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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 disproportionately 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.