Wasit Journal for Science & Medicine **2010 3 (1): (60 - 70)**

The role of low dose furesemide in reducing postpartum blood pressure among women with preeclampsia

Hanan Dh Aljeboury
C.A.B.O.G. Senior In Obstetrics And Gynecology, AL Yarmouk TeachingHospital
Wisam Akram
F.I.C.O.G. Consultant Obstetrician And Gynecologist, AL Yarmouk Teaching Hospital

تاثير العلاج بعقار (لازيكس) او Furesemide بجرعة قليلة على ضغط الدم لدى النساء المصابات بطليعة ماقبل الارتجاج

حنان ضايع الجبوري & وسام اكرم - مستشفى اليرموك التعليمي

نوع الدراسة؛ تطلعية

الطريقة؛ تم اختيار ٢٦٤ مريظة مصابات بطليعة ماقبل الاتجاج. تم تقسيمهم بشكل عشوائي الى مجموعتين؛ مجموعة الدراس (١٣٢) و مجموعةالضابطة (١٣٢) . بعد الولادة ب ٢٤ ساعة اعطيت للنساء بمجوعة الدراسة عقار لازيكس بجرعة ٢٠ ملغرام يوميا لمدة ٥ ايام مع حب بوتاسيوم. بينما لم يعطى أي من الذكور لدى النساء في المجموعة الضابطة. استعملت العقاقير المضادة لارتفاع ضغط الدم حيث كان قياس ضغط الدم الواطي يتجاوز ٩٠ مليميتر زئبقي. تم تقسيم النساء في كلا المجموعتين الى ٣ مجاميع فرعي: النساء المصابات بطليعة ماقبل الاتجاج الخفيف و هن المصابت فقط بارتفاع ضغط الدم مع زلال الادرار فقط. اما المجوعة الثانية فهن المصابات بطليعة ماقبل الارتجاج الشديد؛ عندما كان معدل الصفائح الدموية قليل و مصاحب لارتفاع معدل انزيمات الكبد. اما المجموعة الثالثة فهن النساء اللواتي بدأن الحمل مع ارتفاع ضغط الدم ثم تطور المرض لديهن الى طليعة ماقبل الاتجاج

النتائج؛ كانت نسبة النساء اللواتي احتجن الى ادوية ارتفاع ضغط الم اعلى بتميز احصائي في المجوعة الضابطة مقابل مجموعة العلاج ٢٦ % مقابل ٦ % فقط لدى النساء المصابات بطليعة ماقبل الاتجاج الشديد فقط. لم يلاحظ هذا التميز الاحصائي بالمجوعتين الاخرتين.

الخلاصة: ان استعمال عقار لازيكس بجرعة قليلة ٢٠ ملغرام يوميا لمد ٥ ايام ٢٤ بعد الولادة قد يكون مفيدا لدى النساء المصابات بطليعة ماقبل الاتجاج الشديد

Type of study; Prospective

Methods; A total of 264 women with preeclampsia have been chosen. They were randomly allocated either to the study group (N=132) or control group (N=132). Patients in either group had mild, severe or chronic hypertension with superimposed preeclkampsia. Patients in the study group were assigned to receive

20 mg furesemide plus potassium orally for 5 days only, while patient in the control group received none. Oral antihypertensive drugs were used only when diastolic blood pressure was eeither above 90 mmHg on 2 occasions, or 110 mmHg single reading. The total days for need of oral antihypertensive drugs as well as the total days spent inpatients were recorded. Patients with severe preeclampsia where categorized as those who have low platelets count as well as high serum liver enzymes in addition to the ordinary signs and symptoms of preeclampsia; hypertension, proteinurea and edema.

Results; The number of women with severe preeclampsia who needed oral antihypertensive medication after discharge from hospital was significantly higher in the control group versus study group; 26% versus 6 %, p Value < 0.05. However there was no statistically difference among women with mild preeclampsia and superimposed preeclampsia among the two study groups; 3% versus 5 % and 20 % versus 26 %, respectively.

Conclusion; women with preeclampsia who show low platelets count and elevated liver enzymes may benefit from short 5 day postpartum treatment with 20 mg furesemide, irrespective of antihypertensive adjuvant therapy.

Key words; preeclmpsia, furosemide

Introduction

Hypertensive disorders of pregnancy including pregnancy induced hypertension and chronic hypertension, affect a substantial population of pregnant patients worldwide each year, all of whom must evidence suitable and sufficient recovery postpartum to meet criteria for safe hospital discharge. Although considerable attention has been directed to ante partum and intrapartum management issues regarding patients with preeclampsia and related hypertensive disorders of pregnancy, such as minimizing the development of eclampsia using magnesium sulfate, much less research on the puerperium has been undertaken to illuminate the physiology and relevant interventions for appropriate postpartum management of this heterogeneous group of patients[1].

Puerperal normalization of patients with the spectrum of preeclampsia proceeds variably over time, possibly exaggerating or impeding the normal extent of blood volume shifts that follow the cessation of gestation in a vascular system that is injured, vasospastic, or inflexible. Although complete recovery from severe preeclampsia can require an extended period of time,[2,3,4] most patients who develop complications do this within the first 2 weeks after delivery.[5] These include severe hypertension requiring medication or major fluid shifts that cause cerebral or pulmonary edema. It would be desirable to minimize or eliminate these altogether with use of a low-cost medical intervention such as furosemide to

accelerate recovery and shorten hospitalization without adverse maternal or perinatal consequences[6].

Aim of the study

Accordingly, this study was undertaken in patients with preeclampsia to assess the efficacy of a short 5-day postpartum course of orally administered furosemide to enhance diuresis and lower blood pressure, thereby reducing the need to initiate antihypertensive agents with their attendant cost, potential side effects, and the need to hold the patient longer in the hospital to assure the attainment of blood pressure control.

MATERIALS AND METHODS

Setting

The study was approved by the Institutional Review Board of AL Yarmouk Teaching Hospital. All patients delivered of a pregnancy at or greater than 20 weeks of gestation and diagnosed with mild (MPRE), severe preeclampsia or hemolysis, elevated liver enzymes, low platelets syndrome (SPRE), or chronic hypertension with superimposed preeclampsia (CPRE) between July 1, 2004, and March 31, 2008, were eligible for inclusion in this investigation. Patients were not considered for study enrollment if they were at less than 20 weeks of gestation, had hypokalemia (K < 3.0 mEq/L) on admission, were already taking diuretics or potassium supplements for any reason, demonstrated any hemodynamic instability surrounding the events of delivery, or were unable to understand and sign the informed consent.

Patient protocol

After informed consent was obtained, patients were randomly assigned to groups by opening the next previously prepared sequential and numbered opaque study envelope. Treatment was begun at the time that intravenous magnesium sulfate was discontinued (in those women who required it) and spontaneous diuresis initiated (> 100 mL/h for 2 hours consecutively without stimulus) as soon as 2 hours to as long as 24 hours after delivery. A shortened postpartum course of magnesium sulfate was used as previously described. Patients in the treatment group were assigned to receive furosemide (Lasix) 20 mg/d together with an oral potassium supplement (K-Dur, Schering) 20 mEq/d for a total of 5 consecutive days during hospitalization. Patients in the control group received neither medication, Patients in both groups received similar postpartum surveillance, including blood pressure and pulse assessment every 4 hours, daily weight measurement, and daily urinary output measurements, while hospitalized.

Antihypertensive therapy was administered to patients with intermittent or persistent (>= 2) elevations of systolic (>= 150 mm Hg) or diastolic (>= 100 mm Hg) blood pressure(s) after assignment to receive either furosemide or no medication.

Statistical analysis

Continuous data were presented as mean and standard deviation. Categorical variables were presented as number and percent. Categorical variables were compared by Chi square tese, while continuous variavle among the three groups were compared by ANOVA test. Kruskal Wallis test was used. P Values less than 0.05 were considered as significant. Power analysis was used to estimate the minimum sample size required to show a difference in mean blood pressure of 5 mm Hg with standard deviation 12 mmHg. 132 patients for each group was calculated. Accordingly a total of 264 envelop were pre prepared which assign the women randomly either to the control group or treatment group.

RESULTS

A total of 264 patients were eligible for the study and consented to participate. The composition of each group and demographic characteristics are shown in Table 1, with patients evenly balanced between treatment and control for each disease category. Altogether, 64.0% had MPRE, 26.5% had SPRE, and 9.5% were CPRE. Patients with chronic hypertension and superimposed preeclampsia (CPRE) were significantly older (25.6 ± 7.6 years compared with 22.8 ± 5.9 and 22.2 ± 5.6, $P <$ .05) and heavier (70+4.2 kg compared with 64.1 ± 4.2 kg and 65.6 ± 4.3 kg , $P =$ .002) than patients with mild (MPRE) or severe (SPRE) preeclampsia respectively. Cesarean delivery occurred significantly more often in patients with severe (50%) or superimposed (48%) preeclampsia compared with patients with mild (29.2%) disease. No significant differences were observed for gravidity or parity.

Table 1 Composition of Treatment and Control Patient Groups

characteristics	Study group N=132	Control Group N=132	Total	P Value
MPRE (n %)	81 (47.9%)	88 (52.1%)	169	0.325
SPRE (n %)	35 (50%)	35(50%)	70	
CPRE (n %)	16 (64%)	9 (36%)	25	
Maternal age	22.8+6.1	22.9+6.0		0.847
Maternal weight	66.1+4.1	67+4.3		0.321
Parous women (%)	39.4 %	47.0 %		0.214

MPRE= Mild Preeclampsia, SPRE= Severe Preeclampsia, CPRE= Chronic hypertension with superimposed preeclampsia

Blood pressures and pulse rates immediately postpartum and again at the time of discharge from the Labor/Delivery/Recovery Unit to the postpartum ward when therapy was started are depicted in Table 2 for groups of patients with mild, severe and superimposed preeclampsia. Patients with MPRE immediately postpartum exhibited a pulse rate that was approximately 6 beats per minute faster than patients in the other two groups with a 95% confidence interval of 1.1–10.8. There were no other significant differences at entry among groups. At the time of transfer to the postpartum ward, however, both groups of patients with preeclampsia (MPRE and SPRE) exhibited a lower frequency of hypertension compared with an increase for patients with underlying chronic hypertension. Approximately 20% of those with MPRE and hypertension immediately postpartum became normotensive before transfer to the postpartum ward. Pulse rates were equivalent among groups at the time of transfer to the postpartum ward and initiation of therapy, with a downward trend for patients with MPRE or SPRE and an upward trend for patients with underlying chronic hypertension (CPRE).

Table 2 Postpartum Blood Pressure and Pulse Rate Immediately Postpartum and at Transfer from Labor/Delivery/Recovery Unit to Postnatal Ward for the 3 Patient Groups

Characteristics	MPRE (N=169)	SPRE (N=70)	CPRE (n+25)	P Value
Immediately postpartum				
Systolic BP	**136+18**	**139+18**	**141+22**	**0.391***
Diastolic BP	**71+16**	**75+18**	**73+19**	**0.225***
Pulse Rate	**98+17**	**94+18**	**92+16**	**0.068***
Hypertensive (%)	**44 %**	**51 %**	**60 %**	**0.249 ****
At transfer to ward				
Systolic BP	**131+13**	**138+13**	**146+15**	**< 0.001***
Diastolic BP	**69+13**	**75+10**	**77+10**	**<0.001***
Pulse Rate	**93+14**	**91+14**	**93+11**	**0.500***
Hypertensive (%)	**23 %**	**43 %**	**68 %**	**< 0.001 ****

MPRE= Mild Preeclampsia, SPRE= Severe Preeclampsia, CPRE= Chronic hypertension with superimposed preeclampsia , * Kruskall Wallis test(ANOVA); ** Chi Square test

An analysis of blood pressure values revealed that systolic blood pressure was significantly lower on the second postpartum day in furosemide-treated patients with SPRE (142 ± 13 mm Hg) compared with higher values of control patients with SPRE (153 ± 19 mm Hg, $P < .004$). There were, however, no significant differences in the diastolic blood pressure values or pulse rates observed postpartum between either the MPRE or the chronic hypertension groups that did or did not receive furosemide. The small number of patients in both the treated and control groups with CPRE, however, precludes meaningful evaluation. Data on postpartum maternal weights was inadequate to evaluate.

The frequency of antihypertensive agent use was reduced to some extent in all furosemide-treated patient groups during hospitalization and at the time of hospital discharge (Table 3). The only statistically significant difference observed, however, was an increase in the number of SPRE patients in the control group who required additional antihypertensive medication at the time of hospital

discharge (26%) compared with a much lower incidence of 6% in patients with SPRE who were receiving furosemide therapy (*P* = .045, Table 3).

Table 3. Postpartum Antihypertensive Medication Usage for the 3 Patient Groups is shown both During Hospitalization and at the Time of Hospital Discharge

characteristics	Study Group (N=132)	Control Group (N=132)	P Value
During hospitalization			
MPRE	4 (5%)	5(6%)	1.00000
SPRE	5(14%)	9(26%)	0.371
CPRE	4(27%)	3(30%)	1.000
At hospital discharge			
MPRE	4 (5%)	3 (3%)	0.642
SPRE	2(6%)	9 (26%)	0.045
CPRE	4 (27%)	2 (20%)	1.0000

MPRE= Mild Preeclampsia, SPRE= Severe Preeclampsia, CPRE= Chronic hypertension with superimposed preeclampsia

Length of hospitalization was related to disease category primarily, not to whether the patient received furosemide (*P* = .429) and was not different based on mode of delivery. As expected, patients with MPRE required significantly shorter magnesium sulfate infusion (mean 9 hours, range 6.5–13) compared with SPRE (mean 15 hours, range 12–24) and chronic hypertension (mean 13 hours, range 12–22; *P* < .001). Patients with MPRE also had significantly shorter hospitalizations (mean 2 days, range 2–3) compared with SPRE (mean 3 days, range 2–4) and chronic hypertension (mean 3 days, range 2–5; *P* < .001).

DISCUSSION

We demonstrated that furosemide therapy initiated early in the first 24 hours postpartum to patients with severe preeclampsia, compared with controls, better normalized elevated blood pressure and lessened the need to initiate antihypertensive therapy. No immediate benefit was gained in patients with mild preeclampsia. Length of hospitalization for the total study population, however, seemed not to be significantly shortened by this intervention. Although the frequency of delayed postpartum complications within the first 6 weeks after delivery was similar between groups, the only 2 patients requiring readmission to the Labor/Delivery/Recovery Unit for management of elevated blood pressure and

exacerbation of preeclampsia were 2 patients (one MPRE, one SPRE) in the furosemide group. One patient in the control group with mild preeclampsia did require readmission for delayed puerperal complications related to pulmonary hypertension and congestive heart failure. Based on the size, number and type of hypertensive conditions in the patients studied, we found that the small benefit realized in the patient with severe preeclampsia did not also translate into shorter hospitalization or fewer other complications. We emphasize that the treatment course for postpartum furosemide was only 5 days in duration, involved a relatively low dose of diuretic, and was not initiated until spontaneous diuresis occurred.

The potential benefit of diuretic use for patients with severe preeclampsia or eclampsia is an important issue in contemporary obstetrics and maternal-fetal medicine. Patients with severe and superimposed forms of preeclampsia can suffer sustained hypertension, presumably in response to the presence of excess total body water, impaired sodium excretion due to reduced glomerular filtration, mobilization of interstitial and extravascular fluid, and the difficult task of controlling blood pressure while the parturient is volume overloaded. We interpret the findings from our study to suggest that patients with severe preeclampsia who received furosemide more effectively eliminated intravascular fluid that was mobilized from the interstitium during the early puerperium and thereby reduced blood volume and blood pressure, obviating the need to begin antihypertensive medication.

The underlying pathophysiology of preeclampsia is believed to involve diffuse vasospasm with endothelial cell damage.[7] Thus transudation of plasma proteins across any damaged membrane surfaces can lead to hypoalbuminemia, a lowered intravascular colloid oncotic pressure, fluid migration into the interstitium, intravascular volume depletion, and systemic edema.[8–10] After delivery, fluid that has been sequestered in the extravascular space is mobilized, producing a large autoinfusion of fluid from the extravascular to the intravascular compartment.[11] Colloid osmotic pressure decreases while increases in central venous pressure and pulmonary capillary wedge pressure can develop, conditions that favor the development of pulmonary edema, especially in the patient with severe preeclampsia.[12,13] Protracted use of intravenous magnesium sulfate can exacerbate this process and itself lead to formation of pulmonary edema.[14]

Because postpartum pulmonary edema and congestive heart failure can occur to some degree after delivery as a result of this fluid mobilization process, logical management would direct therapy at maintaining a low central venous pressure and pulmonary capillary wedge pressure and attempting to raise the colloid osmotic pressure to preclude the development of pulmonary edema and congestive heart failure.[12,15] It follows that fluid restriction in the postpartum period coupled

with the administration of a diuretic can be considered appropriate in these circumstances. Risks of low-dose diuretic therapy are minimal and minimized probably by the addition of a modest daily oral potassium supplement. We chose to use furosemide instead of hydrochlorothiazide for this investigation primarily because it has not been associated with neonatal thrombocytopenia in breastfed infants, although it does cross into breast milk and can inhibit milk production.[16]

This approach to management may also apply to minimizing the risk of central nervous system morbidity in puerperal patients, because cerebral edema and postpartum eclampsia, both hypothetically related to cerebral over perfusion rather than decreased cerebral blood flow,[17] might benefit from peripheral fluid offloading and the purported benefit of some diuretics to reduce peripheral venous tone.[18]

Our study has limitations due to small sample size particularly in the SPRE and CPRE groups. Bias is possible, because the clinicians were not blinded to group assignment. Because each patient in the investigation continued treatment a few days after discharge, we do not know how many patients actually took the medication after leaving the hospital. Significant adverse events are relatively infrequent in most traditionally treated patient populations with preeclampsia, thus requiring a very large patient population studied in multiple sites and circumstances to truly evaluate any impact of postpartum diuretic therapy upon delayed fluid mobilization-related complications. Our study was too small to evaluate this issue, because no patient in either group developed such a complication. The only patient in the entire study to develop congestive heart failure did so as a result of previously undiagnosed pulmonary hypertension in association with mild preeclampsia.

This study does not firmly establish a short course of low dose furosemide begun at the time on spontaneous diuresis as a clearly advantageous adjunct to the routine management of patients with severe or superimposed preeclampsia. Although the need for antihypertensive therapy was reduced whenever furosemide was used, it was only significant in patients with severe preeclampsia, and this may not matter to clinicians, because the benefit was not translated into shorter hospitalizations or fewer complications. A larger investigation in these 2 patient populations, perhaps using a larger systemic dose of furosemide initiated soon after delivery, is needed to determine whether there is benefit and minimal risk to using this approach for the prevention of delayed complications, including pulmonary edema, postpartum eclampsia, preeclampsia-related cerebrovascular accidents, and myocardial infarction.

References

1. Ferrazzani S, De Carolis S, Pomini F, Testa AC, Mastromarino C, Caruso A. The duration of hypertension in the puerperium of preeclamptic women: relationship with renal impairment and week of delivery. Am J Obstet Gynecol 1994;171:506–12.

2. Jacober SJ, Morris DA, Sowers JR. Postpartum blood pressure and insulin sensitivity in African-American women with recent preeclampsia. Am J Hypertens 1994;7:933–6.

3. Suzuki S, Gejyo R, Ogino S, Maruyama Y, Ueno M, Nishi S. Postpartum renal lesions in women with preeclampsia. Nephrol Dial Transplant 1997;12:2488–93.

4. Giannina G, Belfort MA, Cruz AL, Herd JA. Persistent cerebrovascular changes in postpartum preeclamptic women: a Doppler evaluation. Am J Obstet Gynecol 1997;177:1213–8.

5. Magann EF, Martin JN Jr. Complicated postpartum preeclampsia-eclampsia. Obstet Gynecol Clin North Am 1995;22:337–56.

6. Ascarelli MH, Johnson V, May WL, Martin RW, Martin JN Jr. Individually determined postpartum magnesium sulfate therapy using clinical parameters to safely and cost effectively shorten treatment for preeclampsia. Am J Obstet Gynecol 1998;179:962–6.

7. Roberts JM, Lain KY. Recent insights into the pathogenesis of pre-eclampsia. Placenta 2002;23:359–372.

8. Mabie WC, Ratts TE, Sibai BM. The central hemodynamics of severe preeclampsia. Am J Obstet Gynecol 1989;161:1443–8.

9. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. Hypertension 1991;17:1072–7.

10. Sibai BM, Mabie BC, Harvey CJ, Gonzalez AR. Pulmonary edema in severe preeclampsia-eclampsia: analysis of thirty-seven consecutive cases. Am J Obstet Gynecol 1987;156:1174–9.

11. Bolton LM, Thomas TH, Dunlop W. Erythrocyte ion and water balance and membrane potential in the puerperium of normal pregnancy. Br J Obstet Gynaecol 1996;103:547–51.

12. Pearson JF. Fluid balance in severe preeclampsia. Br J Hosp Med 1992;48:47–51.

13. Clark SL, Cotton DB. Clinical indications for pulmonary artery catheterization in the patient with severe preeclampsia. Am J Obstet Gynecol 1988;158:453–8.

14. Yeast JD, Halberstadt C, Meyer BA, Cohen GR, Thorp JA. The risk of pulmonary edema and colloid osmotic pressure changes during magnesium sulfate infusion. Am J Obstet Gynecol 1993;169:1566–71.

15. Fadnes HO, Oian P. Transcapillary fluid balance and plasma volume regulation: a review. Obstet Gynecol Surv 1989;44:769–73.

16. Jerkner K, Hitti J, Victorin L. Platelet counts in mothers and their newborn infants with respect to antepartum administration of oral diuretics. Acta Med Scand 1973;194:473–5.

17. Belfort MA, Anthony J, Saade GR, Allen JC Jr. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med 2003;348:304–11.

18. Goodlin RC. Venous reactivity and pregnancy abnormalities. Acta Obstet Gynecol Scand 1986;65:345–7.

Recived …….. (23/3/2009)
Accepted ……... (16/2/2010)