Furosemide Pharmacodynamics and Cardiovascular Effects in Hemodialysis Patients

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Furosemide is a drug that has not only a renal effect, but also a vascular one, resulting in decreased left atrial and ventricular filling pressure accompanied by an increase in venous compliance, all of this with significant effects on central cardiac hemodynamics. In dialysis patients, it is still unclear the efficiency of furosemide, a diuretic drug that inhibits the Na+, K+, 2CL− cotransporter in the renal tubular system. Also, furosemide need to be used at much higher doses because of its pharmacokinetic changes in the context of impaired renal clearance. The aim of our study was to investigate whether furosemide induces changes in cardiovascular hemodynamics in end-stage renal disease (ESRD) patients, using standard echocardiography and Tissue Doppler Imaging (TDI). We found correlations between furosemide use and improved cardiac parameters, assessed by multiple echocardiographic variables, and we consider that furosemide has complementary effects in dialysis patients with residual diuresis.

Keywords: furosemide, dialysis residual diuresis, hemodialysis diuretic.

Diuretics are often stopped when patients start dialysis. Some studies have shown that preserved residual renal function in dialysis patients is associated with better cardiovascular status and although the association between diuretic and preserved residual renal function is still in debating, the clinical and paraclinical benefits offered by furosemide make it valuable in dialysis patients with urine output [1-3]. In dialysis patients, even with some residual diuresis, furosemide has been shown to induce a rapid vascular effect, besides the diuretic effect. Venous dilatation occurs, and therefore a decrease in cardiac preload and filling pressures [1,2,4]. Several parameters, such as left ventricular hypertrophy (LVH) and left ventricular (LV) systolic dysfunction, have been identified as independent outcome predictors in dialysis patients [5-7]. Diastolic heart failure and increased filling pressures in dialysis patients often exists without the presence of significant systolic heart failure, and that may be assessed by Doppler techniques, especially Tissue Doppler Imaging (TDI), that has also demonstrated its significant prognostic value for all-cause mortality and cardiovascular death [8-10]. Novel Doppler techniques should be able to detect even more subtle changes in cardiac function induced by furosemide [2,8-11].

E-wave velocity reflects the left atrium (LA)-left ventricle (LV) pressure gradient during early diastole filling and is affected by impaired LV relaxation and left atrial pressure (LAP) [8,9]. A-wave velocity reflects the LA-LV pressure gradient during late diastole, and it depends by LV compliance and LA contractile function. Mitral E velocity deceleration time (DT) is influenced by LV relaxation, LV diastolic pressures after mitral valve opening, and left ventricular stiffness. Isovolumetric relaxation time (IVRT) is prolonged in patients with impaired LV relaxation but normal LV filling pressures. When LAP increases, IVRT duration shortens and being inversely correlated with LV filling pressures. [8,9] LA volume index (LAVi) reflects the cumulative effects of increased LV filling pressures and increased LAVi is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke. CW Doppler tricuspid regurgitation (CWTR) systolic jet velocity - significant correlation exists between systolic pulmonary artery pressure (SPAP) and noninvasively derived LAP. Increased SPAP suggests elevated LAP, if pulmonary disease is absent [9,10]. E/E’ velocity has a powerful correlation with pulmonary capillary wedge pressure (PCWP) compared with invasive measurements of LV filling pressure. Mitral E velocity obtained by PW Doppler complemented using E/e’ ratio correlates well to the mean pulmonary capillary wedge pressure (PCWP) as obtained by simultaneous catheter measurements [10,12]. E/e’ ratio is a marker of left atrial filling pressure. [9,10,12]

Experimental part

Materials and method

We selected for our study, between January 2015 to December 2016, ESRD patients, who were treated with HD three times a week for more than 6 months, in whom there were some residual diuresis (250 to 650 mL urine/day). We chose the patients in sinus rhythm, without severe valvular heart disease, ischemic heart disease, congestive heart failure (NYHA classes III and IV), pulmonary disease or significant pericardial disease. Conventional two-dimensional echocardiography and TDI were recorded with a Siemens Acuson P300, immediately before the dialysis session, therefore cardiac hemodynamics not being influenced by volume or speed ultrafiltration. The echo report was recorded at baseline and further after in similar
high frame rate (≥normal, and restrictive filling [8,9]. TDI was performed in the filling patterns: normal, impaired relaxation, pseudo-

mitral inflow E/A ratio and DT are used to identify time (DT), and late diastolic wave (A) velocity were measured. Mitral E-wave velocity, E-wave deceleration Doppler (PW) at the tip of the mitral leaflets in the 4-

and two chamber view.

diameter in M mode from parasternal long axis view and dimension (LAd) was measured as anteroposterior (LVEDD and LVESD), end-diastolic and systolic wall thickness of interventricular septum (IVSd and IVSs) and left ventricular posterior wall (PWTD and PWTS) were measured with the M-mode (Mm) technique. Ejection fraction (EF) was determined using M mode and Simpson (LVEDD and LVESD), end-diastolic and end systolic dimensions (LVEDD and LVESD), end-diastolic and systolic wall thickness of interventricular septum (IVSd and IVSs) and left ventricular posterior wall (PWTD and PWTS) were determined with the M-mode (Mm) technique. Ejection fraction (EF) was determined using M mode and Simpson method and complemented by eyeballing. LV mass was calculated by Devereux’s formula using the M-mode of the parasternal long axis view, and indexed to body surface area. LV hypertrophy was defined as LVMi >115 g/m² in men and >95 g/m² in women [8,9]. Left atrium dimensions (LAd) was measured as anteroposterior diameter in M mode from parasternal long axis view and also as left atrial volume using bidisc method in the apical four and two chamber view.

LV diastolic function parameters were assessed both conventional and through TDI. Using pulse-wave Doppler (PW) at the tip of the mitral leaflets in the 4-chamber view, mitral E-wave velocity, E-wave deceleration time (DT), and late diastolic wave (A) velocity were measured. Mitral inflow E/A ratio and DT are used to identify the filling patterns: normal, impaired relaxation, pseudonormal, and restrictive filling [8,9]. TDI was performed in high frame rate (≥100 frames/second) from the apical four chamber view to assess myocardial velocities. Peak annular early diastolic velocity (E’) was measured in annular LV segments (septal and lateral). E/E2 ratio was calculated, and significant LV diastolic dysfunction was defined as E/E’ > 15 is associated with increased filling pressures (PCWP > 15 mmHg) [10,12].

Results and discussions

Statistical analysis

Statistical analysis was performed using GraphPad Software, Inc 3.1. To calculate the statistical significance, we performed comparisons between the two groups using the t-Student test and Fisher exact test. For variables with Gaussian distribution, the values are presented as mean ± standard deviation and p was calculated using unpaired t-Student test. Correlation has been evaluated with Pearson test. Comparisons between baseline and next month measurements were performed using ANOVA with the Turkey post hoc test. Statistical significance was considered if p<0.05.

Table 1: POPULATION BASELINE CHARACTERISTICS

| VARIABLE                        | CONTROL GROUP (N=54) | FUROSEMIDE GROUP (N=47) | P     |
|---------------------------------|----------------------|-------------------------|-------|
| MALE GENDER, N (%)             | 38(73.7%)            | 31(65.9%)               | NS    |
| AGE, YEARS (MEAN± SD)          | 57.2±6.92            | 54.6±6.81               | NS    |
| ETIOLOGY OF RENAL FAILURE, N (%)|                      |                         |       |
| DIABETES MELLITUS              | 21(39.6%)            | 16(34.0%)               |       |
| ARTERIAL HYPERTENSION/RENAL    | 17(31.8%)            | 14(29.8%)               |       |
| VASCULAR DISEASE               | 4(7.6%)              | 4(8.5%)                 |       |
| OBSTRUCTIVE/REPLUX             | 7(12.9%)             | 5(10.6%)                |       |
| POLYCYSTIC KIDNEY DISEASE      | 2(3.7%)              | 1(2.12%)                |       |
| OTHER CAUSES                   | 8(15.5%)             | 6(12.78%)               |       |
| DIALYSIS VINTAGE, YEARS (MEAN± SD) | 2.4±1.7             | 2.4±1.4                 |       |
| DAILY DIURESIS, ml (MEAN±SD)   | 381.3±90.83          | 361.36±87.12            | <.001 |
| FUROSEMIDE DOSE, mg (MEAN±SD)  | -                    | -                       |       |
| AV FISTULA, N (%)              | 43(77.7%)            | 35(74.48%)              | NS    |
| BMI, Kg/m² (MEAN±SD)           | 25±3.4               | 25±4.6                  |       |
| BODY SURFACE AREA, M² (MEAN±SD)| 1.8±0.25             | 1.8±0.21                |       |
| DISLIPIDEMIA, N (%)            | 24(44.4%)            | 20(42.55%)              |       |
| CIGARETTE SMOKING              | 9(16.6%)             | 8(17.02%)               |       |

No patient died or suffered from a major cardiovascular event. In table 1 we can see that there were no significant differences between the group characteristics (gender, age, etiology, dialysis period, vascular access, BMI, BSA and the presence of other risk factors). There was a significantly better urine output in the furosemide group (p<0.0001), proportionally correlated to a higher dose of furosemide. None of the patients had normal diastolic function and all of them had LVH with normal EF (>55%). Also, there were no differences between blood pressure values over time in both groups. All patients were examined immediately before dialysis, so they were overhydrated, which was demonstrated by high E/E’ values, indicating a CPWP > 12 mmHg (E/E’ > 15). E wave, A wave, E/A ratio, DT, LA parameters and SPAP were higher in the control group and it got worse through time reaching statistical significance (p<0.05) as seen in Table 2. Regarding TDI parameters we observe in Table 3 that E’ wave, A’ wave, E’/A’ ratio are direct proportional, with high PCWP and LV filling pressures. Standard echocardiography and a more sensitive method, TDI, showed that furosemide was able to induce changes in cardiac hemodynamics also correlated with urine output. Most of the echocardiographic parameters were significantly better in dialysis patients receiving furosemide, as evaluated through time. Furosemide can cause a rapid venodilatory response, which starts before an effect on diuresis and can be noted via echocardiographic parameters. Previous studies concerning cardiovascular effects of furosemide have shown similar results, due to various methods, vascular status and studied conditions. All patients benefited from cardioprotective medications which had shown to reduce mortality [13] in the general population such as angiotensinconverting enzyme inhibitors, beta-adrenergic antagonists (beta-blockers), acetylsalicic acid, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) and cytoprotective anti-ischemic agent [14]. Dyslipidemia, measured through blood test, (including high levels of cholesterol, triglycerides, LDLc and low levels of HDLc) is part of the factors involved in increased cardiovascular risk associated with CKD and also with progression of kidney failure [15]. Furthermore, the variety of biomarkers available for monitoring and for the prognosis of acute kidney injury (AKI) are limited, and in present numerous biomarkers are available for monitoring and for the prognosis of acute kidney failure [15]. Furthermore, the variety of biomarkers available for monitoring and for the prognosis of acute kidney injury (AKI) are limited, and in present numerous biomarkers are available for monitoring and for the prognosis of acute kidney failure [15]. Furthermore, the variety of biomarkers available for monitoring and for the prognosis of acute kidney failure [15]. Furthermore, the variety of biomarkers available for monitoring and for the prognosis of acute kidney failure [15].
populations. Some studies have suggested that furosemide also has extra renal effects, some vascular effects that may justify its use also in anuric patients [2,19]. However, studies evaluating the vascular effects of furosemide in ESRD patients have shown conflicting results. Schmieder published a study in which an iv bolus of furosemide was given to HD patients [20]. The result was a significant decrease in central blood volume that was seen minutes after the bolus, indicating a redistribution of blood from the cardiopulmonary system to the periphery [20]. Other authors demonstrated that after an intravenous dose of furosemide left ventricular filling pressure decreased. It's important to understand that there is much more to an echo exam than mere EF [5]. eGFR value alone—demonstrated that is a better follow-up parameter then EF, as a marker for cardiovascular morbidity and mortality [21]. So, in this special population we have to come with something more in order to add more prognostic value. The novel tissue Doppler and Speckle tracking techniques can guide us to understand and treat the complex patient involved in this pathophysiological relation between kidney and heart [8-12]. Also, in most studies, arterial stiffness is assessed by carotid-femoral pulse wave velocity (cfPWV), and would have been a useful marker because it is correlated with overall mortality and cardiovascular mortality, even in dialysis patients [22]. Furthermore, we emphasise the need for more large-scale randomized studies in dialysis patients and comprehensive cardiovascular guidelines for their management [2,23].
Conclusions

The aim of this paper was to demonstrate whether diuretics should be continued on hemodialysis patients with some residual diuresis, even after they have been on dialysis for a period of time. For the specific hemodialysis population, the incidence of furosemide, can significantly improve echo parameters, it reduces the weight gain between dialysis, may result in better blood pressure values and possible lower the risk of heart failure and improved symptoms. Furthermore, there may be a favorable impact on cardiac hemodynamics, probably both by vascular and renal effects.

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