COMPARATIVE EFFICACY AND TOLERABILITY OF LASORIDE AND SPIROMIDE IN CONGESTIVE CARDIAC FAILURE

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SUMMARY

Diuretics play primary role in fluid over loaded patients with CCF. Combination of potassium sparing agents with loop diuretics enhance the diuretic effect, conserve potassium and reduce the number of tablet. This study was carried out to see the efficacy, safety and tolerability of lasoride against spiromide. This was a short term, randomised single blind study. Patients were assessed for clinical, hemodynamic and biochemical changes. Patients were well matched regarding age, sex, weight, hemodyamaic and biochemical status. Both the drugs improved clinical signs and symptoms without much effect on biochemical status. Gastrointestinal side effects were more common in spiromide group (42% Vs 5%) and gynaecomastic was more frequent in spiromide group (25% Vs 2.5%) in lasoride ($p<0.05$). Both lasoride and spiromide were effective and safe; lasoride was better in tolerability.

INTRODUCTION

Management of patients with congestive cardiac failure revolves around reducing preload and afterload, optimizing heart rate and improving myocardial contractility.[1] Diuretics are employed in such patients to reduce preload. Patients with congestive cardiac failure (CCF) are usually fluid overloaded. Diuretics are of paramount importance in the management of such patients.

The choice of diuretic depends on its efficacy, effects on potassium and renal function and other adverse events. Various groups utilised include loop diuretics, thiazide and potassium sparing diuretics like spironolactone and amiloride. Loop diuretics are the most potent among these and are the

drugs of choice to get rid of fluid overload. They act, on the loop of henle and inhibit the active absorption of sodium and water. In the distal tubule, however, under the effects of rennin angiotensin system (RAS) and aldosterone the sodium is absorbed in exchange for potassium which is actively secreted, causing marked hypokalemia. In order to balance this, either potassium supplements are given or potassium sparing diuretics are used along with loop diuretics.

Spironolactone and amiloride are known to be weaker diuretics themselves but their main advantage is that they counter the active secretion and hence loss of potassium in the urine. Combining a loop diuretic with potassium sparing agent enhances diuresis, conserves potassium and obviates the need for extra tablets. Combination of diuretics have successfully been used in the treatment of CCF, the most common being frusemide with amiloride (lasoride) and frusemide with spironolactone (spiromide).

There is no prospective study reported in the literature comparing the two combinations in patients with congestive cardiac failure comparing their efficacy, effect on electrolytes, tolerability and side-effects. Especially in patients with renal impairment and with concomitant use of ACE inhibitors.

This study was designed to see the comparative efficacy, tolerability and safety of the two drugs in patients with CCF due to any etiology in the setting of outpatients.

MATERIAL AND METHODS

This was a short term, randomised, single blind study recruiting patients suffering form CCF of any etiologic origin, diagnosed recently or already on heart failure therapy. The study was conducted in the setting of outdoor clinic where patients seen routinely and in daily life were employed.

Detailed clinical history was taken, being assessed for NYHA class, they were examined and findings were documented. Patients were examined at the start and end of study. Standard therapy in the form of ACE inhibitor, digoxin and diuretics were given. Vasodilators were allowed but potassium supplements were not given unless there was any need for it.

The patients were excluded from study if they had severe liver failure, renal failure advanced cancer or other life threatening disease. After initial evaluation the patients were randomly assigned to lasoride or spiromide groups.

Electrolytes, BUN and creatinine were checked at the start and end of study Potassium was however, checked regularly and if there was any change in potassium, appropriate measures were taken.

The effects of two treatments on clinical parameters (weight, HR, BP) symptoms and signs were documented.

RESULTS

Between April to Sep. 1999 a total of 80 patients were studied of which 40 were in lasoride and 40 in spiromide group.

Majority of the patients completed study. The two groups were well matched regarding age, sex, weight, heart rate, blood pressure, and state of heart failure.

SPIROMIDE GROUP:
Patient characteristics:

Average age was 52 $\pm$ 17 with 60% were males. The etiology of CCF was Rheumatic heart disease in 30%, CAD in 55% and Congestive cardiomyopathy in 15%. Twenty six (65%) patients were in

NYHA class III, 13 (32.5%) were in II, and 1 in NYHA I class.

Haemodynamics:

Heart rate was 90 ± 6.7 beats per minute at the start and 84 ± 6.4 beats per minute at end if study. Blood pressure at start was systolic 125 ± 13 mmHg and diastolic 78 ± 14 and at the end of study 121 ± 17 mmHg and diastolic 77 ± 10. The change in heart rate and blood pressure registered a decrease but they were not statistically significant.

Followup:

The functional class of majority of patients treated with spiromide improved to better class ($p<0.01$). The patients in spiromide group revealed marked improvement in dyspnea, palpitation and ankle edema and there was increase in exercise capacity at the end of four weeks. Overall there was significant sense of well being ($p<0.01$). Chest crepitations disappeared and liver size reduced in most of patients (85%).

Side Effects:

The therapy was well tolerated and only 03 patients discontinued the treatment. Complaints regarding gastro intestinal side effects increased as the time passed by and at the end of study 42% Vs 5% at the beginning complained of G.I side effects ($p<0.01$). Gynecomestia was reported in 25% of patients treated with spiromide and it was significant enough to discontinue therapy in 7.5% of patients

Biochemistry:

Urea, Creatinine and electrolytes were checked at the start and at the end of four weeks or more frequently if clinically indicated. There was no rise in BUN and creatinine in the spiromide group. There was mild increase in serum potassium level but that too was clinically not significant. In a few patients with renal impairment the trend in increase of Potassium was more marked but not statistically significant. 85% patients were on various types of ACE inhibitors but no significant increase in Potassium was seen .

LASORIDE GROUP:
Patient characteristics:

Average age was 54 ± 15 with 55% were males. The etiology of CCF was Rheumatic heart disease in 35%, CAD in 45% and Congestive cardiomyopathy in 20%. Thirty (75%) patients were in NYHA class III , 9 (23.5%) were in II, and 1 in 20 NYHA I class.

Haemodynamics:

Heart rate was 88 ± 7.5 beats per minute at the start and 83 ± 6.2 beats per minute at the end of study. Blood pressure at start was systolic 120 ± 12 mmHg and diastolic 75 ± 10 and at the end of study 118 ± 13 mmHg and diastolic 74 ± 9 The change in heart rate and blood pressure registered a decrease but they were not statistically significant.

Followup:

The functional class of majority of patients treated with lasoride improved to a better class ($p<0.01$). Patients reported marked improvement in dyspnea, palpitation and ankle edema and there was increase in exercise capacity at the end of four weeks. Overall there was significant sense of well being ($p<0.01$). Chest crepitations disappeared and liver size reduced in a majority of patients (80%).

Side Effects:

The therapy was well tolerated and no one discontinued the treatment. No significant G.I side effects were seen Gynecomestia was reported in only one patient (2.5%).

Biochemistry:

Urea, Creatinine and electrolytes were checked at the start and at the end of four

weeks or more frequently if clinically indicated. There was no rise in BUN and creatinine in this group. About 90% patients were on various types of ACE inhibitors but no significant increase in Potassium was seen.

Comparative Analysis

Patient characteristics:- Mean age in spirodmide group was (52 Vs 54 years) in lasoride group. Regarding etiology of CCF, RHD in spiromide group was (30% Vs 35%) in lasoride group, CAD in spiromide group 55% Vs 45%) in lasoride group, cardiomyopathy in spiromide group (15% Vs 20%) in lasoride group.

Patients in spiromide group were in NYHA III (65% Vs 75%) NYHA II (33% Vs 23%) and NYHA I (3% Vs 2%) as compared to lasoride group

Hemodynamics: Average HR in spiromide group (90 Vs 88 BPM) in lasoride group.

Average systolic BP in spiromide group (125 Vs 120 mmHg) in lasoride group.

Average diastolic BP in spiromide group (78 Vs 75 mmHg) in lasoride group.

There was trend towards reduction in BP and HR in both groups but that too was clinically insignificant.

Side effects: both the therapies were generally well tolerated and only 3 patients (7.5%) in spiromide and none in lasoride group discontinued therapy.

G.I. side effects were more common in spiromide group (42% Vs 5%) in lasoride group (P<0.05)

Gynecomastia was also more prevalent in spiromide group (25% Vs 2.5%) in lasoride group (P<0.05)

Biochemistry: Urea, creatininee and electrolytes were checked at start and end of study or more frequently if indicated. There was no rise in urea and creatinin level in both groups.

There was mild increase in serum potassium level in both groups but it was clinically insignificant. In a few patients with renal impairment, the trend in rise of potassium was more marked but no statistically significant. Majority of patients (>80%) in both groups were on ACE inhibitor but no significant rise in potassium was seen.

The comparative analysis of spiromide and lasoride groups revealed that the lasoride had good efficacy in (62.5% Vs 32.5%) in spiromide group (P<0.01).

The tolerance good in 65% in lasoride and 20% in spiromide group (P<0.01)

Followup:

The functional class of majority of patients treated with both drugs improved to better class (p<0.01). The patients in both group revealed marked improvement in dyspnea, palpitation and ankle edema and there was increase in exercise capacity at the end of four weeks. Overall there was significant sense of well being (p<0.01). Chest crepitations disappeared and liver size reduced in majority of patients.

DISCUSSION

Management of CCF entails offering a favourable mileu in circulation to optimize the function of heart and ameliorate the clinical features due to reduced cardiacoutput and excessive fluid accumulation. Different drugs are used to achieve this end. Preload is reduced by employing diuretics and venodilators, afterload is decreased by using arteriolar dilators and digoxin is used to enhance myocardial contractility.[1]

In acute failure and fluid overloaded patient, diuretics play the most important

and often life saving role. Among diuretic classes loop diuretics are the most potent diuretics which are commonly used in such patients. These diuretics (frusemide, bumetanide) cause significant potassium loss. Human body has large reserves of potassium in the form of intracellular potassium and a normal serum potassium may sometimes give a false impression of overall potassium balance because potassium moves out of cells to maintain serum potassium at the cost of overall body deficit and is continuously being excreted in urine under the effects of diuretics. So in such situations regular monitoring and conservation of potassium is important to avoid any serious side effects due to hypokalaemia.

Potassium supplemented in tablet and syrup forms are poorly tolerated due to gastric irritation and adds to number of medications. The combination of frusemide with potassium sparing agents is a better choice as it enhances the diuretic effect, conserves potassium and simplifies and reduces the number of medicines to be taken. Addition of potassium sparing agents like Amiloride and Spironolactone to Frusemide increase efficacy and tolerability.

CCF is a state of secondary hyperaldosteronism.[2,3,4] The excess aldosteron has deleterious effects on cardiovascular system by causing retention of sodium and water, loss of potassium and magnesium, sympathetic stimulation, parasympathetic inhibition, myocardial fibrosis and impairment of vascular compliance.[3-11] Recent data shows the favourable effects of Spironolactone in the setting of CCF.

Amiloride has been used in combination with thiazide diuretics in all major hypertension trials and proven to be an effective and safe drug. It has the theoretical advantage to be used in the setting of CCF combined with frusemide. Its role in such a setting in direct comparison to Spironolactone has never been investigated before. Its importance is obvious as many patients with CCF cannot tolerate spironolactone due to gynaecomastia or impaired renal function.

Both groups were well matched in all basic demographic features. In this study the patients treated with lasoride and Spiromide with equal dosage of Frusemide showed similar effects. Patients in both groups improved clinically with significant improvement in their symptoms. Their NYHA classes improved significantly compared to pretreatment status. Clinical signs of cardiac failure improved significantly. These patients continued to receive other drugs like digoxin, nitrate, ACE inhibitors according to physician's discretion.

Both in spiromide and lasoride groups there was no significant rise in serum potassium (K^+ >6mmol/L) necessitating to discontinuation of the therapy. It is therefore deduced that these drugs can safely be used with ACE inhibitors provided the renal function is normal and potassium is monitored regularly. This is specially true in cases where larger doses of diuretics are given causing massive loss of potassium which cannot be compensated by ACE inhibitor alone so one has to either add potassium to therapy or combine potassium sparing agents.

It is generally believed that ACE inhibitor suppress the formation of aldosteron, but it has been shown that the effects are only temporary.[12,13] In this study more than 80% patients were receiving ACE inhibitors and addition of Amiloride or Spironolactone was well tolerated by these patients. It is thus recommended Spironolactone or Amiloride can be safely added to standard therapy of CCF including Digoxin, loop diuretic and ACE inhibitor. It is perhaps helpful to patients in enhancing the diuretic effect and conserving potassium besides having anti aldosteron effects.[14]

Gynecomastia was seen more commonly in spiromide than in lasoride group (25% Vs 5%) This figure is higher than 7-8% reported in other studies.[15,16]

This is the single most common and significant side effect and needs discontinuation of therapy in certain cases. In those patients it may be replaced with Amiloride which proves to be equally effective.

In some studies[17] it has been reported that chronic use of frusemide may lead to rise in BUN and creatinine, but in our study population not much difference was noted at the end of study. It is perhaps as this was a short term study. Extra caution should be exercised in patients with impaired renal functions.

The consequences of secondary aldosteronism observed in CCF contrast with those seen in primary aldorteronism i.e, Conn's syndrome, in which fluid retention is not detectable. In primary aldosternism the sodium and fluid balance is nearly normal and edema does not develop, despite chronic elevation of aldosteron. The mechanism underlying aldosteron's attenuation in primary aldosteronism and its excessive effects in CCF are not fully understood.[18]

Cardiac arrythmias are common in patients with CCF and structural heart disease, including hypertensive patients with left ventricular hypertrophy. Atrial fibrilation and CCF often coexist and this have been confirmed in large scale trial and smaller hospital based studies. Patients suffering from CCF and atrial fibrilation are specifically treated with Digoxin not only for its inotropic but also for chronotropic effect. Digoxin, as is well known, itself is arrythmogenic especially when the serum potassium is either low or low normal. Human body has large reserves of potassium in the form of intracellular potassium and a normal serum potassium may give a false impression of overall potassium balance because potassium moves out of cells to maintain serum potassium at the cost of overall body deficit and is continuously being excreted in urine under the effects of diuretics. So in such situations regular monitoring and conservation of potassium is important to avoid any fatal arrythmias.

The importance of etiological factors in CCF is dependent on nature of population being studied, coronary artery disease and hypertension are common causes of heart failure in western countries, whereas valvular heart disease and nutritional cardiac diseases are more common in developing world. Cardiomyopathy is another important common cause of heart failure both in the developed as well as developing world.

CONCLUSION

Both lasoride and spromide were found to be effective without much adverse effects on potassium level and renal function. The tolerability was better with lasoride.

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