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Research Article

Tolvaptan response predictors in acute heart failure patients with congestion

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ABSTRACT

Tolvaptan has been used in many countries as an adjunct to diuretic therapy for heart failure. The identification of predictors of response to tolvaptan is essential in developing individual treatment plans, and this study therefore aims to identify responders and predictors to the use of this treatment. A total of 75 acute heart failure patients with congestion receiving tolvaptan were analyzed retrospectively. Clinical parameters after tolvaptan treatment were evaluated to provide an overview of the effectiveness and safety of tolvaptan. A predictive model was created, and logistic regression analysis was performed. The criterion for diuresis response was peak fluid balance of >-1000 ml, while the criterion for sodium response was >3.5 mEq/l sodium increase. Clinical parameters of urine volume and fluid balance before and after tolvaptan did not differ significantly, but serum creatinine, eGFR, sodium, potassium, and blood pressure were significantly different. Hypernatremia occurred in one patient. Multivariate analysis of all samples showed that diabetes (OR=4.856; *P*=0.006) and systolic blood pressure (SBP) (OR=1.031; *P*=0.046) affected diuresis response. Analysis in hyponatremic patients demonstrated that sex (OR=0.159; *P*=0.033) and serum sodium (OR=0.83; *P*=0.045) affected sodium response. Administration of tolvaptan significantly changed serum creatinine, eGFR, sodium, potassium, and blood pressure. The predictors for diuresis responders were the absence of type 2 diabetes and having higher baseline SBP, while the predictors for sodium responders were being male and having lower baseline serum sodium levels.

Keywords:
Heart failure, Diuresis response, Sodium response, Tolvaptan

1. INTRODUCTION

HF (heart failure) is associated with significant mortality, morbidity, and health expenditure[1]. HF prevalence in the Indonesian population is 5%, which is higher than Asia as a whole, Europe, and the US[2]. The mortality rate for HF in Southeast Asia is approximately 13%[3]. Diuretics are used in HF patients to treat dyspnea and edema in those with symptoms and signs of congestion as manifested by excess body fluid[4]. The most widely used diuretics are loop diuretics such as furosemide. Tolvaptan, a V2 (vasopressin 2) receptor antagonist, has been used in many countries as an adjunct to diuretic therapy for HF. In the US, tolvaptan is indicated for hypervolemic or euvolemic hyponatremic patients, including those with acute HF[5]. In Asian countries, including Indonesia, tolvaptan can also be used in normonatremic HF patients who have volume overload and do not respond to conventional diuretics[6-7]. Various clinical trials and retrospective studies have demonstrated the efficacy and safety of tolvaptan[8-13].

The EVEREST clinical trial of tolvaptan showed survival rates were not superior to those in the placebo group[8], but survival rate was shown to increase in hyponatremic patients[14]. Therefore, there are indications that the optimal effect of tolvaptan can be achieved by use in specific populations. The identification of responders to and predictors for tolvaptan use are consequently important for developing individual treatment plans. In addition, the use of tolvaptan is still hampered by its relatively high price. National insurance in Indonesia does not cover tolvaptan, thus, health professionals need a strategy for

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deciding when tolvaptan should be administered. Several studies of predictors of tolvaptan response have been carried out[15-19], yet many of the findings are difficult to apply in developing countries since the predictors identified are not routinely tested for in clinical practice. This study aims to identify simpler predictors of responders that are expected to assist health professionals in making better therapeutic decisions.

2. MATERIALS AND METHODS

2.1. Sample

The calculation of sample was based on a rule of thumb that the number of subjects required was 5-50 times the number of independent variables[20]. In this study, 18 independent variables were determined, thus the minimum sample required was 90 subjects. Unfortunately, out of 128 patients using tolvaptan, only 75 patients fulfilled the inclusion and exclusion criteria. Therefore, a total of 75 acute HF patients with congestion who received tolvaptan as an adjunct to conventional therapy in the period 2017 to 2020 were retrospectively evaluated.

Inclusion criteria included adult patients (age >18 years) and patients who received tolvaptan with signs of congestion, i.e. evidence of pulmonary congestion, pleural effusion, or peripheral edema. Patients with estimated glomerular filtration rate (eGFR) of <15 ml/min/1.73 m^2, those undergoing renal replacement therapy, patients with sepsis, cardiogenic shock, and patients who did not receive furosemide before and during treatment with tolvaptan were not included in this study. The study received ethical approval from Harapan Kita National Heart Center, Jakarta, Indonesia.

2.2. Data collection and definition of a responder

Several clinical parameters were evaluated to give an overview of the effectiveness and safety of tolvaptan. The parameters were urine volume, fluid balance, blood pressure, serum sodium, and serum potassium after administration of tolvaptan as endpoints.

Furthermore, to identify response predictors, the independent variable consisted of demographic profile, baseline clinical parameters, concomitant drugs, and concurrent medical conditions. Baseline parameters were taken before tolvaptan administration. The endpoints included status of diuresis response and sodium response. The criterion for diuresis responder, i.e. patients who responded to the diuretic effect of tolvaptan, was peak fluid balance of >-1000 ml. Furthermore, a sub analysis of sodium response was conducted in hyponatremic patients. The criterion for sodium responder, i.e. patients who responded to effect of sodium increase due to tolvaptan, was a >3.5 mEq/L increase in sodium. Causal analysis of adverse drug reaction (ADR) was performed using the Naranjo algorithm[21].

2.3. Statistical analysis

Bivariate analysis of clinical parameters before and after tolvaptan administration was performed using *t*-paired and Wilcoxon tests, depending on the distribution of data. Bivariate analysis between responders and nonresponders was conducted using chi-squared or Fisher's tests for categorical variables and independent *t*-test or Mann-Whitney test for numerical data. Backward logistic regression was carried out on variables with $P<0.25$ in the bivariate analysis. $P<0.05$ was considered significant. To determine the quality of the regression equation, assessment was carried out using the Hosmer-Lemeshow test. Correlation analysis was performed using Spearman rank correlation coefficient. Values are expressed in mean and standard deviation or 95% confidence intervals (CI 95%) for normally distributed data, and median and minimum-maximum for non-normally distributed data. Values are given in *n* and percent for categorical variables. Statistical analysis was performed using SPSS software, version 23.

3. RESULTS

3.1. Patient characteristics

Patients involved in the study were patients with advanced heart failure. The mean age of the patients in the study was 56.1 years old. Median left ventricular ejection fraction (LVEF) was 26%, and 67% of the sample were patients with heart failure with reduced ejection fraction (HF*r*EF). The etiology of HF was dominated by coronary heart disease, which composed 38.6% of the total sample. Furthermore, a total of 60 patients had decreased kidney function with eGFR below 90 ml/min/1.73 m^2. Documented serum electrolyte parameters were means of 129 mEq/l for sodium and 4 mEq/l for potassium. Most of the patients (70%) in the study had hyponatremia. Tolvaptan was administered to patients in varying doses, with most patients receiving a dose of 15 mg/day with a median duration of three days and a mean initiation time of ten days after admission (Table 1).

3.2. Alteration in clinical parameters after administration of tolvaptan

Evaluation of changes in clinical parameters was carried out to provide an overview of the effectiveness and safety of tolvaptan in HF patients. Alteration in parameters is presented in Table 2. Changes of urine volume and fluid balance were not significantly different, with *P* values of 0.235 and 0.154, respectively. The other clinical parameters had *P* values of <0.05, meaning

Table 1. Patient Characteristics.

Characteristics	Value
Age (years)	56.1 (52.7-59.3)
Male (n)	45 (60)
Body weight (kg)	60 (33-110)
Body Mass Index (kg/m2)	23.72 (22.54-24.96)
Systolic blood pressure (mmHg)	98.78 (94.29-103.49)
Diastolic blood pressure (mmHg)	63.11 (13.73)
LVEF (%)	26 (13-85)
Etiology of HF (n)	
Coronary Artery Disease	29 (38.6)
Hypertension	9 (12)
Valve disease	16 (21.3)
Cardiomyopathy	6 (8)
Infarct	11 (14.7)
Congenital Heart Disease	4 (5.3)
Medical history (n)	
Type 2 diabetes	38 (50.7)
Renal insufficiency	60 (80)
Hypertension	20 (26.7)
Infection	31 (41.3)
Atrial fibrillation	21 (28)
Previous hospitalization (n)	51 (68)
Sign of Congestion (n)	
Peripheral edema	54 (72)
Jugular vein distention	43 (57.3)
Pleural effusion	29 (38.7)
Ascites	39 (52)
Pulmonary congestion	57 (76)
Urine volume (ml)	2030 (1063.9)
Fluid balance (ml)	-606 (1151.0)
Hemoglobin (g/dL)	11.77 (2.54)
Hematocrit (%)	34.89 (7.34)
BUN (mg/dl)	35.45 (30.88-40.69)
Serum creatinine (mg/dl)	1.41 (1.26-1.58)
Glomerular Filtration Rate (ml/min/1.73 m^2)	47.67 (41.44-54.85)
Serum sodium (mEq/l)	129 (7.1)
Serum potassium (mEq/l)	4 (3.9-4.1)
Tolvaptan dose (mg/day)	15 (7.5-30)
Tolvaptan duration (days)	3 (1-27)
Tolvaptan initiation (day-)	9.9 (8.3-11.7)
Maximum dose of furosemide (mg/hour)	20 (1.67-40)
Concomitant drugs (n)	
Single diuretic	39 (52)
Combination of diuretic	16 (21.3)
Catecholamines	55 (73.3)
RAAS inhibitor	71 (94.7)
Beta blocker	53 (70.7)
Nitrate	21 (28)
Statin	43 (57.3)
Anticoagulant	33 (44)
Antiplatelet	40 (53.3)
Antimicrobial	52 (69.3)

LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; RAAS, renin-angiotensin-aldosterone system.

Table 2. Changes in Clinical Parameters Before and After Tolvaptan.

Clinical Parameters	Before TLV	After TLV	*p*-value
Urine volume (ml)	2030 (1063.9)	2256 (1523.7)	0.235
Fluid balance (ml)	-606 (1151.0)	-850 (1390.6)	0.154
Systolic blood pressure (mmHg)	100.9 (22.15)	94.5 (21.69)	0.009*
Diastolic blood pressure (mmHg)	63.1 (13.73)	56.89 (11.7)	0.001*
Serum creatinine (mg/dl)	1.41 (1.26-1.58)	2.39 (1.96-2.91)	<0.001*
Serum sodium (mEq/l)	129 (7.11)	132.29 (7.93)	<0.001*
Serum potassium (mEq/l)	4 (3.87-4.13)	4.2 (0.7)	0.013*

TLV, tolvaptan *P<0.05

meaning there were significant differences between parameters before and after administration of tolvaptan. The results showed that statistically the expected increase in sodium from the use of tolvaptan was significant, with a mean increase of 3 mEq/l.

From Table 3 it can be seen that the prevalence of worsening renal function (WRF), indicated by increase in creatinine serum of 0.3 mg/dl from baseline, was 28%. In addition, hypo- and hyperkalemia occurred in 7 (9.3%) and 9 (12%) patients, respectively.

One (1.33%) patient experienced ADR in the form of hypernatremia, with serum sodium increased to more than 150 mEq/l after tolvaptan administration. The increase in serum sodium in this patient was 19 mEq/l, from an initial sodium level of 132 to 151 mEq/l. We assessed the ADR causality using the Naranjo algorithm and obtained a score of 4 (the 'possible' category), meaning that ADR may have occurred due to administration of tolvaptan.

3.3. Response predictors

Table 4 presents the results of the bivariate analysis performed between independent variables and responses. Further, multivariate logistic regression was conducted for variables with $P<0.25$. Variables in the diuresis response with $P<0.25$ were age, systolic blood pressure, serum creatinine, blood urea nitrogen, tolvaptan dose, infarct etiology, and type 2 diabetes mellitus. For sodium response, analysis was generated only for hyponatremic patients. Variables with $P<0.25$ in sodium response included sex, serum creatinine, blood urea nitrogen, serum sodium, tolvaptan dose, day of tolvaptan initiation, maximal dose of furosemide during tolvaptan treatment, diuretic use other than furosemide, and catecholamine administration.

After multivariate analysis (Table 5), factors that most affected the diuresis response were found to be diabetes mellitus (OR=4.856; $P=0.006$) and baseline SBP (OR=1.031; $P=0.046$). Furthermore, factors that most affected sodium response were found to be sex (OR=0.159; $P=0.033$) and baseline serum sodium levels (OR=0.83; $P=0.045$). The P-value of the Hosmer-Lemeshow test in the regression equation was 0.883 for the diuresis response and 0.257 for the sodium response. Accordingly, there was no difference in observed value in respect of expected value, indicating the equation was well calibrated.

We also performed Spearman correlation analysis between changes in fluid balance as diuresis parameter and baseline serum sodium. The result showed that there was no correlation between changes in fluid balance and baseline serum sodium ($P=0.208$, $r = -0.15$).

4. DISCUSSION

Increase in urine volume and fluid balance are two parameters used to assess the diuresis response[4]. The non-significant results obtained for these parameters could be due to the characteristics of patients who have severe HF. The study took place in a national referral hospital and so concurrent conditions could potentially have caused poor diuresis response. This result supports the need to identify predictors of responders and nonresponders to diuresis so that tolvaptan administration can be optimized.

The study results demonstrate a significant increase in sodium, of 3 mEq/l. According to meta analysis, the mean increase in sodium after tolvaptan use was 3.48 mEq/l[22]. This study result only indicates that tolvaptan tends to be effective in increasing patient serum sodium. Comparative studies of sodium elevation with conventional loop diuretics therapy without tolvaptan have been widely performed. Various clinical trials have demonstrated a significant increase in sodium levels in tolvaptan users[9,23]. The mechanism of tolvaptan in increasing sodium lies in its role as an aquaretic. Tolvaptan increases free-water diuresis through V2 receptors in the tubular collecting ducts. In contrast, furosemide removes sodium and water via the Na-K-2Cl cotransporter along the ascending limb of the loop of Henle[24], resulting in inhibition of sodium reabsorption. Other significant results were an increase in serum creatinine and a decrease in eGFR that indicated WRF, but these occurrences may be a combination effect of concomitant drugs.

Further analysis of changes in clinical parameters was carried out to evaluate the safety of tolvaptan. The occurrence of hypokalemia and hyperkalemia can be influenced by various factors, including the use of other diuretics such as furosemide, thiazides, and spironolactone, according to their mechanisms of action[24]. Thiazides cause hypokalemia due to an increase in sodium and fluid in the distal tubule and an increased effect of aldosterone, whereas spironolactone acts by inhibiting aldosterone, thus increasing the risk of hyperkalemia[24].

Based on previous studies, the risk factors for

Table 3. Adverse Events.

Adverse Events	Number of Patients (n, %)
WRF (creatinine ≥0.3 mg/dl)	22 (28)
Hypokalemia (potassium <3.5 mEq/l)	7 (9.3)
Hyperkalemia (potassium >5.0 mEq/l)	9 (12)

WRF, worsening renal function.

Table 4. Bivariate Analysis between Independent Variables and Responses.

Variable	Diuresis Response (n=75)			Sodium Response (n=52)		
	Responders (n=48)	**Nonresponders (n=27)**	***P*-value**	**Responders (n=24)**	**Nonresponders (n=28)**	***P*-value**
Baseline paramaters						
Age 18-65 (n, %)	41 (85.4)	16 (59.3)	0.024*	19 (79.2)	18 (64.3)	0.382
Male gender	31 (64.6)	14 (51.9)	0.404	16 (66.7)	13 (46.4)	0.236*
BMI (mean, 95% CI)	23.42 (22.09-24.81)	24.27 (21.9-26.9)	0.504	23.39 (21.48-25.47)	23.74 (21.45-26.26)	0.825
HF*r*EF (n, %)	33 (68.8)	17 (63)	0.799	14 (58.3)	17 (60.7)	1
SBP (mmHg) (mean, SD)	103.65 (25.33)	96.04 (14.09)	0.099*	99.79 (23.22)	96.04 (17.5)	0.510
Creatinine (mg/dl) (mean, SD)	1.46 (0.65)	1.8 (0.91)	0.060*	1.25 (1-1.55)	1.5 (1.24-1.82)	0.189*
BUN (mg/dl) (mean, 95% CI)	32.26 (26.61-39.1)	41.9 (35.39-49.68)	0.041*	30.24 (21.95-41.63)	41.42 (33.97-50.5)	0.081*
Sodium (mEq/l) (mean, SD)	129.6 (6.98)	128.19 (7.37)	0.410	124.5 (109-133)	127 (116-134)	0.109*
Potassium (mEq/l) (mean, 95%CI)	3.97 (3.82-4.13)	4.04 (3.82-4.28)	0.619	4.06 (0.62)	4.19 (0.64)	0.457
TLV and Concurrent Drugs and Medical Conditions						
TLV dose (mg/day) (median, min-max)	15 (7.5-30)	15 (7.5-26.25)	0.123*	15 (15-25.7)	15 (7.5-28.33)	0.143*
Initiation day (median, min-max)	10 (1-32)	11 (2-29)	0.410	7.97 (5.31-11.95)	10.48 (8.47-12.97)	0.224*
Furosemide maximum dose (mg/h) (median, min-max)	20 (1.67-40)	25 (2.5-30)	0.507	10 (1.67-30)	25 (5-30)	0.003*
Combination of diuretics (n, %)	11 (22.9)	5 (18.5)	0.613	2 (8.3)	10 (35.7)	0.048*
Catecholamines (n, %)	33 (68.8)	22 (81.5)	0.355	13 (54.2)	25 (89.3)	0.011*
Infarct etiology (n, %)	5 (10,4)	6 (22.2)	0.188*	4 (16.7)	5 (17.9)	1
Atrial fibrillation (n, %)	15 (31.3)	6 (22.2)	0.570	5 (20.8)	7 (25)	0.980
Infections (n, %)	33 (68.8)	20 (74.1)	0.824	19 (79.2)	21 (75)	0.980
Diabetes mellitus (n, %)	20 (41.7)	19 (70.4)	0.032*	11 (45.8)	15 (53.6)	0.781

BMI, body mass index; HF*r*EF, heart failure reduced ejection fraction; SBP, systolic blood pressure; BUN, blood urea nitrogen; TLV, tolvaptan.
*$P<0.25$

Table 5. Logistics Regression Results.

Variables	*P*-value	OR	CI 95%
Diuresis Response			
Type 2 diabetes mellitus			
Yes		Reference	
No	0.006	4.856	1.585-14.881
Baseline systolic blood pressure	0.046	1.031	1.001-1.063
Sodium Response			
Sex			
Male		Reference	
Female	0.033	0.159	0.029-0.859
Baseline serum sodium	0.045	0.830	0.691-0.996

early hypernatremia in patients taking tolvaptan are baseline serum sodium of >140 mEq/l, tolvaptan dose of >7.5 mg, and blood urea nitrogen to creatinine ratio of >20[25]. One patient with hypernatremia in this study had baseline sodium of 132 mEq/l-a value that was above the total sample mean, a tolvaptan dose of >7.5 mg, and a blood urea nitrogen to creatinine ratio of 42.25. We also found a high blood urea nitrogen to creatinine ratio in one study patient with a high increase in sodium of 17 mEq/l.

By logistic regression we found that the predictors for diuresis responders were the absence of type 2 diabetes mellitus and having higher baseline SBP. These results are in line with Matsue et al.'s study which states that poor diuresis response was associated with low blood pressure[26], but the factor observed in the study was diastolic rather than systolic blood pressure. Blood pressure that is too low can interfere with kidney function through decreased perfusion, thereby reducing diuresis response. However, the relationship between SBP and renal function depends on the level of SBP itself[27-28]. SBP of 80-89 mmHg was associated with renal insufficiency (OR=1.2), SBP of 90-149 mmHg was associated with a lower incidence (OR <1), while SBP of above 150 mmHg was associated with an increased incidence of renal insufficiency (OR=1.2)[27]. Therefore, further research is needed to determine the optimal SBP cut off in responders to tolvaptan. In addition, although statistically significant, the OR that near one might indicate that baseline SBP is not clinically significant in predicting response.

Diabetes can stimulate the patient's hemodynamics, such as increase in RAAS that causes changes in kidney structure, resulting in glomerular hypertrophy or renal fibrosis[29] that may affect treatment response. In addition, blood glucose contributes to serum osmolality along with blood sodium, potassium, and urea[30]. Arginine vasopressin (AVP) as an antidiuretic hormone is a peptide released from the hypothalamus in response to changes in plasma osmolality[31]. An increase in plasma osmolality-in this case due to an increase in blood glucose in diabetic patients-will cause an increase in AVP[32]. Meanwhile, kidney damage due to diabetes can reduce the number of aquaporin 2 (AQP2) channels that play a role in water reabsorption. If we use the response predictor suggested by Imamura et al.[33], namely AQP2/AVP, generally when a patient's AVP increases and AQP2 decreases, response to diuresis would be diminished. We observed the samples in this study and found that the mean eGFR in nonresponder diabetic patients was lower than responder diabetic patients, which means that there was a higher potential for AQP2 reduction in nonresponders.

Vasopressin levels influence serum sodium levels; therefore diuretic response may be influenced by serum sodium level. However, correlation analysis demonstrated no correlation between changes of fluid balance and baseline serum sodium. This result was aligned with previous study that showed no correlation between diuretic response and serum sodium levels[34]. It also strengthened the present study that showed baseline serum sodium was not predictor for diuresis response.

Logistic regression analysis in hyponatremic patients showed that predictors of sodium response were being male and having a lower level of baseline serum sodium. Sex can affect the body's physiology[35], resulting in different treatment responses between males and females. However, in previous clinical trials, patients' sodium levels were not directly shown to be a predictor of sodium response. A clinical trial by Hauptman et al. showed that cardiovascular mortality and morbidity were increased in patients with severe hyponatremia (sodium <130 mEq/l), but this finding was not proven in moderate hyponatremia[14]. In another study, it was found that plasma sodium levels were negatively correlated to an increase in sodium, i.e. the lower the baseline plasma sodium level, the higher the sodium increase[36].

Our study has some limitations. First, it is a retrospective observational study and prospective studies are therefore needed to confirm its results. Second, the sample number is small so that we consider this study as a pilot study; generalization to the population as a whole is not indicated. Third, as there is no control group as a comparison, the analysis of changes in clinical parameters is limited to descriptive explanation without any conclusion being drawn about which therapy is safer and/or more effective. Fourth, the time period for documenting baseline values before tolvaptan treatment is not uniform because of different initiation days for the treatment; also, laboratory tests were not performed every day and thus it is possible that the actual baseline values were different from those recorded.

The use of response predictors is a shared responsibility among health professionals. Clinical pharmacists play a role in recommending tolvaptan when supported by predictors. Given the relatively high price of tolvaptan, they can also refer to or conduct risk-cost-benefit analysis with physicians when predictors do not support treatment with tolvaptan. One example is a cost-effectiveness study to hyponatremic patients, demonstrated that cost-effectiveness was more apparent in marked hyponatremic patients[37] which is aligned with our study result that lower serum sodium is a predictor of response. Health professionals may want to prioritize tolvaptan to marked rather than mild hyponatremic patients. The accuracy of risk-benefit analysis would be improved by considering the specific predictors indicated by previous studies when health facilities are adequate. By utilizing response predictors it is expected that individual treatment plans in acute HF patients with congestion will be improved.

5. CONCLUSIONS

While there was no significant change in clinical parameters for urine volume and fluid balance after administration of tolvaptan, serum creatinine, eGFR, serum sodium, serum potassium, and blood pressure changed significantly. The use of tolvaptan tends to be safe in patients with acute HF with congestion. The absence of type 2 diabetes mellitus and higher baseline SBP can be good predictors for diuresis responders, whereas predictors for sodium response are being male and having lower baseline serum sodium level.

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Conflict of interest

The authors declare no conflict of interests.

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Ethics approval

The study was approved by Ethics Committee of Harapan Kita National Heart Center, Jakarta, Indonesia, No. LB.02.01/VII/493/KEP 091/2020.

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