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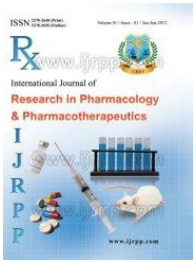

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Comparison of frequency of occurrence of hypokalaemia with torsemide versus furosemide in patients with chronic heart failure: randomized prospective study

C R Jayanthi[1], A Vinayak[*2], K R Raveendra[3], Divya Prakash[4]

[1]*Professor and Head, Department of Pharmacology*
[2]*Postgraduate student, Department of Pharmacology*
[3]*Professor, Dept. of General Medicine;*
[4]*Professor, Dept of Cardiology, Bangalore Medical College and Research Institute, K R Road, Fort, Bengaluru-560002*

***Corresponding author: A Vinayak**
Email: vinayak6491@gmail.com

ABSTRACT

Aim of the study

Loop diuretics are commonly used in heart failure to provide symptomatic relief. Furosemide and Torsemide are the most commonly prescribed loop diuretics for this condition. Although torsemide has been proven to be superior to furosemide in terms of efficacy, evidence is lacking regarding its safety in terms of frequency of occurrence of hypokalaemia.

Materials and Methods

This open label parallel group study was conducted considering 100 patients with chronic heart failure randomized into two groups to receive either oral torsemide 10 mg OD (Group T: n=50) or oral furosemide 20 mg BD (Group F: n=50). Baseline serum levels of Na^+, K^+ and Cl^- and ejection fraction (EF) were recorded and the study drugs were administered. Patients were followed up at 4, 8 and 12 weeks and at each visit, serum Na^+, K^+, Cl^-, and EF were noted.

Results

All the study participants completed the study and data was analyzed using per protocol analysis. Baseline characteristics were comparable between the groups in terms of age, gender, baseline serum electrolyte levels and ejection fraction. There was significant decrease in serum electrolyte levels in both the groups at each follow up. However, potassium levels in torsemide group was significantly greater as compared to furosemide group at 12 weeks (p=0.001). There was significant improvement in EF at each follow up in both the groups. However, there was no significant difference between the groups. The number of patients with reduced EF decreased over each visit. No adverse reaction related to the study drugs were reported for the entire study period.

Conclusion

Oral torsemide 10 mg OD is safer than oral furosemide 20 mg BD in reducing the frequency of occurrence of hypokalaemia in patients with chronic heart failure.

Keywords: Torsemide; Hypokalaemia; Furosemide; Chronic heart failure

INTRODUCTION

Heart failure describes the state that develops when the heart cannot maintain an adequate cardiac output or can do so only at the expense of elevated filling pressures [1]. Chronic heart failure is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues [2]. It is one of the leading causes of mortality of cardiac origin all over the world. 8 out of 10 admissions to the hospital in-patients over the age of 70 years are due to heart failure. When cardiac output falls, stimulation of the renin–angiotensin–aldosterone system leads to vasoconstriction, sodium and water retention, and activation of the sympathetic nervous system. These effects are mediated by release of angiotensin II, aldosterone, endothelin-1 and arginine vasopressin [1]. This causes a decrease in renal blood flow and an increase in the filtration fraction resulting in an increase in water and sodium retention and consequently edema [3].

Diuretics are the mainstay of management of this syndrome of fluid overload. Among diuretics, loop diuretics are important for the symptomatic treatment of CHF and are currently recommended by the European Society of Cardiology (ESC), the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines on the treatment of heart failure [4]. Furosemide is the most commonly used diuretic which acts by inhibiting Na^+ K^+ $2Cl^-$ symporter in the thick ascending loop of Henley. However, it has a plasma half-life of about 1.5 hours with oral bioavailability of about 60%.

Torsemide is a sulphonylurea compound and is available in an oral formulation and has a plasma half-life of about 3.5 hours with oral bioavailability of about 80% [5]. As it has an onset of action of 1-hour, peak onset of 1-2 hours, longer half-life, a longer duration of action of 6-8 hours and a higher bioavailability, [6] torsemide would be more beneficial than furosemide in patients with systolic HF. Moreover, torsemide may have beneficial effects on myocardial fibrosis, ventricular structure and the neuro hormonal milieu [7].

Although the efficacy of torsemide over furosemide is well established, there is paucity of studies with respect to its safety in terms of frequency of occurrence and degree of hypokalaemia. Hence this study is undertaken to assess the effect of torsemide versus furosemide on serum potassium levels in patients with chronic heart failure.

MATERIALS AND METHODS

Patient selection and recruitment

After obtaining approval from institutional ethics committee, this randomized open label study was conducted between August to December 2019 in hospitals attached to Bangalore Medical College and Research Institute, Bengaluru. 100 patients diagnosed with chronic heart failure according to Framingham Diagnostic Criteria and staged according to New York Heart Association functional stages as II and III requiring diuretic therapy for maintenance of euvolaemia aged between 18-60 years of either gender, willing to give written informed consent were randomized in the ratio of 1:1, into two groups of 50 each using computer-generated simple randomization technique. Patients with acute decompensated heart failure, impaired serum potassium levels, on treatment with potassium supplements or other diuretics, patients with uncontrolled diabetes, hypertension, impaired renal function tests, acute coronary syndromes, or any indications for cardiac surgery were excluded.

Group T (n=50) received oral tablets of Torsemide 10 mg/day administered once daily and Group F (n=50) received oral tablets of Furosemide 40 mg/day administered as equally divided doses 12 hours apart. In addition, both the groups received oral atorvastatin 20 mg hs, oral clopidogrel 75 mg od, carvedilol 3.125 mg bd for 2 weeks, subsequently increased to 6.25 mg bd. Baseline characteristics were recorded from all eligible patients. A recording of 2D echocardiogram with color Doppler was performed to note structural changes and to estimate

ejection fraction (EF). Baseline values of serum electrolytes were noted. Patients were followed up after 4, 8 and 12 weeks of initiation of treatment. At every visit, 2D echocardiogram with color Doppler was performed to note structural changes and to estimate EF. Serum electrolytes were assessed at each visit to note any changes. Any adverse drug reaction reported either on time of first visit or in subsequent follow ups were noted and reported in CDSCO-ADR form. Data obtained were analyzed for difference between as well as within the two groups in terms of serum levels of electrolytes and EF at every visit.

Statistical tests

Data obtained were entered and analyzed using Microsoft Excel. Categorical data were expressed as numbers and proportions with percentage and continuous data were expressed as mean ± standard deviation. Nonparametric data were analyzed using chi-square test. Parametric data were analyzed using unpaired 'T' test and repeated measures ANOVA. The time required for conversion from reduced EF to normal EF between the two groups was compared using Kaplan-Meier time to event analysis and log rank test.

Sample size estimation

Sample size was estimated considering 5% alpha error and 80% power. With a difference of hypokalaemia of 0.2 [8] and standard deviation of 0.3 [8], a sample size of 50 per group was estimated.

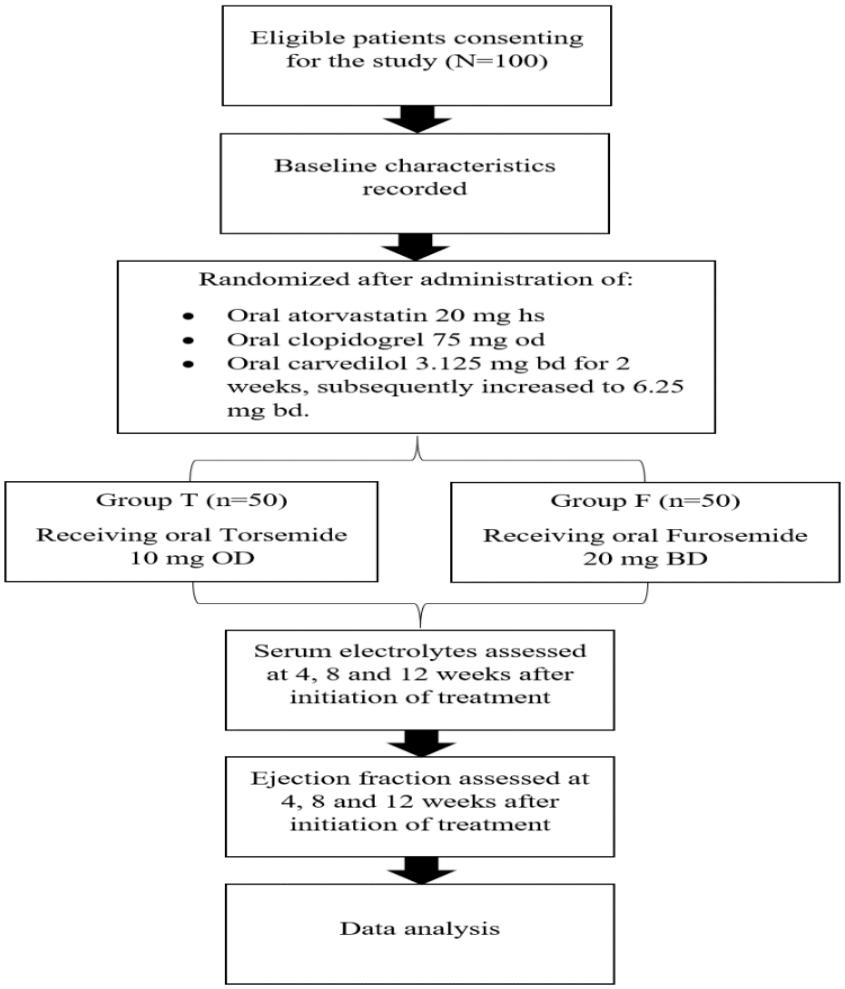

Figure 1: CONSORT participant flow diagram

RESULTS

Baseline characteristics were comparable between the groups with respect to age, gender, baseline serum electrolyte levels and baseline EF as presented in Table 1.

Table 1: Baseline characteristics of patients enrolled in the study.

Parameter		Group T	Group F	p value
Age in years (Mean±SD)		50.22±6.54	51.3±6.06	0.394$
Gender	Males	15	17	0.671@
	Females	35	33	
Baseline serum Na^+ in mmol/l (Mean±SD)		137.22±3.88	137.8±3.41	0.429$
Baseline serum K^+ in mmol/l (Mean±SD)		4.51±0.48	4.496±0.45	0.846$
Baseline serum Cl^- in mmol/l (Mean±SD)		103.5±1.78	102.9±2.73	0.196$
Baseline % EF (Mean±SD)		52.38±8.38	56±10.17	0.055$

p values estimated using $- unpaired t test and @- chi-squared test. SD: Standard Deviation.

Serum electrolyte levels at each follow up are represented in Table 2. There was a significant decrease in serum Na^+ and serum K^+ levels but non-significant decrease in serum Cl^- levels at every follow up in both the groups. Although there was no significant difference in serum K^+ levels between the groups at baseline or after 4 and 8 weeks of administration, there was a significant decrease in furosemide group compared to torsemide group after 12 weeks of administration. However, at each follow up, there was no significant difference in serum Na^+ and serum Cl^- levels between the groups.

Table 2: Serum electrolyte levels at every visit

Serum electrolyte levels in mmol/l at every visit		Group T	Group F	p value
Serum Na^+ (Mean±SD)	Week 4	134.04±3.89	135.02±3.06	0.165
	Week 8	131.5±3.59	132.32±3.38	0.243
	Week 12	129.08±2.78	129.3±2.91	0.700
Serum K^+ (Mean±SD)	Week 4	4.18±0.42	4.13±0.41	0.531
	Week 8	3.872±0.32	3.804±0.41	0.358
	Week 12	3.63±0.28	3.43±0.32	0.001*
Serum Cl^- (Mean±SD)	Week 4	102.32±1.89	102.8±1.94	0.214
	Week 8	101.26±2.47	101.98±2.08	0.117
	Week 12	100.18±2.59	100.96±2.51	0.129

p values estimated using unpaired t test. * indicates $p<0.05$ showing statistically significant difference. SD: Standard Deviation.

EF at every visit is represented in Table 3. There was significant improvement in the EF in both the study groups with no significant difference between the groups at each visit.

Table 3: Ejection fraction at every visit

Ejection Fraction in %	Group T	Group F	p value
Week 4 (Mean±SD)	57.2±6.98	60.02±8.53	0.055
Week 8 (Mean±SD)	62.7±5.70	64.04±6.88	0.074
Week 12 (Mean±SD)	66.86±4.27	67.36±5.51	0.292

p values estimated using unpaired t test. SD: Standard Deviation.

Proportion of patients with reduced EF over the entire study period is represented in Table 4. Effect of both the study drugs on improvement in EF was assessed as time taken for conversion to normal EF as depicted in Figure 2. The mean duration for conversion to normal EF in torsemide group was 4.16

weeks (95% CI: 2.96 to 5.37 weeks) and in furosemide group was 3.36 weeks (95% CI: 2.07 to 4.65 weeks). However, the difference was not statistically significant (p=0.659). No adverse reactions related to the study drugs were reported for the entire study period.

Table 4: Proportion of patients with reduced EF at every visit

Proportion of patients with reduced EF at every visit	Group T	Group F
Baseline	28/50 (56%)	20/50 (40%)
4 weeks	18/50 (36%)	14/50 (28%)
8 weeks	6/50 (12%)	8/50 (16%)
12 weeks	0/50 (0%)	0/50 (0%)

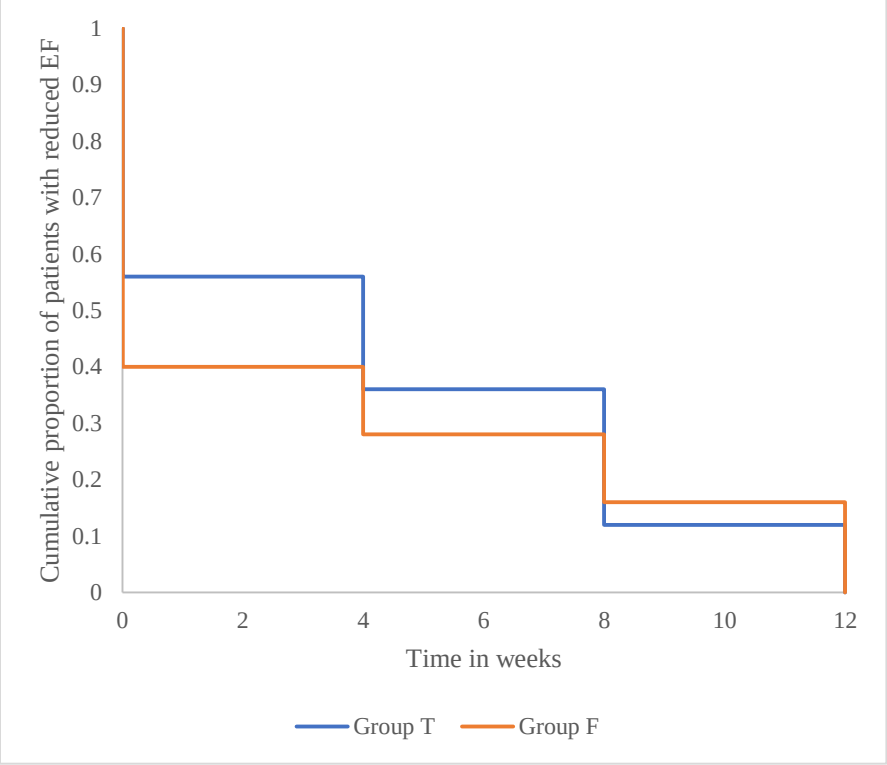

Figure 2: Figure depicting time required by patients in each group for conversion from reduced EF to normal EF

DISCUSSION

The present open label, randomized comparative study was designed considering 100 patients diagnosed of heart failure. The present study showed mean age of 50.76±6.29 years and a female preponderance. However, the INDUS study [9], reported the mean age of patients to be 58.3±10.4 years with male preponderance. Serum electrolytes in the present study decreased with increase in the duration of therapy with both the drugs. However, the serum potassium levels were significantly higher in torsemide group as compared to furosemide group after 12 weeks of treatment. As diuretics are administered over a prolonged duration in case of heart failure, torsemide proved to be more efficacious than furosemide in maintaining normal serum potassium levels. Although both the study groups showed hyponatremia, none of the patients were symptomatic. This may be due to the grade of hyponatremia being mild to moderate and also the duration for occurrence of hyponatremia, occurring over weeks. The potassium sparing effect has also been reported in previous studies [3, 6, 8 and 10]

In the present study, there was improvement in the EF in both the study groups, comparable to previous studies [8] However, among the patients presenting with reduced EF at baseline, the mean

duration of conversion to normal EF was lesser in furosemide group as compared to torsemide group and the difference was not statistically significant, similar to PROTECT trial [7]. Further studies are needed to confirm this finding. No adverse reactions related to the study drugs were reported for the entire study period.

Potassium plays a major role in normal functioning of all the cells as it is a major intracellular cation. It is also involved in maintenance of potential difference between either side of cell membrane of excitable tissues like nerves and muscles. Potassium also plays a role in acid-base balance by getting exchanged with extracellular proton. It also influences the rate of renal ammonium production [11]. Hypokalaemia causes hyperpolarization of membranes leading to non-responsiveness of excitable tissues [12]. There is malfunctioning of the heart manifested as altered electrical conduction, arrhythmias and also chances of sudden death [13].

Diuretics are commonly used to provide symptomatic relief in patients with chronic heart failure. Loop diuretics like furosemide and torsemide are the commonly used drugs in this condition [14, 15]. Being high efficacy diuretics, they act on the Na^+ K^+ $2Cl^-$ symporter on the thick ascending loop of Henle, preventing reabsorption of Na^+, K^+ and Cl^-. However, increased sodium concentration sensed by the cells of Lacis present in the distal convoluted tubule, leads to stimulation of the JG cells and initiation of Renin-Angiotensin-Aldosterone pathway. Aldosterone causes recruitment of the epithelial Na^+ channels in the distal part of distal convoluted tubule and collecting ducts leading to exchange of Na^+ and excretion of K^+ thus leading to hypokalaemia.

Torsemide increases urinary excretion of sodium, chloride and water but does not significantly alter GFR, renal blood flow or cause acid-base balance. Dose to dose kaliuretic effect of torsemide is approximately 3 times lesser than furosemide and 8 times more effective in natriuretic, chloruretic and diuretic effects. It is shown to be clinically well tolerated and effective in several short-term studies. The longer duration of action, potassium sparing effect, significantly better lowering of systolic blood pressure by torsemide seems to be ideal for treatment of heart failure when compared to furosemide. With the daily doses between 10-20 mg, tolerability data demonstrated a very low incidence of adverse effects, lower discontinuation rates and long-term safety. Thus, the present study adds to the evidence that torsemide is safer than furosemide in reducing of frequency of occurrence of hypokalaemia in patients with chronic heart failure.

Strengths of the present study include the design being randomized study conducted at a tertiary care center and the primary outcome being safety of torsemide as compared to furosemide in terms of frequency of occurrence of hypokalaemia in patients with chronic heart failure. Limitations of the present study are that urinary electrolyte levels, humoral factors like brain natriuretic peptide, plasma renin activity and serum aldosterone levels could not be assessed.

CONCLUSION

Torsemide 10mg OD maintains the serum potassium level and thus reduces the frequency of occurrence of hypokalaemia in patients with chronic heart failure.

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