #275061 as human subject research under Exempt, category [4c] based on Title 45 CFR 46.104 on 11/18/2022.

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Declaration of Competing Interest

None. All authors declare they have nothing to disclose.

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Disclaimer

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