Original Article

Short Term Efficacy and Safety of Low Dose Tolvaptan in Patients with Acute Decompensated Heart Failure with Hyponatremia: A Prospective Observational Pilot Study from a Single Center in South India

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ABSTRACT

Background: In acute decompensated heart failure (ADHF), diuretic use, the mainstay therapy for congestion, is associated with electrolyte abnormalities and worsening renal function. Vasopressin mediates fluid retention in heart failure. In contrast to diuretics, the vasopressin antagonist tolvaptan may increase net volume loss in heart failure without adversely affecting electrolytes and renal function. Hyponatremia (serum sodium concentration, <135 mEq/L) is a predictor of death among patients with heart failure.

Objective: We prospectively observed the short term efficacy and safety of low dose (15 mg) tolvaptan in admitted patients with hyponatremia and ADHF in Indian population.

Methodology: A total of 40 patients with ADHF along with hyponatremia (<125 mEq/L) on standard therapy were treated with 15 mg of tolvaptan at a single oral dose for 7 days.

Results: Serum sodium concentrations increased significantly after treatment with tolvaptan from baseline (P < 0.02). There was a significant improvement in symptoms and New York Heart Association (NYHA) class after starting tolvaptan (P ≤ 0.05). Total diuretic dose and mean body weight was reduced non-significantly at 7th day from the baseline. Side-effects associated with tolvaptan included increased thirst, dry mouth and increased urination. Few patients had worsening renal function. However, several patients developed hypernatremia.

Conclusion: In this small observational study, tolvaptan initiation in patients with ADHF with hyponatremia in addition to standard therapy may hold promise in improvement in NYHA class and serum sodium. At the same time, we observed that serious adverse events such as renal function deterioration and hypernatremia developed after tolvaptan treatment, which needs to be addressed in future by randomized study with larger sample size.

Key words: Acute decompensated heart failure, hyponatremia, tolvaptan, vasopressin antagonist

INTRODUCTION

Heart failure is a clinical state of volume overload in both extra and intra vascular space. It is one of the major public health problems and one of the leading causes of hospital admissions in the world.[1] Arginine-vasopressin levels are elevated in heart failure.[2,3] It results in myocardial fibrosis/hypertrophy and vasoconstriction by activating V1a receptors. Water retention and hyponatremia are mediated thru activation of V2 - receptors.[3] In heart failure, vasopressin antagonists prevent progression of left ventricular dysfunction.[3] In contrast to angiotensin-converting

How to cite this article: Patra S, Kumar B, Harlalka KK, Jain A, Bhanuprakash HM, Sadananda KS, et al. Short term efficacy and safety of low dose tolvaptan in patients with acute decompensated heart failure with hyponatremia: A prospective observational pilot study from a single center in South India. Heart Views 2014;15:1-5.
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In patients with heart failure, tolvaptan added to standard diuretic therapy including potassium-sparing and non-potassium-sparing diuretics resulted in a significant decrease in body weight and edema and increase serum sodium concentrations without adversely affecting serum electrolyte levels, vital signs or renal function. In this first study on Indian population, we prospectively observed the short term efficacy and safety of low dose tolvaptan in admitted patients with hyponatremia and acute decompensated heart failure (ADHF) in addition to the ongoing management for heart failure.

**METHODOLOGY**

**Study design**
It was a prospective and observational study. This study was conducted in a cardiac care center in South India.

**Study population**
All consecutive patients of aged more than 18 years who met the inclusion criteria were included in this study.

**Eligibility criteria**

**Inclusion criteria**
Patients of age more than 18 years admitted with a clinical diagnosis of ADHF, evidenced by jugular venous distention, rales or peripheral edema and those who had serum sodium of <125 mEq/L were included in this study.

**Exclusion criteria**
Criteria for exclusion included cardiac surgery within 60 days of enrolment, cardiac mechanical support, biventricular pacemaker placement within the last 60 days, co-morbid conditions with expected survival of less than 6 months, refractory end-stage heart failure, hemofiltration or dialysis, hemoglobin level less than 9 g/dL, pregnancy and serum sodium >125 mEq/L.

**Ethics**
The study protocol was approved by the Ethics Committee of the respective authority of our institution. Written informed consent was obtained from all patients, before inclusion in the study.

**Methods**
Written proformas were filled up during inclusion of patients, which contained epidemiological information (age, sex, occupation and place), questionnaires for risk factor evaluation (diabetes, drug history, malignancy, comorbid condition, hypertension etc.), information of clinical presentation (dyspnea, edema, etc.) and clinical signs. All patients received standard heart failure therapy, including diuretics, digoxin, ACEI/angiotensin II receptor blockers (ARB), BB, aldosterone blockers, hydralazine and/or nitrates, at the discretion of the treating physician.

All enrolled patients according to our study protocol were treated with oral tolvaptan at doses of 15 mg daily for maximum 7 days or until discharge if it was before 7th day of therapy. Patients were advised fluid restriction during the treatment for ADHF.

**Investigations**
All patients had the following investigation performed after hospital admission.
1. Complete hemogram, fasting lipid profile, blood sugar, liver function test.
2. Renal function test (daily until 7th day or discharge).
3. Serum electrolytes (daily until 7th day or discharge).
4. Chest X-ray and electrocardiogram.
5. Echocardiography.

**Outcome**

A. The Primary outcome of this study was to observe the changes in New York Heart Association (NYHA) grade, body weight, serum sodium and serum creatinine and blood urea at 7th day or at discharge of oral tolvaptan therapy with 15 mg from the day of enrollment.

B. Secondary outcome was to observe the adverse events, which were defined as any new medical problem or exacerbation of an existing medical problem in a patient enrolled in the study. Among the adverse events, hypernatremia was defined as serum sodium of >145 mEq/L and renal dysfunction was defined as >25% increase in blood urea or serum creatinine from the baseline value during treatment with tolvaptan.

**Statistics**
All data was compiled at the end of the study and the sample was analyzed with Chi-square. The P < 0.05 will be considered as statistically significant.

**RESULTS**
Sixty-five patients with ADHF were admitted during the study period. Among these patients, two of them had expired due to heart failure and other three patients had stopped taking treatment on their own within 7th days of starting tolvaptan treatment. Another 20 patients had serum sodium of >125 mEq/L. Finally, data of those 40 patients who completed the study was compiled and analyzed.
Baseline demographic and clinical profile of the study patients

In our study group, more number of cases was male with the male-female ratio of 11:9. The mean age of our study patients was 70 ± 13.6 years. The mean body weight at admission was 72 ± 11.2 kg. Among the risk factors for ADHF, 60% (24/40) patients had previous myocardial infarction or ischemic heart disease, 50% had hypertension and 40% had diabetes. Among the etiology for ADHF, 60% patients had heart failure due to ischemic heart disease, followed by dilated cardiomyopathy in 30% and valvular heart disease in 10% of patients. 85% (34/40) of our study patients had NYHA class III/IV status at admission. Eighty percent and 60% patients had features of pulmonary edema and congestive heart failure, respectively. Mean ejection fraction of our patients at admission was 38 ± 5%. Forty percent of patient with ADHF had baseline renal dysfunction [Table 1].

Treatment received during the study period (other than Tolvaptan)

All patients in our study received loop diuretics. Sixty percent patients received ACE/ARB and spironolactone. Eighty percent of patients were also received oral digoxin; 50% of our study patients received ivabradine for rate control, whereas, only 10% of our patients received oral BB. Sixty percent of our study patients received inotropic support during the treatment [Table 1].

Comparison of clinical and investigational parameters between day of enrollment and at 7th day or at discharge of Tolvaptan (15 mg) therapy

Among the primary outcome determined at the beginning of the study, mean serum sodium was increased and normalized after tolvaptan therapy (121 mEq/L vs. 136 mEq/L) and this result was statistically significant (P = 0.02). Interestingly, there was non-statistically significant rise in mean blood urea after tolvaptan treatment (58 mg/dl vs. 86 mg/dl) though serum creatinine was reduced non-significantly (2.1 mg/dl vs. 1.9 mg/dl). Both the mean body weight and total dose of injection Furosemide dose were reduced at 7th day of tolvaptan therapy from the enrollment value. However, these results were statistically insignificant. There was a statistically significant (P = 0.046) improvement seen in NYHA stage after starting tolvaptan at 7th day (85% vs. 20%) [Table 2].

Adverse events of oral tolvaptan therapy

Among the observed side-effects of Tolvaptan treatment, dry mouth was most common (40%), followed by nausea, vomiting (35%), thirst (30%), abdominal pain (20%) and muscle cramps (15%) of study patients. One interesting observation after starting Tolvaptan treatment was that 10% (4/40) patients developed hypernatremia and 15% (6/40) patients developed renal dysfunction during Tolvaptan therapy [Table 3].

DISCUSSION

In our study, we prospectively observed the effects of oral once-a-day, V2-receptor antagonist tolvaptan in patients hospitalized for symptomatic ADHF when added to standard therapy including diuretics and vasopressor.[7] The majority of patients hospitalized...
for ADHF have signs and symptoms of pulmonary congestion and followed by systemic congestion.\[^2\] Hence, removal of excess fluid from either pulmonary or systemic bed represents a major treatment goal.

The symptomatic benefit exerted by loop diuretics has led to their wide clinical acceptance, even in the absence of efficacy and safety data from large randomized trials.\[^8\] However, this improvement can be associated with electrolyte abnormalities, renal dysfunction, neurohormonal activation, and hypotension.\[^10\] Hence, there is a concern regarding the adverse impact of aggressive diuresis, particularly the impact on renal function and serum electrolytes, and this represents an important contributor to the frequent inadequacy of fluid management during hospitalization.\[^10\]

In our study, the use of tolvaptan resulted in a mean reduction from baseline in the daily use of furosemide at 7th day of therapy. However, it was statistically insignificant, which was in contrast to the previous studies on tolvaptan.\[^11,12\] Though there was a reduction in diuretics use, we found rising of blood urea at 7th day after therapy with tolvaptan with decrease serum creatinine, which was suggestive of renal cause with intracellular dehydration due to excess free fluid diuresis with tolvaptan treatment. This finding in our study was also not seen in previous studies where tolvaptan treatment did not have any impact on renal function.\[^3-7\] Possible hypothesis for this observation may be due to fluid restriction, which was also advised and our patients may have lower body mass index than patients of western countries, so they have less free fluid in the body. Similar excretion of free fluid in our patients may cause hyponatremia and pre renal azotemia.

Inappropriate elevation of arginine vasopressin, which is seen in human with acute heart failure plays a key role in mediating water retention, contributing to both congestive symptoms and electrolyte imbalance.\[^13,14\] Tolvaptan was effective most likely because of its impact on fluid balance.\[^14\] Consistent with its mechanism of action, it influenced the primary end point mainly by reducing body weight and maintaining serum sodium.\[^15\] Hyponatremia occurs in 15-20% of hospitalized patients and constitutes a common serum electrolyte abnormality.\[^16\] Hyponatremia is reported to be an independent predictor of complications and death in patients with heart disease. So far no trial has demonstrated mortality benefits of tolvaptan in acute heart failure.\[^17\] Findings of our study were also similar from the previous studies in these aspects.\[^16\] The mean serum sodium was significantly increased and hyponatremia was corrected after starting oral tolvaptan. Mean body weight was also decreased at 7th day from the baseline, but this finding was not statistically significant like previous study. Similar to previous studies,\[^18\] our patients significantly became asymptomatic after starting of tolvaptan.

Currently available therapeutic options in the management of ADHF have several limitations in their efficacy, safety or both.\[^2,3\] As our patients had pulmonary and systemic congestion, so we can’t use BB in all patients and that is why ivabradine was used in almost 50% of study patients to control the heart rate. ACEI/ARB or spironolactone was used only in 60% of patients as the rest of them had renal dysfunction. Though 60% of our patients received intravenous inotropes, such as dobutamine and dopamine to improve hemodynamics; however, this improvement is often associated with significant adverse effects that include hypotension, atrial and ventricular arrhythmias and possibly increased post-discharge mortality and this number was higher than the previous study may be due to our patients presenting in decompensated NYHA class III and IV.\[^20\]

As expected and similar with previous studies, the incidence of adverse effects associated with the pharmacological effects of the drug like dry mouth and thirst was seen frequently in patients after receiving tolvaptan.\[^4-13,21\] This was unusual in our study that some patients had hyponatremia and worsening of renal function after starting tolvaptan treatment.

Our study has several limitations. This was a prospective observational study with small study group, so results of this study cannot be generalized. We used a fixed dose of tolvaptan for 7 days without any titration. We used tolvaptan only in hospitalized cases with acute heart failure who has hyponatremia. We cannot be certain whether our findings would be replicated in other populations, including those patients with acute heart failure with normal serum sodium. As we have used tolvaptan in addition to diuretics, our data would not support the use of an arginine vasopressin antagonist in lieu of diuretics.

**CONCLUSION**

Though our study was a prospective observational study, we found some similar results as in previous studies. Tolvaptan initiation in patients with ADHF with hyponatremia has significant improvement in NYHA grade and serum sodium and has non-significant decrease in body weight and diuretics doses at 7th day of therapy. At the same time, we observed that some serious adverse events developed after starting tolvaptan treatment such as deterioration in renal function and hyponatremia in

### Table 3: Side effects of tolvaptan 15 mg

| Side effects          | N=40 (%) |
|-----------------------|----------|
| Thirst                | 12 (30)  |
| Dry mouth             | 16 (40)  |
| Hyponatremia          | 4 (10)   |
| Renal dysfunction     | 6 (15)   |
| Nausea/vomiting       | 14 (35)  |
| Abdominal pain        | 8 (20)   |
| Muscle cramp          | 6 (15)   |
a few patients, which needs to be addressed in future randomized study with larger sample size.

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Source of Support: Nil, Conflict of Interest: None declared.