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Ultrafiltration is not Superior than Diuretics in Type 4 Cardiorenal Sydrome

Tip 4 Kardiyorenal Sendromda Ultrafiltrasyon Diüretiklerden Daha Üstün Değildir

ABSTRACT

OBJECTIVE: Cardiorenal syndrome (CRS) describes a dysregulation of the heart and kidneys affecting each other. Recently hemodialysis treatments were used more frequently. Aim was to analyze the effects of conventional diuretic and UF treatments.

MATERIAL and METHODS: Thirty-four Type 4 CRS diagnosed patients were included. Baseline characteristics were recorded. Echocardiography measured at the admission and at the end of the treatment.

RESULTS: The mean age 67.4±9.3 (51-93) years and follow-up period were 15.9±11.5 months. The patients were grouped as diuretic group, n=12 and UF group, n=22. At the beginning mitral valve A wave, blood urea nitrogen and creatinine values were higher in the UF group while creatinine values were higher in the UF group compared to diuretic group at the end of the study. Although basal ejection fraction (EF) values were not different, it was higher in the UF group at the end of the study (42.38±12.70 % and 29±3.67 %, p <0.05). During follow-up mortality rates were not different in both groups (diuretic group, 6 patients (17.6 %), the UF group 1 patient (2.9 %), (p> 0.05).

CONCLUSION: In Type 4 CRS, mortality and hospital admissions were not reduced by UF treatment but cardiac function assessed by EF was significantly improved suggesting this therapy to be beneficial in appropriate patients.

KEY WORDS: Type 4 Cardiorenal syndrome, Mortality, Ultrafiltration

ÖZ

AMAÇ: Kardiyorenal sendrom (KRS) birbirlerini etkileyen kalp ve böbrek bozukluklukları olarak tanımlanır. Son zamanlarda bu alanda hemodiyaliz tedavisi tercihi artmıştır. Bu çalışmada amaç geleneksel diüretik ve UF tedavilerinin etkilerini karşılaştırmaktır.

GEREÇ ve YÖNTEMLER: Çalışmaya Tip 4 KRS tanısı konulan 34 hasta alındı. Hastaların bazal özellikleri kaydedildi. Başlangıçta ve tedavinin sonunda ekokardiyografik değerlendirme yapıldı.

BULGULAR: Hastaların yaş ortalaması 67.4 ± 9.3 (51-93) yıl ve takip süresi 15.9 ± 11.5 ay idi. Hastalar diüretik, n = 12 ve UF grubu, n = 22 olarak sınıflandırıldı. Çalışmanın başında mitral kapak A dalgası, kan üre nitrojeni ve kreatinin değerleri UF grubunda yüksek, çalışmanın sonunda UF grubunda kreatinin değerleri diüretik grubuna göre daha yüksek olarak bulundu. Bazal ejeksiyon fraksiyonu (EF) değerleri her iki grupta farklı olmamasına rağmen UF grubunda çalışmanın sonunda bazale göre artış mevcuttu (42.38 ± 12.70 ve% 29 ± 3.67%, p <0.05). Takip sırasında ölüm oranları her iki grupta farklı değildi (diüretik grubu, 6 hastada (% 17.6), UF grubu 1 hasta (% 2.9), (p> 0.05).

SONUÇ: Tip 4 Kardiyorenal sendromda, UF tedavisi uygulananlarda mortalite ve hastaneye başvurular azalmasa da EF ile değerlendirilen kardiyak fonksiyonlarda anlamlı olarak düzelme olması ile seçilmiş hastalarda bu tedavi etkili olabilir.

ANAHTAR SÖZCÜKLER: Tip 4 Kardiyorenal sendrom, Mortalite, Ultrafiltrasyon

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INTRODUCTION

Heart and kidneys are collaborating organs, as working together; dysfunction affects the other which determines mortality, morbidity and cost of treatment (1,2). This interaction simply termed as cardiorenal sydromes. Kidney injury associated with acute /chronic heart failure strongly determines the outcome (3-6) so CRS has raised interest among both nephrologists and cardiologists because of its association with low survival rates. Initial organ and the chronicity of dysfunction used for describing the interactions a clinical classification system formed. Type 1 CRS: Acute cardiac decompensation leading to kidney injury, Type 2: Chronic heart failure leading to worsening renal function, Type 3: Acute kidney injury leading to cardiac dysfunction, Type 4: Chronic kidney disease leading to heart failure, Type 5: Systemic conditions leading to both cardiac and renal dysfunction (e.g; amyloidosis, diabetes mellitus)(7).

Heart failure treatment is very expensive the total estimated direct and indirect cost in the United States for 2010 is $39.2 billion (8) Especially patients admitted to emergency department with congestion are at important risk of survival than with stable heart failure (9). Dyspnea, orthopnea symptoms of congestion and hypervolemia is present most of the patients with heart failure. Therapy directed at relieving congestion and volume overload is essential. Loop diuretics have been used for more than 50 years for this purpose. As heart failure worsens patients may develop renal function deterioration and a diuretic unresponsiveness may lead difficulties in volume removal with diuretics. In this setting alternative fluid removal strategies like ultrafiltration come in use for means of fluid removal.

In conjunction with the improving access, there is an increasing interest in ultrafiltation (UF) treatment. Aim was to analyze the effects of conventional diuretics and UF treatments on survival of patients with Type 4 CRS.

MATERIAL and METHODS

Patients admitted to the hospital with a primary diagnosis of Type 4 CRS (chronic renal failure with decompensated heart failure) were included in the study. The procedures followed were in accord with the ethical standards of the committee on human experimentation and in accord with the Declaration of Helsinki and its revisions (10).

Exclusion Criteria: Patients scheduled HD before admission, intravascular volume depletion observed clinically, acute coronary syndrome within the 4 weeks, alternative explanation for worsening renal function, such as obstructive nephropathy, contrast-induced nephropathy, or acute tubular necrosis, poor venous access, use of iodinated radiocontrast material in the 72 hours before study entry or anticipated use of IV contrast during the current hospitalization, active myocarditis, severe valvular stenosis, complex congenital heart disease and cardiomyopathy, sepsis or ongoing systemic infection

Primary outcomes were all cause mortality and days spent in hospital.

Secondary outcomes

Echocardiography: Changes in Aortic diameter, aortic velocity, septum thickness, Left ventricular end diastolic diameter (LVEDD), Left ventricular end systolic diameter (LVESD), Ejection fraction (EF), Posterior Wall thickness (PWT), Mitral valve E wave (MVEW), Mitral valve A wave (MVAW), E wave deceleration time (EWDT), Systolic Pulmonary arterial pressure (SPAP) in echocardiographic measurements at admission and at the end of treatment.

Laboratory measurements: Adverse changes in lab parameters.

Persistent hypervolemia diagnosed by pretibial edema and/or pulmonary edema or pleural effusions on chest x-ray, jugular venous pressure greater than 10 cm on physical examination [or central venous pressure greater than 10 cm H_2O when measured] NYHA class III – IV, hepatomegaly or ascites and neck vein distension ≥ 7 cm) and weight gain ≥ 2 kg during the previous week.

Acute kidney injury: Serum creatinine or urine output criteria indicative of modified RIFLE (AKI: risk) class at least 1 (increase x 1.5 in serum creatinine or decrease > 25% in GFR or urine output < 0.5 ml/kg/hour for more than 6 hours) (11).

Echocardiographic examination: Standard echocardiographic examinations were performed using a Vingmed Vivid System 5 (General Electric, Horten, Norway) device. A 2.5 MHz probe and a 2.5-3.5 MHz probe was used for the Doppler measurements and for tissue Doppler measurements respectively. All measurements were averaged from three cardiac cycles. 2D echocardiographic measurements were performed according to the standards outlined by the American Society of Echocardiography (12). LV dimensions and wall thickness were obtained from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the ventricle. LVEDD and LVESD diameter, thickness of the interventricular septum (IVS) and PW were measured. LV ejection fraction was calculated according to the Simpson method (13). Mitral inflow velocities were evaluated by pulse-wave Doppler echocardiography with the sample volume placed at the tip of the mitral leaflets from the apical four-chamber view. Diastolic peak early (E) and peak late (A) transmittal flow velocity, peak E to peak A velocities (E/A), and deceleration time of peak E velocity (EDT) were measured. The LV-pulsed tissue Doppler imaging (TDI) was performed in the apical four-chamber view using a 5-mm pulsed Doppler sample volume with as minimum optimal gain as possible to obtain the best signal to- noise ratio. Care was taken to align the echo image so that the annular motion was parallel to the TDI cursor. Spectral pulsed wave Doppler signal filters were adjusted until a Nyquist limit of 15–20 cm/s was reached. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. The sample volume was placed at the junction of the LV wall and the septal annulus from the four chamber view sequentially. The myocardial peak early (Em) velocities were obtained from the septum of the left ventricle. All echocardiographic measurements were performed by the same observer. The ratio of E/ Em for septal segment was measured. While echocardiographic examination was performed to obtain blood pressure data required to calculate the aortic elastic parameters.

Statistical considerations

Statistical analyses were performed using SPSS, version 13 (Chicago, IL, USA). All parameters were expressed as mean ± standard deviation. Intra-group comparisons were performed with a paired t-test or Wilcoxon signed ranks test if the data was not normally distributed. Intergroup comparisons between two groups were assessed by independent sample t test. P value < 0.05 was considered as statistically significant.

RESULTS

Totally 34 (of 21 male) patients were included. The patients were grouped as conventional therapy (diuretic group, n=12) and hemodialysis (UF group, n=22) in according to their treatment modality. The mean age 67.4±9.3 (51-93) years and follow-up period were 15.9±11.5, months. Diabetes mellitus present among 19 (55.9%) patients in both groups (Table I).

Renin angiotensin system blocking drugs were used in 50% of diuretic group than UF group (9%) (p <0.05). At the beginning echocardiographic parameters were similar in both groups except mitral valve A wave (MPV-A) which is higher in UF group 0.80±0.22 than diuretic group 0.56±0.15 m/sec. As expected blood urea nitrogen (BUN) and creatinine values were higher in the UF group 63.56±27.23 and 4.34±2.21 mg/dl than diuretic group 41.67±20.67 and 2.25±0.98 mg/dl (p <0.05). Creatinine values were higher 4.95±1.96 in UF group than diuretic group 2.23±0.85 mg/dl at the end of the study (p< 0.01). Although basal ejection fraction (EF) values were not different, it was higher in the UF group at the end of the study compared to diuretic group (42.38±12.70 % and 29±3.67 %, p <0.05) (Table II). Mean hospitalization period were 19.4±17.3 days and during follow-up mortality rates were not different in both groups (diuretic group, 6 patients (17.6 %), the UF group 1 patient (2.9 %), (p> 0.05) (Figure 1).

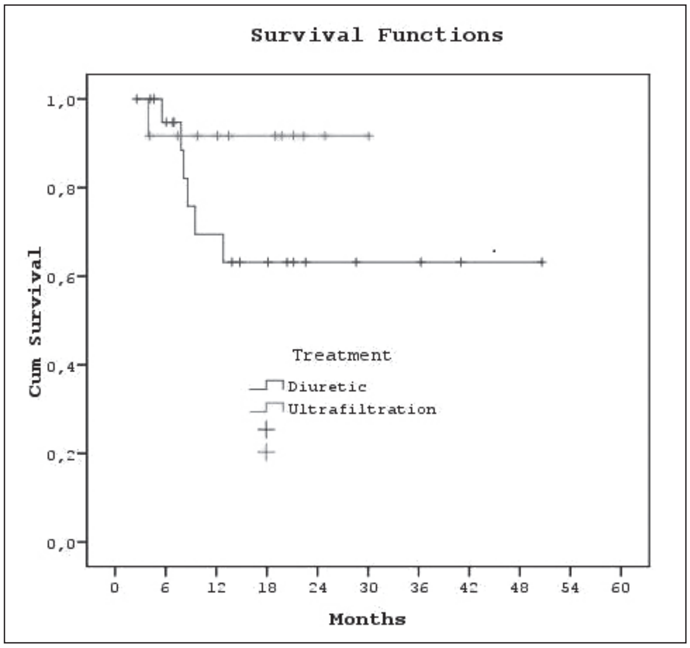

Figure 1: *Survival functions p > 0.05*

Table I: Basal characteristics of the patients.

	Diuretic group (n=12)	Ultrafiltration group (n=22)	Total (n=34)
Age (years)	70.4±7.7	65.7±9.8	67.4±9.3
Sex (M/F)	9/3	12/10	21/13
Diabetes Mellitus (%)	6 (50)	13 (59)	22 (55.9)
ACEi/ARB use (%)	6 (50) a	2 (9)	8 (24)
Hepatomegaly (%)	2 (17)	3 (14)	5 (15)
Parathormone (pg/ml)	261.1±79.8	527.5±554.0	448.6±479.1
Proteinuria (mg/day)	2200±3415	2218±2070	2212±2537
Follow-up (months)	15.7±8.5	16.0±13.0	15.9±11.5
Time period between echocardiographies (months)	12.4±8.4	13.2±13.9	12.9±12.1
Hospitalization time during follow-up period (days)	21.1±14.9	18.5±18.9	19.4±17.3

Values expressed as mean ± Standard deviation. [a]p<0.05. for between-group comparison.

Table II: Changes in biochemical and echocardiographic parameters in diuretic and ultrafiltration groups.

	Diuretic group, Basal (n=12)	Diuretic group, End (n=12)	UF group Basal (n=22)	UF group, End (n=22)
Creatinine (mg/dl)	2.25±0.98b	2.23±0.85b	4.34±2.21	4.95±1.96
BUN (mg/dl)	41.67±20.67a	57.08±30.40	63.56±27.23	92.05±148.85
Hematocrite (%)	33.87±6.06	32.42±7.42	31.15±5.80	32.29±6.88
WBC (/mm3)	9.04±2.59	7.29±1.61	9.39±4.24	8.99±3.61
Na (meq/L)	137±2.86	136 ±4.65	137±5.54	139±4.48
K (meq/L)	4.77±0.73	4.77±0.94	5.06±0.96	4.80±0.80
LVEDD (cm)	5.53±0.73	5.70±0.50	5.21±0.62	5.28±0.63
LVESD (cm)	4.13±1.00	4.22±0.79	3.65±0.71	3.88±0.74
EF (%)	37.42±13.27	29.00±3.67a	43.65±11.84	42.38±12.70
Aortic diameter (cm)	2.93±0.56	3.02±0.89	3.04±0.35	3.04±0.34
Septum thickness (cm)	1.19±0.12	1.20±0.09	1.29±0.17	1.31±0.21
PWT (cm)	1.18±0.13	1.19±0.09	1.24±0.16	1.23±0.12
MVEW (m/sec)	0.69±0.26	1.00±0.28	0.71±0.29	0.72±0.29
MVAW (m/sec)	0.56±0.15b	0.75±0.21	0.80±0.22	0.88±0.22
EWDT (m/sec)	213±81	200 ±42	248 ±60	235 ±83
Aortic velocity (m/sec)	1.28±0.12	1.20±0.17	1.39±0.28	1.36±0.29
SPAP (mmHg)	41.6±20.5	36.7±10.2	42.8±13.3	36.8±11.4
Pulmonary velocity (m/sec)	0.83±0.34	0.73±0.12	1.24±2.00	0.78±0.12

Values expressed as mean ± Standard deviation. [a]p<0.05. for between-group comparison [b]p<0.01 for between-group comparison. [c]p<0.05. for within-group comparison (compared with baseline status).

BUN: Blood urea nitrogen, **LVEDD:** Left ventricular end diastolic diameter, **LVESD:** Left ventricular end systolic diameter, **EF:** Ejection fraction, **PWT:** Posterior Wall thickness, **MVEW:** Mitral valve E wave, **MVAW:** Mitral valve A wave, **EWDT:** E wave deceleration time, **SPAP:** Systolic Pulmonary arterial pressure.

DISCUSSION

Usually main purpose of hemodialysis (HD) is solute clearance, UF also achieved at the same time and smaller molecules less than 300 Dalton in size passively diffuses across the semi-permeable membrane. Clearance of fluid could be adjusted by changing transmembrane pressure difference between (ΔP) by increasing the blood flow or forcing suction to the filtration side (14).

Heart failure patients usually admit emergency services with the complaint of venous congestion symptoms. Third heart sound and jugular venous distenstion show poor prognosis (15). Before cardiovascular symptoms, reducing the congestion signs are very important. Furosemide has been used for more than four decades. This drug must be passed into the tubular lumen so block the sodium-potassium-chloride transport in the ascending Loop of Henle. The pharmacokinetics and pharmacodynamics of this drug could vary individually therefore needs titration (16).

A review of 12 randomized clinical trials of renin angiotensin aldosteron system blockers (ACE inhibitor / ARB) therapy in patients with chronic kidney disease, with or without diabetes mellitus or heart failure were conducted. Studies with a minimum of two years follow up, 1102 patients were randomized to receive ACE inhibitors or ARBs, examined the changes in serum creatinine or glomerular filtration rates (GFR). Authors concluded that in patients with renal insufficiency (serum creatinine >1.4 mg/dL) treated with ACE inhibitors, there was a strong association between early (within the first 2 months) and moderate (not exceeding 30% over baseline) rise in serum creatinine. They recommends not to stop ACE inhibitor therapy unless serum creatinine level rise above 30% over baseline during the first 2 months (17).

In our study renin angiotensin system blocking drugs were used in half of patients in diuretic group and less than one tenth of patients in UF group. Serum creatinine levels were higher in UF group than diuretic group both baseline and at end of the study. UF group patients were composed of patients who were more advanced renal disease and this may explain the RAS blockage preference of diuretic group. In diuretic group BUN levels were increased significantly at the end of study.

Treatment of high dose loop diuretics analyzed in 1389 acute heart failure patients. It was shown that the risk association with high dose diuretics in patients after hospitalization for heart failure was dependent on the levels of BUN and Carbohydrate antigen 125 (CA125). They found that the use of high dose loop diuretics (HDLDs) was independently associated with increased mortality, but associated with CA125-BUN categories. In patients with normal CA125, use of HDLDs was associated with higher mortality if BUN was above the median, but not in those with BUN below the median. Conversely, in patients with high CA125, HDLDs showed an association with increased survival if BUN was above the median but was associated with increased mortality in those with BUN below the median (18). In our study we did not measure CA-125 level, so we couldn't interpret the BUN levels with mortality in diuretic group. Loop diuretic such as furosemide when administered at excessive doses can cause decreased blood pressure, perfusion and/or relative dehydration in decompensated CHF patients.

A case-control observational study established in CRS patient who was demonstrated to develop a rise in creatinine the end of i.v. diuretic therapy in 6-8 days and they found aggravated renal disease risk factors as previous renal injury. High doses of furosemide caused more serious harm, perhaps due to their hemodynamic effects on venous return and cardiac preload, as compared to CRS patients with reduced (45-30%) EF (19). In placebo group of EVEREST trial (n=2061) also showed the declining the renal function during hospitalization and shortly after discharge in patients admitted for worsening heart failure using diuretics (20).

The incidence of worsening renal function, as seen in EVEREST study and the recently completed PROTECT trial, was 15% or less and they pointed out worsening renal functions during hospitalization was most likely related to hypotension leading arterial underfilling occurring as a result of aggressive decongestion therapy rather than worsening heart failure or kidney injury (21).

In present study basal EF values were same in both groups; it was improved in the UF group at the end of the study. This was most probably due to more precise hypervolemia management. Ultrafiltration has an advantage over diuretics by the way of removal of isotonic fluid compared to the hypotonic losses from diuretics. Consequently for the same amount of fluid removed, UF may provide much more sodium loss. In a study with the same baseline Na^+ concentration ultrafiltrate Na^+ loss was 2 fold of diuretic induced urine loss (22). In our study baseline Na^+ levels of both diuretic and UF groups were similar and also at the end of the study, there were no difference. This is may be attributed to less number of cases in groups.

Additionally extra-renal removal of fluid and salt spares exposure of the tubules to Na^+, so not leading the harmful transforming growth factor typically found in diuretic usage. Although this seems as advantage, it is not clear whether UF superior or not on renal and cardiac functions. Finally a hypothesis is that UF may help to removal of cytokines and other mediators of inflammation that are associated with worsening of heart failure but this issue has not been studied enough and there may not be a clearance of short lived molecules to have clinical importance. Although UF seems a smart therapeutic approach for decompansated heart failure patients, it needs further studies whether a traditional hemodialysis machines or new hemofiltration devices must be preferred. Hemofiltration devices also have the advantages of smaller size, portability, and low blood pump speeds which can be as low as 40 ml/min and are designed to the use of peripheral veins rather than central veins. It must be remembered that high UF rates that might cause prerenal azotemia, hypotension, or excessive hemoconcentration thereby risk of acute kidney injury and the need for dialysis. Finally, there is no consensus on the advantages of practical dedicated UF device with what could potentially be higher costs for disposable supplies (23).

Present study does provide some short-term data regarding the safety of UF and intravenous loop diuretics in the inpatient setting. Although it's found that survival rates and hospitalization duration were similar in both groups, EF progression in UF group was better than diuretic group. Long term follow up with a large study groups may provide data for constriction of guidelines for CRS patients.

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