Use of Tolvaptan 15 mg in Heart Failure Patients to Improve Sodium Level (Serum & Urinary) and Urinary Osmolality

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Decompensated Heart Failure (HF) due to volume overload often results in adverse clinical outcomes. Hyponatremia has been reported to be a potent predictor of poor outcome in patients hospitalized for heart failure (HF). The aim of the study was to observe improvement in serum and urinary sodium along with urinary osmolality in HF patients due to any cause. 25 patients with Heart failure were recruited. Their body weight, serum sodium, urinary sodium and urinary osmolality were measured at admission and at one week after starting of Tolvaptan 15 mg. Out of 25 patients, 20 (80%) were males and 5 (20%) females having mean age of 63.28 year. 10 (40%) patients were between 61-70 year of age, followed by 9 (36%) patients were between 51-60 year. 16 (64%) patients had old ischemic heart disease, 5 (20%) had diabetes, 2 (8%) had valvular and 2 (8%) had idiopathic dilated cardiomyopathy as cause of heart failure. 24 (96%) patients had reduced ejection fraction (mean value 30%), while 1 (4%) had preserved ejection fraction. 14 (56%) patients had acute decompensated heart failure, while 11 (44%) had acute on chronic decompensated heart failure. All 25 (100%) patients were on optimal medical management for heart failure. It was found that mean weight of the patients was reduced significantly at 1 week follow up (62.52±9.32 kg to 61.4±9.20 p value 0.001). It was also found that mean serum sodium and urinary sodium level significantly improved at 1 week follow up (129.64±5.64 mmol/L to 136.28±4.48 mmol/L, p value 0.001 & 46.20±34.30 meq/L to 28.12±10.98 meq/L, p value 0.004 respectively). Tolvaptan acts as aquaretics without affecting urinary osmolality with reduction of body weight and increases serum sodium level. It also improves dyspnea in heart failure patients.

Keywords: Heart failure, Hyponatremia, Urinary sodium, Urinary osmolality, Body Weight, Tolvaptan

INTRODUCTION

Hyponatremia is a commonly found in Congestive Heart Failure (CHF) and the most common electrolyte abnormality found in hospitalized patients with HF [Gerasimos Filippatos FD et al., 2009, Oren RM et al., 2005]. In patients hospitalized with HF plasma sodium concentration below 135 mmol/L is considered as Hyponatremia [Ghali JK et al., 2010, Bettari L et al., 2010]. It is recommended that such patients are followed in specialized HF clinics [Dickstein K et al., 2008]. It has been found U-shaped association with mortality risk in heart failure patient, when serum sodium is 135-139 mmol/L, patient had high mortality risk while with 140-145 mmol/L had low risk [Deubner et al., 2012]. Those patients should be managed with optimal management of diuretic therapy and strict compliance with fluid restriction [Deubner et al., 2012]. Pathophysiologically elevated levels of plasma vasopressin is primarily responsible for free water retention and hyponatremia in a heart failure patient [Gerasimos Filippatos FD et al., 2009].

Elevated vasopressin level is associated with more severe clinical manifestations, [Gustafsson F et al., 2005, Lee CR et al., 2003, Goldsmith SR et al., 1983, Szatalowicz VL et al., 1981] where alternative signals, such as haemodynamic and neurohormonal factors, override the suppressive effect of hypo-osmolality in driving vasopressin secretion [Francis GS et al., 1990]. Study by [Aronson et al. 2012], showed improved Serum sodium levels in such patients, the majority of whom had heart failure, with the V2-selective vasopressin receptor antagonist, Sarvpantan. It has found effective in treating the patients with heart failure. Though diuretics have been the
mainstay in the treatment of fluid retention, but their use has been associated with adverse neurohormonal activation, [Uretsky BF et al., 1985, Francis GS et al.,1985] worsening renal function, electrolyte abnormalities, increased parathyroid hormone levels, and urinary calcium and magnesium excretion [Bayliss J et al., 1987, Butler J et al., 2004, Greenberg A et al., 2000]. Use of it is also associated with proinflammatory vascular response, [Weber KT et al 2004] which has adverse effect on remodeling, and higher doses of diuretics have been associated with higher mortality. [Weber KT et al., 2004, McCurley JM et al., 2004, Cooper HA et al., 1999, Ahmed A et al., 2006, Hasselblad V et al., 2007]

Tolvaptan is selective vasopressin receptor 2 antagonist. It acts as aquaretic. It is used for hyponatremia associated with congestive heart failure, cirrhosis and syndrome of inappropriate antidiuretic hormone. [G. Michael et al., 2017]

The aim of the study was to observe the effectiveness of Tolvaptan 15 mg in patients of Heart Failure in terms of body weight reduction, improvement of serum & urinary sodium levels, urinary osmolality and dyspnea improvement.

METHODS

Study design and assessments

This was an interventional study, carried out at tertiary care center in which patients of either gender of age more than 18 years with signs and symptoms of acute, chronic, acute on chronic HF, defined as requiring standard HF treatment were included in the study if they had both documented left ventricular ejection fraction (LVEF) determination (by Simpson volumetric method), reduced or preserved, on admission. whereas patients with Acute ST elevation myocardial infarction or stroke; major surgery within 3 months, hypothyroidism, tuberculosis, active myocarditis and chronic kidney disease were excluded.

Total 25 consecutive patients who were admitted in tertiary care centre with history and clinical findings of heart failure with hyponatremia (euvolemic or hypervolemic) and on optimal congestive cardiac failure medications were given Tolvaptan 15 mg. Before starting drug patient parameters, body weight, serum sodium, spot urinary sodium, spot urinary osmolality was measured. After one week of starting Tolvaptan 15 mg, same parameters were measured.

Venous sample was taken for serum sodium measurement. Urinary sodium and osmolality were measured with spot urine sample. Body weight was measured as per WHO norm [Mielniczuk LM et al., 2008, WHO technical report series 854, 1995]. Serum sodium and urinary sodium were analysed using auto analyzer Hitachi P800/ISE 900. Urinary osmolality was analysed using osmometer. Normal values for serum sodium, urinary sodium and osmolality were 138-145 mmol/L, 15-200 meq/L and 50-650 mosm/kg of water as laboratory reference values.

Statistical Analysis

In this study discrete data are presented as frequencies and percentages. Continuous variables as mean and standard deviation. Independent t test was used to find significant mean difference of parameters. Non parametric test wilcoxon signed rank test was applied to find statistical significance. P value<0.05 was consider statistically significant. Data were analysed using SPSS version 16.

RESULTS

Table 1: Baseline characteristics of the patients.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>80%</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>20%</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>16</td>
<td>64%</td>
</tr>
<tr>
<td>Valvular</td>
<td>2</td>
<td>08%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>5</td>
<td>20%</td>
</tr>
<tr>
<td>DCMP (Idiopathic)</td>
<td>2</td>
<td>08%</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>08%</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>08%</td>
</tr>
<tr>
<td>IV</td>
<td>21</td>
<td>84%</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>24</td>
<td>96%</td>
</tr>
<tr>
<td>≥ 50</td>
<td>01</td>
<td>04%</td>
</tr>
</tbody>
</table>

Table 1 shows that in present study 4/5th of enrolled patients were male whereas remaining were female and majority of them were in 6th decade of their age with the mean age of 63.28±11.57 years. Among all the patients, Ischemic Heart Disease (64%) was found as most common cause of Heart Failure followed by Diabetes Mellitus (20%), Valvular Heart Disease and Idiopathic Dilated Cardiomyopathy respectively. Majority (84%) of our study patients had NYHA Class IV symptoms with significantly reduced ejection fraction (96%). More than half of the patients (56%) were admitted with acute cardiac failure symptoms whereas 44% of the patients had acute on chronic heart failure symptoms. 100% patients were on optimal cardiac failure drugs starting from Angiotensin Converting Enzyme Inhibitors (ACEI)/ Angiotensin Receptor Blockers (ARBs), Beta Blockers (BB), Aldosterone antagonist, Diuretics, etc.
Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV) showed that tolvaptan was associated with body weight reduction at 24 hours and often-normalized serum sodium levels among patients with hyponatremia. However there was no long-term mortality improvement but lower mortality was found in patient with clinical congestion ,hyponatremia or abnormal renal function.

In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial showed no effect of tolvaptan initiated for acute treatment of patients hospitalized with HF on long-term mortality or HF-related morbidity nor was there any interaction between plasma sodium (hyponatremia) and treatment effect on outcome in this trial. This study demonstrated a beneficial volume unloading by the selective V2 receptor blocker Tolvaptan in participants with HF and volume overload. Tolvaptan significantly reduced body weight 1 day after administration and maintained this effect with continued administration over the 1-week treatment period. Body weight reduction occurred irrespective of baseline LVEF (Preserved or Reduced). Improvements in orthopnea and dyspnea were also observed in the Tolvaptan group during the1-week course of therapy. The beneficial effects of Tolvaptan on body weight were noted due to possible aquaretic effect of Tolvaptan in patients with HF. The sustained reductions in body weight seen in the current study are consistent with those reported with Tolvaptan in patients with HF [Gheorghiade M et al 2003., Verbrugge FH et al2015, Gheorghiade M et al., 2004].

Fluid retention is considered as common cause for development of the Heart Failure. Diuretics are main stay in its management; however, treatment with these agents may be associated with unfavourable effects like electrolyte abnormalities, worsening renal function, and activation of the neurohormonal system. In contrast, the actions of vasopressin antagonists are mediated by blocking the activation of V2 receptors in the collecting ducts, thus leading to decreased free water resorption [Konstam MA et al 2007]. This aquaretic effect—electrolyte-free water excretion—combined with no worsening renal function or activation of the neurohormonal systems place this class of drugs as a useful complement to currently available agents for the treatment of HF and potentially better alternative to diuretics.

Recent research studies concluded that Tolvaptan add on therapy neither improve worsening of renal function nor short term mortality in acute decompensated heart failure patient [Guang Ma et al., 2019]. Main benefit found was an add on therapy which reduced body weight and improved serum sodium of the patient and these results are consistent with our study results.

Patient with renal impairment and diuretic resistance low dose tolvaptan i.e. 15 mg as add on therapy increase urine
volume without deteriorating renal function [Inomata T et al., 2017]. Tolvaptan added to standard HF therapy demonstrated a favorable safety profile in our study. Further investigation is needed to identify the ideal Tolvaptan dosing regimen to optimize fluid/electrolyte balance in patients with HF, as the we used a fixed-dose regimen.

LIMITATIONS

This study was designed to assess the effects of fixed dose Tolvaptan 15 mg in HF with very limited numbers of patients (i.e.25). Probably long term follow up study required to evaluate morbidity and mortality benefit of drug.

CONCLUSION

In our patients with HF and volume overload, the addition of Tolvaptan 15 mg once daily to standard therapy reduced body weight, improved dyspnea, decrease urinary sodium excretion and was well tolerated. It also increases serum sodium level. It has no effect on urinary osmolality.

CONFLICT OF INTEREST: None

REFERENCES


Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, ZampinoM,Orlandi C; Tolvaptan


