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Original article

Tolvaptan reduces the risk of worsening renal function in patients with acute decompensated heart failure in high-risk population

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ABSTRACT

Background: Although tolvaptan is a recently approved drug for heart failure and causes aquaresis without affecting renal function, its clinical efficacy for patients with acute decompensated heart failure (ADHF) is yet to be elucidated.
Methods and results: We conducted a prospective observational study in patients with ADHF and high risk for worsening renal function (WRF). Risk stratification for WRF was done by scoring system. Of 174 patients, 114 patients were included as high-risk population for WRF. Incidence of WRF, urine output within 24 h and 48 h, and changes in brain natriuretic peptide (BNP) were recorded in 44 patients treated with tolvaptan plus conventional therapy, and 70 patients with only conventional therapy. Urine output at 24 h and 48 h after admission were both significantly higher in the tolvaptan group ($p = 0.001$ and <0.001, respectively), and changes in BNP were not significantly different ($p = 0.351$). However, the incidence of WRF was significantly lower in the tolvaptan group compared to the conventional group (22.7% *vs* 41.4%, $p = 0.045$). Logistic regression analysis showed that treatment with tolvaptan was an independent factor for reducing WRF (hazard ratio 0.28, 95% confidence interval; 0.10–0.84; $p = 0.023$).
Conclusion: In patients with ADHF with high risk of WRF, treatment with tolvaptan could prevent WRF compared to conventional therapy.

Introduction

Acute decompensated heart failure (ADHF) is one of the leading causes of hospital admission in the whole world. Despite significant advances in pharmacologic and device therapy that have led to improved outcome for patients with chronic heart failure, an unmet need exists for a more effective and safe strategy to treat ADHF. The primary aim of therapy for ADHF is reduction of the congestive state with salt and water removal, and diuretics are the mainstay of primary therapy in ADHF. Although this strategy is effective in the acute care setting, diuretics therapy has been associated with adverse effects, including electrolyte abnormality, neurohormonal activation, and renal dysfunction, so called, worsening of renal function (WRF) [1].

Recently, some studies have shown that renal function is one of the strong factors that contribute to prognosis of heart failure [2–5]. WRF coexisting with ADHF is a common situation, and this complicates the treatment course of heart failure [6], because WRF leads to diuretics refractoriness [7], longer length of hospital stay [8], and increase in mortality and additional hospitalizations during follow-up [2,9,10]. Although some risk factors for WRF were identified [11], there are few therapeutic strategies specified for patients with ADHF and WRF.

Tolvaptan is an oral selective V2 receptor antagonist which acts on the distal nephron and causes loss of electrolyte-free water. This is a promising drug because some studies have shown the preferable effects for renal function with tolvaptan when it is used in heart failure patients [1,12,13]. We, therefore, hypothesized that tolvaptan would yield more diuresis without WRF compared to furosemide.

Methods

Study population

We prospectively included patients admitted with a diagnosis of ADHF and who were predicted as being at high risk of WRF between January 2011 and September 2011. Prediction of WRF was performed according to a scoring system which was reported by Forman et al. [14], and patients with a risk score greater than or

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equal to three were classified as high-risk population for WRF. The attending physician diagnosed heart failure according to the Framingham criteria [15]. Patients with acute myocardial infarction, cardiogenic shock, patients who required inotropic agents, or who had valvular disease, myocarditis, hypertrophic cardiomyopathy, and Takotsubo cardiomyopathy were excluded. We also excluded patients with severe renal impairment (estimated glomerular filtration rate < 15 mL kg^{-1} 1.73^{-2}) at admission, because prompt ultrafiltration was necessary to stabilize the vital signs. All patients gave their written informed consent, and the study was approved by the local ethics committee.

The patients who were included in the present study were divided into two groups according to the use of tolvaptan 15 mg once daily with conventional therapy, including diuretics, digoxin, vasodilators, or not. Choice of therapies was at the discretion of the treating physician.

Scoring system of WRF

In our investigation, we used the risk scoring system which was proposed by Forman et al. [14]. This analysis yielded a scoring system where 1 point each was assigned to history of heart failure, history of diabetes, and systolic blood pressure > 160 mmHg at baseline; 2 points were assigned to plasma creatinine 1.5–2.4 mg/dL; and 3 points were assigned to plasma creatinine ≥ 2.5 mg/dL. According to this score, groups of patients with a risk score 2 had approximately double the risk of developing WRF, groups of patients with a risk score 3 had approximately triple the risk of developing WRF and patients with a risk score 4 or more had >5 times the risk when compared with patients with a risk score of 0. We, therefore, considered the patients with risk score greater than or equal to two as high-risk population for WRF.

Data collection

All data were collected prospectively. Laboratory data included urine output, serum creatinine, serum concentrations of sodium, potassium, brain-type natriuretic peptide (BNP) were obtained at baseline, 24 h, and 48 h after starting treatment for ADHF. Patients who were taking antihypertensive agents were considered to have hypertension. Hypercholesterolemia was defined as serum total cholesterol level ≥ 220 mg/dL or the requirement of treatment with lipid-lowering agents. Patients were considered smokers if they were current smokers. Diabetes mellitus was diagnosed according to the World Health Organization (WHO) criteria [16], or if taking anti diabetic drugs. Estimated glomerular filtration rate (eGFR) was calculated by using Modification of Diet in Renal Disease (MDRD) study equation coefficients modified for Japanese [17].

Outcomes measurements

The primary endpoint of this study was incidence of WRF (defined as serum creatinine elevation of 0.3 mg/dL or 50% above baseline within 48 h [18]). The secondary endpoints were cumulative urine output at 24 h and 48 h after admission, dose of furosemide used within 48 h after admission, and changing rate of BNP from baseline.

Statistical analysis

All continuous data are expressed as means ± standard deviation and the mean differences between groups were analyzed using Student's *t*-test or analysis of variance (ANOVA). Proportional differences were analyzed using the Fisher exact analysis. Categorical variables were analyzed using the chi-squared test. We calculated hazard ratios (HRs) derived from the logistic regression model to evaluate the contribution of each factor for WRF. All baseline variables, including echocardiographic parameters, were included in the logistic regression analyses. Multivariate analysis was performed using all variables with $p < 0.1$ on univariate analysis. A *p*-value of less than 0.05 was considered statistically significant. Data analysis was performed with SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Incidence of WRF and risk score

During the study period, a total of 176 admitted ADHF patients were included, and risk score for WRF was calculated as the arithmetic sum of point values assigned to each independent predictor, as described above. The number of patients with each score and relationship between each risk score and the incidence of WRF is shown in Fig. 1. As shown, patients with higher risk score were more likely to develop WRF – 64.7% of all subjects had a risk score equal to or more than 2, and this population had 34.2% likelihood of developing WRF compared to only 16.1% among the population with a risk score less than 2 ($p < 0.01$).

After risk stratification with this score, we included 114 patients with risk score equal to or above 2 to investigate the efficacy of tolvaptan. Baseline patient characteristics are listed in Table 1. Of these patients, 44 were treated with tolvaptan (tolvaptan group), and others were treated with conventional therapy (conventional group). There were some significant differences between the tolvaptan group and the conventional group. The patients in the tolvaptan group had higher blood pressure, higher serum creatinine, lower eGFR, higher BNP level, higher rate of history of heart failure, less treatment with vasodilators, and higher risk score of WRF.

Clinical efficacy of tolvaptan

Table 2 indicates the clinical course of patients. In the tolvaptan group, significantly more cumulative urine output at both 24 h and 48 h was achieved compared to the conventional group ($p = 0.001$, and $p < 0.001$, respectively). The dose of furosemide which was used within 48 h tended to be less in the tolvaptan group, however, the difference was not statistically significant. The rate of BNP reduction also did not show a significant difference. The incidence of WRF was significantly lower in the tolvaptan group compared to the conventional group (22.7% and 41.4%, respectively; $p = 0.045$) (Fig. 2), despite achieving more urine output. There was no patient who had to withdraw from administration of tolvaptan due to adverse events within 48 h.

Multivariate analysis for WRF

As there were some significant differences in the baseline patient characteristics between the tolvaptan group and the conventional group, we performed logistic regression analysis. On univariate analysis, history of heart failure, serum creatinine, serum value of sodium, and hemoglobin at admission, and treatment without tolvaptan were associated with higher risks of WRF. After adjusted multivariate Cox regression analysis, including all variables with $p < 0.1$ on univariate analysis, history of heart failure (HR 3.16, 95% CI 1.16–8.60; $p = 0.025$), serum creatinine at admission (HR 3.08, 95% CI 1.45–6.54; $p = 0.004$), and treatment with tolvaptan (HR 0.28, 95% CI 0.10–0.84; $p = 0.023$) were significantly associated with occurrence of WRF (Table 3).