Abstract

Objective: To examine the effect of furosemide on hypertension and edema in patients with pre-eclampsia experiencing high cardiac output.

Methods: The present cohort study enrolled patients with pre-eclampsia who were admitted to the pregnancy pathology unit of the Department of Obstetrics and Gynecology, University of Pécs, Hungary, between January 1 and December 31, 2015. Eligible patients had singleton pregnancies with no fetal anomalies, high blood volume, visible edema, and a hematocrit concentration below 37 L/L. Blood pressure was measured and impedance cardiography was used to determine cardiac output for all patients before they received a 40-mg dose of furosemide; after 60 minutes blood pressure and cardiac output were measured again.

Results: The study enrolled 14 patients. Lower cardiac output ($P=0.002$), systolic blood pressure ($P=0.002$), and diastolic blood pressure ($P=0.002$) were recorded after furosemide administration, with patient heart rates remaining stable.

Conclusion: The heart-rate stability suggests that the change of cardiac output was due to a decrease in blood volume. These data suggest that diuretics could be useful in the management of late-onset pre-eclampsia, indicating that an increase in water retention could play a role in the development of late-onset pre-eclampsia.

Keywords: Furosemide; High cardiac output; Late-onset pre-eclampsia; Management
the presence of different hemodynamic profiles across patients with pre-eclampsia.8,9 According to the simplified form of Poiseuille–Hagen equation:

\[
\text{Cardiac output} = \frac{P}{R}
\]

where \( P \) is pressure and \( R \) is resistance, pressure increases as either resistance or cardiac output (in this case an individual’s blood volume) increases. Among patients with pre-eclampsia with high cardiac output, the use of diuretics to decrease blood volume would appear to be justified. Consequently, with the ability to non-invasively measure cardiac output, the aim of the present pilot study was to evaluate the effect of administering the diuretic furosemide among patients with pre-eclampsia who had high blood volume.

2 | MATERIALS AND METHODS

The present cohort study enrolled patients who were admitted to the pregnancy pathology unit of the Department of Obstetrics and Gynecology at the University of Pécs, Hungary, with pre-eclampsia between January 1 and December 31, 2015. Pre-eclampsia was diagnosed based on new-onset hypertension (two blood-pressure measurements of at least 140/90 mm Hg with a 4-hour interval) with proteinuria (at least 0.3 g in 24 hours) after 20 weeks of pregnancy. The other inclusion criteria were singleton pregnancies, high blood volume (cardiac output >7.48 L/min), absence of known cardiac disease, visible edema, hematocrit level below 37 L/L, and an absence of any fetal anomalies. Absence of fetal anomalies was established through active/reactive response to non-stress test, normal estimated fetal weight (above the 10th percentile for a given duration of pregnancy), normal amniotic fluid index (8–16 cm), and normal fetal descending aortic flow. The study protocol was approved by the institutional ethics committee and all participants provided written informed consent.

All patients had their blood pressure measured frequently (every 2–3 hours). Patients with blood pressure repeatedly exceeding 160/105 mm Hg in a 24-hour period received alpha-methyldopa (Dopegyt; EGIS Pharmaceuticals, Budapest, Hungary) monotherapy for hypertension; otherwise, patients received no antihypertensive medication.

Participants’ blood pressure and hemodynamic parameters were evaluated in a left lateral recumbent position. Hemodynamic parameters were measure using impedance cardiography (M401; ASKIT, Budapest, Hungary). The parameters included were stroke volume, cardiac output, and the total peripheral resistance. Cardiac output was calculated as:

\[
\text{Cardiac output} = \text{Stroke volume} \times \text{Pulse rate}.
\]

The total peripheral resistance was calculated as:

\[
\text{Total peripheral resistance} = 80 \times \frac{\text{Mean arterial pressure}}{\text{Cardiac output}}
\]

and the mean arterial pressure was calculated as:

\[
\text{Mean arterial pressure} = \frac{\text{Systolic blood pressure} + (2 \times \text{Diastolic blood pressure})}{3}
\]

All patients received a dose of 40 mg of furosemide (Sanofi, Budapest, Hungary) and 1 g of potassium chloride. Blood pressure and hemodynamic parameters were re-examined after 60 minutes. During this period, patients’ activities (e.g. fluid intake) were not limited.

The pre- and post-furosemide data were compared with the Wilcoxon signed-rank test. The statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY, USA) and \( P<0.05 \) was considered significant.

3 | RESULTS

There were 15 patients eligible for inclusion during the study period; 14 patients agreed to participate and were included in the present study. The baseline data revealed no indicators of organ damage outside proteinuria, with platelet counts within the range considered normal (Table 1). All participants experienced pre-eclampsia symptoms after 33 weeks of pregnancy and, consequently, were considered to have late-onset pre-eclampsia.

Cardiac output \((P=0.002)\), systolic blood pressure \((P=0.002)\), and diastolic blood pressure \((P=0.002)\) were significantly decreased following furosemide administration (Table 2). Heart rate and total peripheral resistance remained stable over both evaluation points.

The mean neonatal weight at delivery was 3386.0±410.2 g (Table 1), which is within for 50th–75th percentiles for delivery at 39 weeks of pregnancy.

No maternal or neonatal adverse events were recorded single furosemide administration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pregnancy at onset of pre-eclampsia, wk</td>
<td>36.4±1.2</td>
</tr>
<tr>
<td>Duration of pregnancy at enrollment, wk</td>
<td>37.2±1.1</td>
</tr>
<tr>
<td>Duration of pregnancy at delivery, wk</td>
<td>39.0±0.9</td>
</tr>
<tr>
<td>Maternal age, y</td>
<td>29.6±4.2</td>
</tr>
<tr>
<td>Pre-pregnancy weight, kg</td>
<td>76.6±8.4</td>
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<tr>
<td>Weight gain during pregnancy, kg</td>
<td>15.8±4.2</td>
</tr>
<tr>
<td>BMI at enrollment</td>
<td>32.0±6.4</td>
</tr>
<tr>
<td>Hematocrit, L/L</td>
<td>36.4±1.8</td>
</tr>
<tr>
<td>Platelet count, (10^9)/L</td>
<td>219.6±64.7</td>
</tr>
<tr>
<td>Creatinine, (\mu)mol/L</td>
<td>62.6±13.1</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>25.6±16.0</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>32.6±17.2</td>
</tr>
<tr>
<td>Neonatal delivery weight, g</td>
<td>3386.0±410.2</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

\(^a\)Values are given as mean±SD.
4 | DISCUSSION

In the present study, furosemide-reduced blood volume resulted in decreased blood pressure among patients with pre-eclampsia experiencing high cardiac output. Heart rate and total peripheral resistance remained stable owing to the decreased stroke volume. Notably, high pre-pregnancy weight and weight gain during pregnancy were recorded; both are common findings among patients with late-onset pre-eclampsia.

Reduced blood volume (low cardiac output) and vasoconstriction are classical hallmarks of pre-eclampsia. Indicators of end-organ dysfunction (e.g. proteinuria) and fetal growth restriction with oligohydramnios are primary characteristics of this hypo-perfusion condition. The presence of high cardiac output with low vascular resistance among patients with pre-eclampsia was first reported in 1990 by Easterling et al. who suggested the use of beta-blocker medications to manage this hyper-dynamic state. High neonatal weight at delivery among patients with pre-eclampsia was first reported by Xiong et al. in 2000; subsequently, a Scandinavian group obtained similar findings, reporting an elevated number of high birth-weight neonates among patients admitted with a diagnosis of pre-eclampsia. A positive correlation between neonatal weight at delivery and maternal cardiac output has been reported among both healthy pregnant patients and those with pre-eclampsia; it can be supposed that pre-eclampsia with low cardiac output is associated with fetal growth restriction, while neonatal weight tends to be higher among patients with high cardiac output. When considering this correlation and pregnancy outcomes among patients with early- or late-onset pre-eclampsia, it is tempting to assume that low cardiac output with vasoconstriction is typical among patients with early-onset pre-eclampsia, whereas vasorelaxation and high cardiac output could be common features among patients with late-onset pre-eclampsia.

Among 100 patients with full-term pregnancies, an average cardiac output of 6.8 L/min cardiac has been demonstrated. The use of 7.48 L/min in the inclusion criteria represented an increase of 10% on this previously reported value; the pre-treatment 8.3-L/min cardiac output recorded in the present study indicates remarkably augmented blood volume among the study participants. The increase in blood volume beyond normal vascular capacity likely explains the elevated blood pressure and fluid accumulation in the extravalvular compartment.

Hematocrit levels of approximately 34 L/L are considered normal by the end of pregnancy; based on this, an increase of 10% was considered to indicate a high concentration in the present study.

During pregnancy, salt and water retention are responsible for changes to physiologic blood volume. Disturbances to this complex mechanism (e.g. enhanced sodium-pump inhibition) could lead to increased water retention. Consistent with this presumption, extravascular fluid content is determined by body sodium content. The kidney is highly sensitive to hypoxia and proteinuria, which is part of the diagnostic criteria for pre-eclampsia, is an early indicator of organ damage and dysfunction. Whether proteinuria always results from a decreased blood supply among patients with pre-eclampsia has not been fully elucidated. Hypertension itself is known to provoke proteinuria; relaxed terminal arterioles and capillary beds could be damaged by hypertensive overflow exposure, and mesangial and subendothelial deposits with focal segmental hyalinosis are typical findings during hypertension. Additionally, parenchymal tissue edema could contribute to organ dysfunction.

There has been little discussion in the literature regarding the use of diuretics during pregnancy. A meta-analysis that included nearly 7000 pregnant women treated with a diuretic drug to prevent pre-eclampsia demonstrated lower incidences of stillbirth and hypertension, and lower perinatal mortality. In a study by Carr et al., patients with elevated cardiac output received doses of 20 mg of furosemide per day, with treatment beginning between 13 and 32 weeks of pregnancy. Patients underwent repeated hemodynamic examinations after 3 weeks and significant decreases in stroke volume and cardiac output were recorded; however, no change in blood pressure was observed. In a study by Ascarelli et al., patients with pre-eclampsia received doses of 20 mg of furosemide during the postnatal period to decrease blood pressure. Furosemide administration for 5 days enhanced patient recovery by decreasing blood pressure and antihypertensive demand. In another trial, 14 patients with pre-eclampsia were randomized to receive 40 mg of furosemide or a placebo after delivery but no differences were recorded between the two groups. It is noteworthy that there were no diuretic-related adverse effects recorded in either of these studies.

Impedance cardiography has been demonstrated to be an ideal non-invasive tool for measuring maternal central hemodynamics in both healthy pregnant patients and those with pre-eclampsia. However, the accuracy of impedance cardiography has been questioned in the presence of significant edema because a patient’s baseline impedance can occasionally be low. The possibility of edema-induced invalidity in the present study was minimalized through the collection of identical data (before and after furosemide administration) for comparison. Furthermore, the second patient examinations were repeated at 60 minutes; this was done because furosemide rapidly increases urine
production, leading to decreased blood volume. It likely takes a longer time for edema to exert its blood-volume decreasing effects.

The present preliminary study was a simple, basic examination and its main limitation was the relative low number of patients included; however, the highly significant differences following furosemide administration were remarkable.

The duration of time before patient blood volume returned to its previous level and the resultant effects on blood pressure were not evaluated and could be subject to further study in the future. Additionally, the effects of the sequential or maintenance administration of diuretics in patients with pre-eclampsia and high blood volume could be included in further studies. Further, furosemide is known to pass through the placenta and augment fetal urine production. No significant change in amniotic fluid index was found secondary to maternal furosemide administration in the present study; however, further study is necessary to ensure the safety of single-dose or sequential furosemide administration in patients with pre-eclampsia with high blood volume.

Guidelines for managing gestational hypertension or pre-eclampsia do not recommend the use of diuretics; however, the present preliminary results draw attention to the potential usefulness of diuretics in the management of pre-eclampsia in patients with high cardiac output, obvious edema, and no fetal anomalies. Based on the results of the present study, diuretics appear to be appropriate for patients with late-onset pre-eclampsia. These findings support the assertion that pathological increased water retention could play a crucial role in the development of late-onset gestational hypertension or pre-eclampsia. Large, more intensive and detailed studies are needed to confirm these observations.

AUTHOR CONTRIBUTIONS

PT contributed to the design of the study. EH contributed to the study design and data acquisition. BF contributed to the interpretation of study data. ZI contributed to data acquisition. JBo contributed to the conception of the study. JBe contributed to the conception of the study. All authors participated in the preparation and revision of the article, and approved the final manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts interest.

REFERENCES