Original Article

Effect of tolvaptan on acute heart failure with hyponatremia – A randomized, double blind, controlled clinical trial

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ABSTRACT

Objectives: To assess the efficacy of tolvaptan in acute heart failure with hyponatremia using a randomized double-blinded placebo-controlled study design.

Background: Tolvaptan is a selective vasopressin receptor 2 antagonist. There are no published clinical trials on the utility of tolvaptan in acute heart failure with hyponatremia in the Indian population.

Methods: After screening and informed consent, 51 HF patients with hyponatremia were randomized using computer-generated randomization sequence to receive placebo or 15 mg of tolvaptan for 5 days along with conventional medical therapy. The patient’s perception of dyspnea using Likert score and the plasma sodium was measured at baseline and for the next 4 days.

Results: There was a mean improvement in sodium concentration by 5 mEq/L (p = 0.001) in patients receiving tolvaptan, whereas no significant improvement was seen in the placebo group (p = 0.33). Significant improvement in Likert score was observed in both the groups (p = 0.001), even though there was no difference between both the groups. Dry mouth and thirst were the most commonly occurring adverse effects observed in both the groups. There were no significant hemodynamic changes with tolvaptan therapy.

Conclusion: Tolvaptan at a dose of 15 mg is effective in reversing hyponatremia in acute heart failure and may be a suitable option in these patients.

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1. Introduction

Hyponatremia is a condition characterized by plasma sodium less than 135 mEq/L and is a complication that is seen in over 20% of patients with heart failure. \(^1\) When hyponatremia is left untreated, it can result in severe neurological symptoms, such as seizures and obtundation. \(^2,3\) Hyponatremia has been shown to be associated with increased rate of rehospitalization, length of stay, utilization of greater hospital resources, increased complications, and greater economic burden. \(^4\) Studies have also shown that hyponatremia is a critical predictor of survival in patients with heart failure. \(^5,6\) Arginine-vasopressin (AVP) concentration is disproportionally elevated in decompensated heart failure and hyponatremia. The increased AVP is responsible for the impaired free water clearance in heart failure. One of the mechanisms responsible for this is the increase in the number of AQ2 water channels in the collecting duct that promote excess water retention resulting in hypervolemia and hyponatremia. \(^7\) Thus vasopressin plays a central role in the development of hyponatremia in heart failure. Loop and thiazide diuretics are considered to be the mainstay therapy for reversal of complications related to water retention. However, use of such diuretics is known to be associated with worsening of hyponatremia, renal dysfunction, and hypotension due to loss of intravascular volume with sodium depletion. \(^8-10\)

Tolvaptan, a non-peptide vasopressin type 2 receptor antagonist, is now available for patients with heart failure with hyponatremia. Tolvaptan stimulates free water clearance by inhibiting vasopressin-mediated water reabsorption in the renal collecting ducts. \(^11,12\) Studies have been published on the efficacy and safety of tolvaptan in patients with heart failure. The EVEREST trial, which included 4133 patients from the American and European population, showed that tolvaptan when added to standard diuretic therapy was able to improve most of the signs and symptoms of heart failure. \(^13\) In acute heart failure, tolvaptan at doses of 15–45 mg was able to reverse the signs of fluid overload in Japanese population. \(^14\) The drug was approved in India in 2012 for the treatment of hyponatremia associated with SIADH or euvolemic or hypervolemic hyponatremia due to CHF, cirrhosis, or SIADH. Since there are no clinical trials performed with tolvaptan in the Indian population till date, we performed this study to evaluate the short-term efficacy of tolvaptan in patients with acute heart failure and hyponatremia.

2. Methodology

This study was a randomized placebo-controlled double-blinded clinical trial that was conducted in the Department of Cardiology at SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India between April 2013 and August 2014. The protocol was approved by the Institute Ethics Committee of SRM Medical College Hospital and was registered in the Clinical Trial Registry of India CTRI/2013/05/003643.

2.1. Inclusion criteria

We included patients admitted with a clinical diagnosis of acute heart failure and concomitant hyponatremia presenting with dyspnea at rest or minimal exertion with evidence of at least one of the following features, such as orthopnea, peripheral edema, elevated JVP, pulmonary rales, or congestion on chest X-ray.

2.2. Exclusion criteria

Patients with systolic blood pressure less than 90 mmHg, serum sodium greater than 140 mEq/L, and serum creatinine greater than 3 mg/dl were not included in the study. Patients with history of acute coronary syndrome in past 4 weeks, valvular heart disease and terminal illness due to other causes, pregnant, and nursing women were also excluded from the study.

All demographic information, such as age, sex, previous medical history, clinical features, current drug history, and routine laboratory investigations were recorded. Written informed consent was taken from all the patients included in the study. Patients were randomized using a computer-generated randomization sequence (Random Allocation software, version) to receive tolvaptan 15 mg or placebo in a 1:1 ratio for a maximum duration of 5 days. The protocol required that the study drug/placebo be stopped if the plasma concentration of sodium exceeded 145 mEq/L, irrespective of the number of days of therapy. Block randomization was performed with a block size of 6. Allocation concealment was maintained using serially numbered opaque sealed envelopes and was maintained by one of the investigators not involved in patient recruitment. Background medical therapy was given as directed by the treating cardiologist. There was no restriction applied on the dose of diuretic used in the study patients.

2.3. Measurement of end points

The plasma sodium and the patients perception of dyspnea were assessed before administration of the study drug or placebo. The patient’s perception of dyspnea was assessed using Likert score. The score was recorded as –3 to +3, with −3 being markedly worse, −2 being moderately worse, −1 mildly worse, 0 as no change, +1 being mildly better, +2 being moderately better and +3 being markedly better. Plasma sodium, Likert score, urine output and adverse events were recorded daily for 5 days. The adverse events which we mainly looked for in the study patients were dry mouth, thirst, polyuria, ventricular extrasystoles, constipation, atrial fibrillation, ventricular tachycardia, worsening cardiac failure, hypotension, hypokalemia, and worsening renal failure. Patients were assessed at the end of 30 days to assess cardiovascular outcomes such as death, recurrent hospitalization, and revascularization.

ES and MG were involved in designing the study protocol. CRM, KA, BK, and ES were involved in recruiting patients. MR, KA, BK, and AJ were involved in data collection. MG and AJ performed the statistical analysis. The manuscript was prepared by AJ and MG and was edited by CRM and ES. All authors approved the final version of the manuscript.
2.4. Statistical methods

Data are expressed as mean ± SD or median with interquartile range or percentages. The baseline characteristics of the study patients were compared using Student’s t-test or Pearson’s Chi-squared test. The sodium concentration before and after 5 days of therapy with drug therapy in each group was compared using paired t test, and the difference between the change in sodium concentration in tolvaptan and placebo groups was compared using independent ‘t’ test. The Likert score between D1 and D5 was compared using Wilcoxon signed rank test. The BP and heart rate before and after therapy with study drug and placebo were also compared using paired t test. In patients who did have data of D4 or D5, the last observation was carried forward (LOCF). A p value of <0.05 was considered statistically significant. Data were analyzed using SPSS v.16.

3. Results

A total of 51 patients with acute decompensated heart failure were enrolled in the study. Most patients had mild to moderate hyponatremia. 25 patients were randomized to tolvaptan 15 mg and 26 patients received placebo (Fig. 1). The study drug was given for a time period of 5 days. Background medical therapy was given as directed by the treating cardiologist. There was no restriction applied on the dose of diuretic used in the study patients.

Fig. 1 – Flowchart showing study recruitment.
Table 1 – Baseline characteristics of study patients.

| Characteristic | Tolvaptan (n = 25) | Placebo (n = 26) | p value |
|---------------|--------------------|------------------|---------|
| Age (years)   | 58.9 ± 12.1        | 57 ± 12.0        | 0.71    |
| Male (%)      | 19(76.0)           | 17(65.4)         | 0.40    |
| Diabetes mellitus (%) | 14(60.9) | 13(50)  | 0.44    |
| Hypertension (%) | 11(44.0) | 10(38.5)  | 0.68    |
| Smoking (%)   | 3(13.0)            | 4(16)            | 0.77    |
| Dyslipidemia (%) | 3(13.0) | 4(16)  | 0.77    |
| Arterial fibrillation (%) | 2(8.3)  | 3(12)  | 0.67    |
| Previous myocardial infarction (%) | 8(34.8) | 12(48)  | 0.35    |
| Previous hospitalization for HF (%) | 11(50) | 13(50) | 0.87    |
| Previous CARG (%) | 3(13.0) | 5(19.2)  | 0.55    |
| CRF (%)       | 5(21.7)            | 3(12.0)          | 0.36    |
| PVD (%)       | 3(13.0)            | 0                | 0.06    |
| Stroke (%)    | 1(4.5)             | 2(7.7)           | 0.65    |
| Previous COPD (%) | 1(4.5) | 2(7.7)  | 0.62    |
| BMI (kg/m²)   | 23.3 ± 3.2         | 27.4 ± 5.7       | 0.01    |
| SBP (mmHg)    | 114.6 ± 16.9       | 122.4 ± 21.6     | 0.28    |
| DBP (mmHg)    | 73.5 ± 6.78        | 80.1 ± 14.5      | 0.07    |
| Heart rate (beats/min) | 93.0 ± 22.1 | 90.3 ± 15.0 | 0.65    |
| Raised jugular venous pulse (%) | 6(24) | 9(34) | 0.72    |
| Pedal edema (%) | 11(44) | 9(34)  | 0.75    |
| Rales (%)     | 4(16)              | 7(26)            | 0.49    |
| Urea (mg/dl)  | 49.3 ± 28.1        | 46.2 ± 38.1      | 0.74    |
| Creatinine (mg/dl) | 1.3 ± 0.56 | 1.3 ± 0.69 | 0.88    |
| LVEF (%)      | 31.9 ± 12.2        | 29.2 ± 8.7       | 0.36    |

Values are expressed as means ± SD or frequency with percentages. BMI: body mass index; CARG: coronary artery bypass graft; COPD: Chronic obstructive pulmonary disease; CRF: chronic renal failure; DBP: diastolic blood pressure; HF: heart failure; LVEF: left ventricular ejection fraction; PVD: peripheral vascular disease; SBP: systolic blood pressure.

3.1. Baseline characteristics of patients

Table 1 shows the baseline characteristics of the randomized patients. No significant difference was found in the baseline characteristics of the patients between the two groups except the increased frequency of PVD in the tolvaptan group. There was no difference in drug therapy between the two groups (Table 2).

3.2. Serum sodium concentration

Among patients in tolvaptan therapy there was a mean improvement in sodium concentration by 5 mEq/L that was statistically significant (p = 0.001). There was no improvement in serum sodium levels among patients in the placebo group (p = 0.33). The change in sodium concentration between day 5 and day 1 was compared between the two study groups. There was a significant difference in the improvement seen in the tolvaptan group compared to placebo (Table 3). The progression of sodium is displayed in Fig. 2.

3.3. Change in Likert score

We also observed mean changes in Likert’s score for all patients in the both groups from day 1 to day 5, as seen in

Table 2 – Drug therapy among the study patients.

| Drugs          | Tolvaptan (n = 25) | Placebo (n = 26) | p value |
|----------------|--------------------|------------------|---------|
| ACE inhibitors | 9(36.0)            | 12(46.2)         | 0.32    |
| Dobutamine     | 8(32.0)            | 15(53.8)         | 0.09    |
| Dopamine       | 1(4.0)             | 1(3.8)           | 0.74    |
| Furosemide     | 21(84.0)           | 26(100)          | 0.05    |
| Digoxin        | 7(28.0)            | 10(38.5)         | 0.31    |
| Trimetazidine  | 12(48.0)           | 13(50.0)         | 0.55    |
| Aspirin        | 8(32.0)            | 7(26.9)          | 0.46    |
| Clopidogrel    | 12(48.0)           | 13(50)           | 0.55    |
| Heparin        | 10(40.0)           | 6(23.1)          | 0.15    |
| Statins        | 16(64.0)           | 15(57)           | 0.43    |
| Ixabradine     | 2(8.0)             | 4(15.4)          | 0.35    |
| Nitrates       | 15(60.0)           | 11(42.3)         | 0.16    |
| Spironolactone | 16(64.0)           | 21(80.8)         | 0.15    |
| Olmesartan     | 0                  | 1(3.8)           | 0.51    |
| Nicorandil     | 5(20.0)            | 4(15.4)          | 0.47    |
| Beta blockers  | 10(40.0)           | 9(36.4)          | 0.62    |
| Amiodopine     | 4(16.0)            | 4(15.4)          | 0.62    |
| Amiodarone     | 1(4.0)             | 1(3.8)           | 0.74    |
| Verapamil      | 1(4.0)             | 0                | 0.49    |

Table 3. There were significant changes in both the groups (p = 0.001). However there was no significant difference in the changes seen in Likert score between the two study groups. The progression of Likert score over 5 days is displayed in Fig. 3.

3.4. Adverse effects

There were no serious adverse events attributable to the study drug. Table 4 shows the frequency of adverse events observed in both the study groups. Dry mouth and thirst were the most common adverse effects seen among the study patients. Patients were followed up for 30 days from the day of admission to assess major adverse cardiovascular events. A total of four patients (two in each group) died within 30 days of hospital admission. Among them, three occurred during the period of hospitalization. All four deaths were due to refractory LV failure. There was an increase in the number of recurrent hospitalizations in the tolvaptan group within 30 days, but this was not statistically significant (p = 0.55).

Fig. 2 – Change in sodium concentration over 5 days of therapy in both the study groups.
Patients with HF had higher baseline levels of sodium. In our study, the mean change seen after 24 h of tolvaptan 15 mg therapy was 3.31 mEq/L. Kinugawa et al. found that in patients with baseline sodium <135 mEq/L, tolvaptan was able to significantly increase the plasma sodium concentration, a finding that was not seen in those with baseline sodium >135 mEq/L. A maximal increase by 15 mEq/L was observed among patients with ADHF at the end of 7 days in an observational study performed in 40 patients. Although it can be hypothesized that a higher dose of tolvaptan could have led to greater increase in sodium levels, earlier studies have not demonstrated a dose-dependent rise in sodium levels. This finding is intriguing considering the fact that dose-dependent aquaretic effects have been observed in studies performed on healthy volunteers. Nevertheless, this is a beneficial effect to avoid the development of hyponatremia.

Patients who received tolvaptan did have an improvement in dyspnea as assessed by Likert score over 5 days, but this was not significantly different from that observed in the placebo. In contrast, a post hoc analysis, conducted by Pang et al. in his study, observed that majority of patients in the study had an improvement in dyspnea at all time points relative to hospital admission, with a significant statistically higher rate in tolvaptan group compared with placebo group in addition to standard medical therapies. In a study conducted by Hauptman et al., more patients with hyponatremia receiving tolvaptan had a better improvement of dyspnea compared to placebo. In patients with normonatremia, there were a lesser number of cases that had dyspnea improvement in tolvaptan compared to placebo. As most of the patients in our study had mild to moderate hyponatremia, it could possibly explain the lack of substantial benefit of tolvaptan over placebo in dyspnea relief. In addition, our study was not powered sufficiently to demonstrate the improvement in dyspnea.

4. Discussion

To the best of our knowledge, this is the first randomized clinical trial on the efficacy of tolvaptan in hyponatremia in the setting of HF among Indian population. Our study showed that tolvaptan at a dose of 15 mg given for 5 days reverses the hyponatremia in patients with acute decompensated HF. There was a mean increase of sodium by 6.7 mEq/L at the end of 5 days of tolvaptan therapy. The findings of our study are consistent with other published studies. A study by Gheorgiade et al. had also shown that patients receiving tolvaptan in different doses ranging from 30 to 60 mg had a mean increase in sodium by 4 mEq/L within 24 h of therapy. In our study, the mean change seen after 24 h of tolvaptan 15 mg therapy was 3.31 mEq/L. Kinugawa et al. found that in patients with baseline sodium <135 mEq/L, tolvaptan was able to significantly increase the plasma sodium concentration, a finding that was not seen in those with baseline sodium >135 mEq/L. A maximal increase by 15 mEq/L was observed among patients with ADHF at the end of 7 days in an observational study performed in 40 patients. Although it can be hypothesized that a higher dose of tolvaptan could have led to greater increase in sodium levels, earlier studies have not demonstrated a dose-dependent rise in sodium levels. This finding is intriguing considering the fact that dose-dependent aquaretic effects have been observed in studies performed on healthy volunteers. Nevertheless, this is a beneficial effect to avoid the development of hyponatremia.

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3.5. Hemodynamic changes

Tolvaptan showed neither a significant reduction in the blood pressure nor the heart rate over the period of 5 days (p > 0.05). Patients in the placebo arm showed a significant drop in both systolic and diastolic BP at the end of 5 days (p < 0.01) without any change in heart rate (p = 0.07).
Tolvaptan did not cause a significant change in the heart rate or blood pressure during the study period and these findings are in line with earlier published reports on the lack of hemodynamic changes observed with the drug. In a double-blinded study investigating the effects of three doses of tolvaptan and placebo in patients with CHF by Gheorgiade et al., no vital changes in heart rate or systolic or diastolic blood pressure, in supine or standing position, were observed in the tolvaptan groups during the study. In a phase III, randomized, double-blind, placebo-controlled study (QUEST Study) conducted by Matsuji et al., there was a minimal difference in blood pressure or heart rate between the tolvaptan and the placebo groups. Udelson et al. in his multicenter, randomized, double-blinded, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction found no significant changes in blood pressure or heart rate after administration of tolvaptan or furosemide or their combination.

Dry mouth and thirst were the major adverse effects observed with tolvaptan in the present study. Although there were two deaths in the tolvaptan group, these were attributable to the recalcitrant AHF in these patients, rather than any effect of the study medication. One patient in our study discontinued the medication after the third day due to persistent nausea. In the study conducted by Gheorgiade et al., in which dry mouth, thirst, and polyuria, including urinary frequency, were higher in the tolvaptan-treated patients and only two patients in the 60-mg tolvaptan group discontinued the drug on account of polyuria. Most frequently reported adverse drug reactions observed in the study conducted by Inomata et al. were thirst, increased blood urea, and pollakiuria. Similarly no serious adverse effects were observed in the study by Matsuji et al. The small sample size and the short duration of drug administration precluded us from observing other adverse effects as seen in earlier studies.

5. Limitations

Although we were able to demonstrate the therapeutic potential of tolvaptan in this clinical trial, the study had certain limitations. As this was a single-center study, we were able to recruit only 51 eligible patients during the study period, who met the inclusion-exclusion criteria. Most of the patients in our study had only mild to moderate hyponatremia. For logistic reasons, we could not assess the body weight of the patients, an end point which has been used in some of the earlier studies to measure the drug effect.

6. Conclusion

Tolvaptan when given at a dose of 15 mg/day is effective in reversing hyponatremia when given over a period of 5 days. The drug was well tolerated with increased thirst and dry mouth being the most common adverse effects. Thus tolvaptan may be safely used to treat hyponatremia in the setting of acute decompensated heart failure.

Conflict of interest

The authors have none to declare.

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REFERENCES

1. Gross P, et al. Treatment of hyponatremia. Inter Med. 2006;47:885–891.
2. Filippatos TD, Elisa MS. Hyponatremia in patients with heart failure. World J Cardiol. 2013;5:317–328.
3. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1–S42.
4. Amin A, Deitelzweig S, Christian R, Friend K, Lin J, Lowe TJ. Healthcare resource burden associated with hyponatremia among patients hospitalized for heart failure in the US. J Med Econ. 2013;16:415–420.
5. Felker GM, Leimberger JD, Califf RM, et al. Risk stratification after hospitalization for decompensated heart failure. J Card Fail. 2004;10:460–466.
6. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290:2581–2587.
7. Nielsen S, Frekiar J, Marpes D, Kwon T-H, Agre P, Knepper MA. Aquaporins in the kidney: from molecules to medicine. Physiol Rev. 2002;82:205–244.
8. Imamura T, Kinugawa K, Ohtani T, et al. Assessment of quality of life during long-term treatment of tolvaptan in refractory heart failure: design and rationale of the AQUA-TLV study. Int Heart J. 2014;55:264–267.
9. Inomata T, Izumi T, Matsuji T, Hori M, Hirayama A, Tolvaptan Investigators. Phase III clinical pharmacology study of tolvaptan. Cardiaco Drugs Ther Spons Int Soc Cardiaco Pharmacother. 2011;23(Suppl 1):S57–S65.
10. Goldsmith SR. Hyponatremia and outcomes in patients with heart failure. Heart Br Card Soc. 2012;98:1761–1762.
11. Patra S, Kumar B, Harlalka KK, 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 Off J Gulf Heart Assoc. 2014;15:1–5.
12. Matsuji T, Hori M, Izumi T, Fukunami M, Tolvaptan Investigators. Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST).
13. Konstam MA, Gheorghiade M, Burnett JC, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297:1319–1331.

14. Matsuzaki M, Hori M, Izumi T, Asanoi H, Tsutamoto T, Tolvaptan Investigators. Effects of tolvaptan on volume overload in Japanese patients with heart failure: results of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Cardiovasc Drugs Ther Spons Int Soc Cardiovasc Pharmacother. 2011;25(Suppl 1):S19–S31.

15. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation. 2003;107:2690–2696.

16. Kinugawa K, Sato N, Inomata T, et al. Efficacy and safety of tolvaptan in heart failure patients with volume overload – an interim result of post-marketing surveillance in Japan. Circ J. 2014;78:844–852.

17. Kim SR, Hasunuma T, Sato O, Okada T, Kondo M, Azuma J. Pharmacokinetics, pharmacodynamics and safety of tolvaptan, a novel, oral, selective nonpeptide AVP V2-receptor antagonist: results of single- and multiple-dose studies in healthy Japanese male volunteers. Cardiovasc Drugs Ther Spons Int Soc Cardiovasc Pharmacother. 2011;25(Suppl 1):S3–S17.

18. Pang PS, Gheorghiade M, Dihu J, et al. Effects of tolvaptan on physician-assessed symptoms and signs in patients hospitalized with acute heart failure syndromes: analysis from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) trials. Am Heart J. 2011;161:1067–1072.

19. Hauptman PJ, Burnett J, Gheorghiade M, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail. 2013;19:390–397.

20. Udelson JE, Blisker M, Hauptman PJ, et al. A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. J Card Fail. 2011;17:973–981.