

Tolvaptan for Heart Failure with Volume Overload not Responding to Conventional Treatment: A Retrospective Analysis

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Abstract

Introduction: To study outcomes in patients with heart failure (HF) resistant to conventional diuretic therapy receiving add-on tolvaptan (vasopressin 2 receptor antagonist) or ultrafiltration.

Methods: In this study, a retrospective analysis was performed on the patients with HF who had significant volume overload, ischemic dilated cardiomyopathy, and hyponatremia (serum sodium: 125-135 mEq/L) resistant to conventional treatment who received add-on oral tolvaptan 15 mg/day or ultrafiltration.

Results: Outcomes included a change from baseline in serum sodium, blood urea nitrogen (BUN), serum creatinine and body weight after three days. Changes in baseline hepatic enzymes and fasting blood glucose were analyzed in the tolvaptan arm 24 hours after stopping treatment. The analysis included 26 patients (tolvaptan: n=13; ultrafiltration: n=13). The overall baseline median (min, max) values were as follows: serum sodium 131 (122, 140) mEq/L, BUN 60.5 (21, 120) mg/dL, serum creatinine 1.6 (0.8, 3.7) mg/dL, body weight 76 (51, 92) kg. After three days, baseline serum sodium increased significantly in both arms with a significantly greater median % change in the tolvaptan arm (5 [-7, 12]) versus ultrafiltration (1 [-1, 8], p=0.037). No significant change in baseline BUN in the tolvaptan arm while it decreased in ultrafiltration arm (p=0.001). In both arms, there was significant weight loss and no significant change in serum creatinine versus baseline. No significant change was observed in baseline fasting glucose or hepatic enzyme levels in the tolvaptan arm. There were not any serious adverse events.

Discussion and Conclusion: The outcomes of patients with HF whose volume overload resistant to conventional treatment receiving add-on tolvaptan or ultrafiltration were not different concerning improving hyponatremia and inducing weight loss, without worsening of renal function.

Keywords: Heart failure with volume overload; tolvaptan.

Heart failure is a widely prevalent condition affecting over 23 million people worldwide and accounting for substantial morbidity, mortality, and health care expenses due to hospitalization, readmissions, and outpatient visits [1]. The conventional treatment for heart failure patients with volume overload includes loop diuretics, thiazide diuretics, aldosterone antagonists, and salt and water re-

striction [2]. However, treatment with diuretics may often be ineffective due to the development of resistance [3, 4], and high-dose diuretic therapy may be associated with worsening of renal function [5], poor 6-month outcomes, and increased mortality [6]. Ultrafiltration is recommended for patients who have persistent congestive symptoms despite conventional therapy as it is effective in improv-

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ing the symptoms of volume overload [2] and may lead to decreased rate of readmissions for heart failure, and shortened hospital stay [7]. However, the procedure is expensive, needs trained nursing staff, and may be associated with excessive volume removal leading to hypotension, worsening of prerenal azotemia, or acute renal failure [7]. Thus, there is a need for alternative treatments for better management of heart failure patients with volume overload.

Tolvaptan, an oral, selective vasopressin 2 receptor antagonist, is a novel drug indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion [2,8]. Tolvaptan is also indicated for the treatment of heart failure patients with volume overload who do not show adequate response with other diuretics, such as loop diuretics [2,4,9]. Tolvaptan produces a free water diuresis to decrease body weight and edema and increases serum sodium levels without any adverse effects on serum electrolyte concentrations, renal function, vital signs, or hemodynamic and neurohormonal stimulation observed with high-dose diuretic therapy [10–13]. Furthermore, as a once-daily oral tablet, tolvaptan is convenient to administer, unlike ultrafiltration, which is an invasive procedure.

Heart failure is very common in Turkey, and the prevalence is estimated to be higher than in western countries [14]. However, there are scant observational data on the effectiveness of treatments in Turkish heart failure patients. Furthermore, to date, the effectiveness and safety of tolvaptan in heart failure patients have not been compared with ultrafiltration in controlled trials or in real-life settings. Therefore, we performed a retrospective analysis to study the outcomes of heart failure patients with volume overload resistant to conventional treatment who received add-on therapy with tolvaptan or ultrafiltration.

Materials and Methods

Patients

In this study, we retrospectively analyzed data from heart failure patients hospitalized in the Siyami Ersek Training and Research Hospital, Istanbul, Turkey, from January 2013 to December 2013, who did not respond to conventional treatment and received add-on therapy with tolvaptan or isolated ultrafiltration. All these patients had signs and symptoms of significant volume overload, such as fatigue, dyspnea, pitting edema, ischemic dilated cardiomyopathy

on echocardiography, and serum sodium level between 125 to 135 mEq/L. Patients using vasodilator and inotropic drugs or with pulmonary edema, glomerular filtration rate less than 10 mL/min or anuria were excluded from the analysis. In addition, those who needed dialysis or sodium profiling were also excluded. All patients continued with their concomitant medications, which included beta-blockers, digoxin, and renin-angiotensin system inhibitors.

Patient consent was not needed as this was a retrospective analysis and all data were routinely collected for clinical purposes before research analysis.

Treatments

Patients received add-on therapy with ultrafiltration or oral tolvaptan 15 mg/day for three days when the congestive symptoms of heart failure could not be effectively managed despite three days of conventional treatment at maximum dosages (i.e., furosemide 300 mg/day, hydrochlorothiazide 25 mg/day, or spironolactone 50 mg/day) and a salt-restricted diet (1 g/day). The dose of furosemide was restricted to 300 mg/day to minimize the risk of adverse effects, such as hypotension, renal insufficiency, and electrolyte depletion observed in patients receiving a combination of more than two diuretics [2]. The choice of add-on therapy was based on the physician's preference. Criteria for non-response to conventional treatment included urine output less than 500 cc/day with pretibial edema, lung edema, pleural effusion, interstitial edema, or ascites. After cannulation of the brachial-cephalic vein and standard heparin priming, ultrafiltration was instituted as an isolated treatment (without dialysis modality) for two hours every day at a maximum rate of 1500 cc/hour.

Tolvaptan was administered for a mean duration of 2.69 days (standard deviation: 1.8). Treatment was discontinued earlier than three days when the symptoms of congestion were resolved, or serum sodium levels were normalized.

Assessments

Serum sodium levels, blood urea nitrogen (BUN), serum creatinine, and weight were recorded at admission (baseline) and every morning at the same time for three days. In patients receiving tolvaptan, serum aspartate aminotransferase and alanine aminotransferase, and fasting blood glucose levels were recorded at baseline and 24 hours after stopping tolvaptan to evaluate the metabolic effects of the drug.

Statistical Analysis

Baseline characteristics were summarized with descriptive statistics. In both treatment arms, the Wilcoxon test was

used to compare clinical values at baseline with the values after treatment. The comparison of outcomes between the tolvaptan and ultrafiltration arms was performed with the Mann-Whitney U test. A p-value <0.05 was used for statistical significance. Statistical data were analyzed using Statistical Package for the Social Sciences (SPSS) 18.00 program (SPSS Inc, Chicago, IL, USA).

Results

Totally, 26 patients met the inclusion criteria and were included in the analysis: 13 each in the tolvaptan and ultrafiltration arms.

Table 1 summarizes the baseline patient characteristics. The median age and gender distribution were similar in both treatment arms. All patients were Caucasian. The median (minimum [min], maximum [max]) ejection fraction of the overall population was 45% (25%, 65%). At baseline, the overall population had serum sodium 131 [122, 140] mEq/L, elevated BUN (60.5 [21, 120] mg/dL), elevated serum creatinine (1.6 [0.8, 3.7] mg/dL), and body weight over 75 (76 [51, 92] kg). All p-values in the analysis were exploratory only and should be interpreted with caution as the sample size was small. After three days of treatment, serum sodium levels increased significantly versus baseline in both the tolvaptan (p=0.015) and ultrafiltration (p=0.032) arms (Table 2). The median % increase in baseline serum sodium was significantly higher in patients receiving tolvaptan compared with patients receiving ul-

trafiltration (p=0.037) (Table 3; Fig. 1).

Median BUN did not change significantly versus baseline in the tolvaptan arm (p=0.916), while it decreased in the ultrafiltration arm (p=0.001) (Table 2). At the end of 3 days, there was no significant difference in the median % change in baseline BUN between patients receiving the two treatments (p=0.073) (Table 3; Fig. 1).

Serum creatinine values did not change significantly versus baseline in either treatment arm (Table 2), and the median % change from baseline was comparatively greater in the tolvaptan arm, but the difference was not statistically sig-

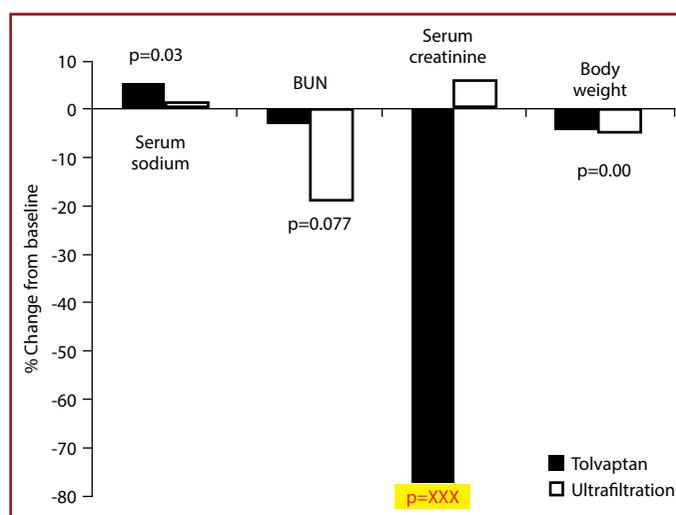


Figure 1. Change from baseline in clinical and laboratory outcomes with tolvaptan versus ultrafiltration. BUN: blood urea nitrogen.

Table 1. Baseline patient characteristics

Characteristic	Tolvaptan n=13	Ultrafiltration n=13	Overall
Age, years	65 (42, 87)	67 (49, 80)	66 (42, 87)
Gender, n (%)			
Female	7 (53.8)	5 (38.5)	12 (46.2)
Male	6 (46.1)	8 (61.5)	14 (53.8)
	110/70	115/75	110/70
Blood pressure, mmHg	(90/50, 130/80)	(85/60, 130/80)	(85/50, 130/80)
Body weight, kg	74 (51, 86)	78 (53, 92)	76 (51, 92)
Serum sodium, mEq/L	127 (122, 134)	134 (122, 140)	131 (122, 140)
BUN, mg/dL	52 (21, 106)	86 (38, 120)	60.5 (21, 120)
Serum creatinine, mg/dL	1.6 (0.9, 3.7)	1.5 (0.8, 3.2)	1.6 (0.8, 3.7)
Ejection fraction, %	50 (35, 65)	35 (25,55)	45 (25, 65)
Diuretic doses			
Furosemide, mg/day	240 (240, 300)	300 (240, 300)	240 (240, 300)
Thiazide, mg/day	12.5 (12.5, 25)	25 (12.5, 25)	18.8 (12.5, 25)
Spironolactone, mg/day	25 (25, 50)	50 (25, 50)	50 (25, 50)

BUN: blood urea nitrogen; max: maximum; min: minimum; N: total number of patients; n: number of patients.

Table 2. Impacts of tolvaptan and ultrafiltration on laboratory and clinical outcomes

Analyte	Tolvaptan n=13		Ultrafiltration n=13		p ^b
	Median (min, max)	p ^a	Median (min, max)	p ^a	
Serum sodium, mEq/L					
At baseline	127 (122, 134)	0.015	134 (122, 140)	0.032	0.017
After treatment	135 (114, 140)		136 (132, 138)	0.979	
BUN, mg/dL					
At baseline	52 (21, 106)	0.916	86 (38, 120)	0.001	0.020
After treatment	55 (37, 67)	70 (30, 90)		0.081	
Serum creatinine, mg/dL					
At baseline	1.6 (0.9, 3.7)	0.183	1.5 (0.8, 3.2)	0.096	0.545
After treatment	1.6 (0.9, 2.6)		1.4 (1.0, 3.4)	0.081	
Weight, kg					
At baseline	74 (51, 86)	0.004	78 (53, 92)	0.001	0.336
After treatment	72 (49, 84)		74 (50, 87)	0.475	

^aWilcoxon test; ^bMann-Whitney U test; BUN: blood urea nitrogen; max: maximum; min: minimum; N: total number of patients.

Table 3. Change from baseline in clinical and laboratory outcomes with tolvaptan versus ultrafiltration

Analyte	Tolvaptan, n=13 Median (min, max)		Ultrafiltration, n=13 Median (min, max)		p ^a
	Absolute change from baseline	% change from baseline	Absolute change from baseline	% change from baseline	
Sodium	7 (0, 15)	5 (-7, 12)	2 (0, 10)	1 (-1, 8)	0.037
BUN	14 (2, 45)	-3 (-42, 100)	13 (8, 30)	-19 (-33, -13)	0.073
Serum creatinine	0.4 (0.1, 2.1)	-77 (-154, 31)	0.2 (0, 0.3)	6 (-9, 33)	0.081
Weight	2.5 (2, 4)	-4 (-5, -2)	4 (3, 6)	-5 (-8, -4)	0.003

^aMann-Whitney U test; BUN: blood urea nitrogen; max: maximum; min: minimum; N: total number of patients.

nificant (p=0.081) (Table 3; Fig. 1).

There was significant weight loss compared to baseline in both tolvaptan (p=0.004) and ultrafiltration (p=0.001) arms (Table 2), but the median % change in weight was significantly greater in patients treated with ultrafiltration versus tolvaptan (p=0.003) (Table 3; Fig. 1).

After three days of tolvaptan treatment, there was no significant change in baseline fasting blood glucose or hepatic enzyme levels (Table 4). None of the patients receiving either tolvaptan or ultrafiltration experienced any complications or serious adverse events during the study period.

Discussion

To our knowledge, this is the first analysis in real life comparing the outcomes between patients receiving add-on therapy with tolvaptan versus ultrafiltration who had heart failure and volume overload despite conventional

treatment, as well as impaired renal function. The efficacy of tolvaptan in improving the symptoms of volume overload and hyponatremia in heart failure patients has been proven in randomized studies [10,15-19], and confirmed in large observational studies [4,21]. Hyponatremia is strongly associated with morbidity and mortality in patients with heart failure, and correction of hyponatremia can improve survival [20].

Patients included in our analysis showed elevated serum creatinine and BUN at baseline, indicating that they had impaired renal function. The outcomes after admission for such heart failure patients are poor, especially if their renal function worsens [13,22,23]. We did not, however, observe any deterioration of renal function (concerning BUN or serum creatinine elevation) in patients receiving either tolvaptan or ultrafiltration. A prospective observational study in 114 patients with acute decompensated heart fail-

Table 4. Impacts of tolvaptan on metabolic parameters

Analyte	Tolvaptan, n=13	
	Median (min, max)	p ^a
Fasting glucose, mg/dL		
At baseline	107 (81, 188)	0.456
After treatment	113 (80, 217)	
Aspartate aminotransferase, U/L		
At baseline	20 (11, 1124)	0.689
After treatment	20 (13, 521)	
Alanine aminotransferase, U/L		
At baseline	18 (3, 1278)	0.074
After treatment	16 (3, 798)	

^aWilcoxon test; max: maximum; min: minimum; N: total number of patients.

ure and high risk of worsening renal function found that patients receiving tolvaptan had significantly higher diuresis and decreased the incidence of renal deterioration compared with those receiving conventional treatment [24].

Worsening of renal function may occur due to under diuresis, over diuresis, or a transient reduction in intravascular volume [13]. Thus, it is imperative to ensure that clinical decongestion in heart failure is achieved without causing deterioration of renal function. Previous studies in patients with acute heart failure have shown that high-dose loop diuretic therapy and ultrafiltration may lead to a worsening of renal function due to transient depletion of intravascular volume or overdiuresis [13]. Being an aquaretic agent, tolvaptan relieves congestion by inducing free water diuresis leading to increased plasma osmolality, which in turn increases the oncotic pressure. In addition, it causes a gradual decline in the intravascular volume and pressure, leading to a sustained movement of fluid from the extravascular to the intravascular compartment without any disruption in renal function [13]. Therefore, patients on tolvaptan can freely consume water and fluids, which improves their quality of life. Furthermore, they have decreased morbidity as hypo-osmolality due to solute diuresis is prevented or corrected [25]. In contrast, loop diuretics and ultrafiltration cause rapid reduction in intravascular volume and pressure, have no impact on the oncotic pressure, and may lead to a transient or ongoing fluid imbalance in the intra- and extravascular compartments and increased serum creatinine [13].

This analysis has several limitations. As it was a retrospective analysis of patients who were treated for heart failure in our hospital, there was no randomization or blinding, and all treatments were determined according to the

physicians' preference. Thus, the two treatment groups were not balanced concerning BUN and serum sodium levels at baseline. The sample size was small, and this could be related to the restrictive eligibility criteria. However, to our knowledge, this is the first observational study to directly compare the outcomes of add-on therapy with tolvaptan versus ultrafiltration in this patient population. Over a treatment period of three days, we did not find any significant differences between the outcomes concerning effectiveness or safety signals. We believe our data will serve to provide clinicians with a rationale for considering add-on therapy with tolvaptan for heart failure patients with volume overload who respond inadequately to conventional treatment. Given the exploratory nature of this study, however, our findings should be interpreted with caution and confirmed in large prospective studies.

Conclusion

In conclusion, in this retrospective analysis of heart failure patients with volume overload resistant to conventional treatment, the outcomes of patients receiving add-on therapy with tolvaptan or ultrafiltration were not different concerning improving hyponatremia and inducing weight loss, without worsening of renal function. This indicates that tolvaptan should be considered as a treatment option for this group of patients, although these findings should be confirmed in prospective studies with larger sample size.

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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