Assessment of the effect of adding furosemide to antihypertensive treatment on postpartum hypertension in women with preeclampsia; a randomized clinical trial

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Abstract

Introduction: One of the probable mechanisms of hypertension that may occur in women with preeclampsia after delivery is returning of interstitial and extravascular fluid into the bloodstream.

Objectives: The present study aimed to investigate the effect of furosemide to control postpartum hypertension in women with preeclampsia.

Patients and Methods: This randomized clinical trial was conducted on 116 patients with preeclampsia with a blood pressure (BP) of more than 150/100 mm Hg in the first 24 hours after delivery. Patients were randomly divided into two groups of nifedipine (taking 10 mg tablets every 8 hours) and nifedipine plus furosemide (nifedipine plus 20 mg furosemide tablet once daily). Patients were monitored until the fifth day after delivery. After the first 48 hours, patients with a BP lower than 150/100 mm Hg were discharged from the hospital and the treatment continued at home.

Results: Systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) were significantly reduced in all patients and in each group on the first to fifth days after delivery. On the second day, DBP in the nifedipine group was significantly lower (P = 0.005). On the third to fifth days, SBP in the nifedipine plus furosemide group was significantly lower (P < 0.05), while DBP did not change (P > 0.05). On the third and fourth days, MAP was significantly lower in the nifedipine plus furosemide group (P < 0.05), however it was not significantly different on the fifth day (P = 0.383). The need for additional medication to control BP was higher in the nifedipine group than in the nifedipine plus furosemide group. BP became normal (less than 120/80 mmHg) in 74 patients (68%) within five days after delivery; which was more popular in the nifedipine plus furosemide group (P < 0.001).

Conclusion: The findings of the present study showed that inclusion of furosemide in nifedipine regimen was associated with a further reduction in SBP and MAP. Furosemide also reduced the need for additional medication to control BP and increased the frequency and speed of reaching toward normal BP.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20191031045289N2; https://irct.ir/trial/49806, ethical code; IR.SBMU.MSP.REC.1399.067).

Implication for health policy/practice/research/medical education:

One of the probable mechanisms of hypertension that may occur in women with preeclampsia after delivery is returning of interstitial and extravascular fluid into the bloodstream; hence, loop diuretics may be administered to better control BP during this period. In a randomized clinical trial, we showed that including furosemide to nifedipine was associated with a further reduction in SBP and MAP. We also found that furosemide reduced the need for additional medications to control BP.

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Introduction

Preeclampsia is the third most common cause of maternal mortality in the world and the second most common cause of maternal mortality in Iran (1,2). It is a pregnancy-specific disorder and is diagnosed in women with high blood pressure (BP) and new onset proteinuria following the 20th week of pregnancy (3). Preeclampsia occurs in 5%-8% of all pregnancies and 20% of first pregnancies (4). Despite extensive research in recent decades, the mechanism of developing and worsening preeclampsia during pregnancy is still unknown (5).

Preeclampsia has several risk factors such as nulliparity, maternal underlying diseases, molar pregnancy, multiparity, maternal infections, advanced maternal age, maternal overweight, and family history of preeclampsia (6). Complications associated with preeclampsia are categorized into two categories including maternal complications (such as premature placental abruption, seizures, edema and cerebral hemorrhage and acute renal failure) and fetal complications (such as intrauterine growth restriction, hypoxia and intrauterine death). However, it may also cause long-term complications in both mothers and babies (7).

Although various methods are utilized to prevent or reduce the severity of preeclampsia, none of them have been fully effective in reducing the rate of preeclampsia (8). Treatment of preeclampsia includes antihypertensive therapy and seizure prevention (9). Magnesium sulfate is the most important and effective drug utilized for controlling patients’ BP and preventing seizures before delivery. This drug should be prescribed to all women at risk of eclampsia (10-14).

Although termination of pregnancy is the only definitive treatment for preeclampsia, the complications of preeclampsia such as high BP or even seizures may occur within several days to a week after delivery, while in 0.3%-27.5% of cases, hypertension or new preeclampsia occurs during postpartum period (15). Due to the return of interstitial and extravascular fluid into the bloodstream, elevated BP is common during postpartum period while high BP under such a condition leads to increased maternal mortality. Therefore, it is necessary to continue the treatment during this period, especially on the first few days after delivery. Considering the possible mechanism leading to the return of interstitial fluid into the bloodstream that could cause hypertension during this period, it might be helpful to facilitate fluid excretion using diuretic antihypertensive drugs. Loop diuretics can increase urinary excretion through inhibiting sodium and chloride channels in the ascending part of the loop of Henle to prevent sodium reabsorption (16). However, despite the existing evidence on the effectiveness of loop diuretics in the prevention of persistent postpartum hypertension (2,17-19), the administration of loop diuretics in preeclampsia during the postpartum period is still not approved (20).

Objectives

The aim of this study was to evaluate the effect of furosemide on controlling postpartum BP in women with preeclampsia.

Patients and Methods

Study design

This randomized clinical trial was performed in Mahdieh hospital in Tehran in 2019-2020. This study was conducted on 160 patients with preeclampsia and with a BP higher than 150/100 mm Hg 24 hours after delivery who were treated prophylactically using magnesium sulfate to prevent eclampsia. Inclusion criteria were; systolic BP (SBP) ≥150 mm Hg or diastolic BP (DBP) ≥100 mm Hg, urine volume higher than 50 mL/h, and termination of magnesium sulfate treatment. Exclusion criteria were; history of chronic hypertension, BP lower than 150/100 mm Hg, administration of diuretics, previous underlying renal impairment, diabetes, hemodynamic instability, potassium level lower than 3 mEq/L, contraindications for the administration of furosemide and hematocrit more than 37%.

After explaining the method of the study to the patients, written consent was obtained from all the patients. Additionally, the patients’ data including age, pregnancy status (gravity, parity and history of abortion), preterm delivery and postpartum BP were recorded. Then, all the patients received nifedipine 10 mg tablets every 8 hours. The patients were then randomly divided into two groups. The first group only received nifedipine, while the second group in addition to nifedipine received furosemide 20 mg tablets once a day following the second to the fifth day after delivery. A stat dose of 10 mg nifedipine was used whenever a patient’s BP was higher than 160/110 mm Hg. On the first day of hospitalization, the patients’ BP were recorded at 1, 2, 3, 6, 12, 18 and 24 o’clock. From the second day onwards, the patients’ BP were recorded at 6, 12, 18 and 24 o’clock. Moreover, the patients’ urine volumes were recorded on the first day of hospitalization after delivery. After the first 48 hours, patients with a BP lower than 150/100 mm Hg in two consecutive measurements were discharged from the hospital and treatment was continued at home. At the time of discharge, every patient was instructed to continue the medication continuously, measure and record her BP at the abovementioned times with a digital manometer at home or at a nearby clinic and then collect the daily urine. The patients were also recommended to refer to a hospital if their BP exceeded 150/100 mm Hg, as a warning sign. For the patients who did not experience high BP, it was requested to refer to the hospital at the end of the fifth day to review the BP chart and continue treatment. Finally, the duration of hospitalization, the patient’s BP during the second to fifth days after delivery, the urine volume during the first five days after delivery, and the need for additional medication to control BP during hospitalization were recorded. The
mean arterial pressures (MAPs) of the patients were also calculated using the following formula; MAP=DBP+(SBP-DBP)/3. The times to reach normal BP (SBP ≤ 120 mm Hg and DBP ≤ 80 mm Hg) and remain in a stable condition were also recorded.

In this study, it was necessary to regularly register their BP in a chart and collect urine after discharge from the hospital, hence they were followed up by making phone calls. Since it was not possible to follow up a total of seven patients (three patients in the nifedipine group and four patients in the nifedipine plus furosemide group), therefore they were excluded from the analysis (Figure 1).

**Statistical analysis**

SPSS 25 statistical software was used for data entry and analysis. Qualitative variables were described using frequency and percentage and quantitative variables were described using mean and standard deviation. In addition, chi-square, independent t test and repeated measure ANOVA were used to analyze the data. The level of significance was set at \( P < 0.05 \).

**Results**

The mean (SD) age of the patients was 28 ± 5 years, ranging from 17 to 40 years old. There was no significant difference between the two groups regarding age and pregnancy characteristics (Table 1). There was no significant difference between the groups in terms of prenatal BP \( (P>0.05) \). However, on the first day after delivery, DBP and MAP were significantly lower in the nifedipine group \( (P<0.001; \text{ Table 2}) \).

Table 3 presents the patients’ BPs from the second day to the fifth day after delivery. The results of repeated measure ANOVA showed that the mean SBP, DBP and MAP were significantly reduced in all the patients and in each individual group on the first day to the fifth day after delivery \( (P<0.001; \text{ Figure 2}) \). Comparing the groups in each day, showed that DBP in the nifedipine group was significantly lower on the second day \( (P=0.005) \), however SBP and MAP were not significantly different between the two groups \( (P>0.05) \). On the other hand, SBP was significantly lower in the nifedipine plus furosemide group on the third day to the fifth day \( (P<0.05) \), while DBP was not significantly different between the two groups on the third to fifth days \( (P>0.05) \). MAP was significantly lower in the nifedipine plus furosemide group on the third and fourth day \( (P<0.05) \); however, no significant difference between the groups on the fifth day was observed \( (P=0.383) \).

Considering SBP ≤120 mm Hg and DBP ≤80 mm Hg as the normal BP, 35 patients (32%) did not develop normal BP during the five days after delivery. We also found, three patients (3%) had normal BP on the third day, 27 patients (25%) on the fourth day, and 44 patients (40%) on the fifth day had normal BP. The frequency of reaching normal BP was significantly higher in the nifedipine plus furosemide
The findings of the present study showed that SBP, DBP and MAP were significantly reduced in all patients and in each individual group on the first to fifth day after delivery.
Adding furosemide to nifedipine was associated with a significant reduction in SBP on the third and fifth days. There was also a lower need for additional medication to control BP by adding furosemide to the regimen.

The mechanism of developing gestational hypertension, prenatal preeclampsia and postpartum preeclampsia is not well understood. Following delivery, fluids trapped outside the vascular space return to patients’ bloodstream. As a result, the fluids increase the pressure of the central venous vessels and the pulmonary capillary wedge pressure. Therefore, diuretics may be administrated as antihypertensive drugs in such cases (17). However, there are few studies on the effect of loop diuretics on postpartum BP control in patients with preeclampsia.

Studies investigating the effect of furosemide on postpartum BP have reported different results. According to the study by Matthews et al, furosemide reduced MAP after delivery more rapidly. However it did not reduce the need for additional medication to control BP and the length of hospital stay (18), though the sample size of the mentioned study was low. Ascarelli et al reported that only people with severe preeclampsia compared with the control group, had a significant reduction in BP on the second day after delivery while their need for antihypertensive drugs was lower. No significant difference between patients with moderate and mild preeclampsia or preeclampsia in terms of hypertension, as compared with the control group was detected in their study. There was no significant difference between the two groups regarding the length of hospital stay too (17). As compared with the mentioned study, our findings showed a decrease in SBP three to five days after delivery. Moreover, Amorim et al conducted a three-blind clinical trial and reported that SBP and DBP were significantly lower in the furosemide group. In the furosemide group, the significantly lower episodes of hypertension on the second and fifth days were detected. The need for antihypertensive drugs on the third day was also lower in the mentioned group. In the furosemide group, BP control was faster and less antihypertensive drug was required (21). Furthermore, Veena et al did not report a significant difference in SBP, DBP and MAP on the first to third days of treatment and also in the mean reduction in SBP, DBP and MAP on those days by including furosemide. Although the need for additional

| Normalization of blood pressure | Nifedipine group (n=55) | Nifedipine plus furosemide group (n=54) | P value* |
|--------------------------------|------------------------|----------------------------------------|---------|
| None                           | 23 (42%)               | 12 (22%)                               | <0.001  |
| On day 3                       | 0 (0%)                 | 3 (5%)                                 |         |
| On day 4                       | 4 (7%)                 | 23 (43%)                               |         |
| On day 5                       | 28 (51%)               | 16 (30%)                               |         |

* Chi-square test.
antihypertensive drug was lower in the furosemide group, the duration of hospitalization was not different (19). In the study by Viteri et al the rate of stable postpartum hypertension was 44% in the torsemide group and 58% in the placebo group, while no significant difference between the groups regarding the rate of hypertension 7-10 days after delivery, severe hypertension and the length of hospital stay were detected. Therefore, it was concluded that a 5-day administration of postpartum torsemide was not effective in controlling postpartum hypertension (2).

Following the inclusion of furosemide in the regimen of our patient, SBP was more reduced after delivery in terms of time to reach normal BP and regarding its frequency. In addition, the need for more medication to control BP was lesser in this group of patients. Similar to other studies, the duration of hospitalization was not significantly different. Inconsistency between the results of various studies could be due to differences in sample selection criteria. Due to the significance of controlling of postpartum BP in patients with preeclampsia, it is necessary to conduct studies on the effect of different drugs during this period. Moreover, given the scarcity of studies on the effect of loop diuretics and the contradictions between the results, it is recommended to conduct multicenter studies with a larger sample size, and a longer follow-up time, with other drugs.

**Conclusion**

The findings of the present study showed that SBP, DBP and MAP were significantly reduced in all the patients in each individual group on the first to fifth days after delivery. On the third to fifth days, the mean SBP and MAP in the furosemide group were significantly lower than those in the nifedipine group, while DBP was not significantly different between the groups. Furosemide also reduced the need for additional medication to control BP, while the frequency of achieving normal BP had become higher and faster. Therefore, it seems that furosemide can be administered along with other drugs to control BP in patients with postpartum preeclampsia. However, larger studies are needed to evaluate its efficacy and safety.

**Authors’ contribution**

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. Both authors (TGB and ZD) designed the protocol of study and performed it. Analysis of data performed by PA. Both authors write the manuscript and approved the final paper.

**Conflicts of interest**

There is no conflict of interest among authors.

**Ethical issues**

The research followed the tenets of the Declaration of Helsinki. Accordingly, written informed consent was taken from all participants before any intervention. The study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (Ethical code; IR.SBMU.MSPREC.1399.067). Besides that, the study protocol was registered as in the Iranian registry of clinical trials (#IRCT20191031045289N2; https://irct.ir/trial/49806). Additionally, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors. This study was extracted from M.D thesis of Pegah Azadi at this university (Thesis #18825).

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