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STUDY ON EFFICACY OF LOSARTAN ON REGRESSION OF LEFT VENTRICULAR HYPERTROPHY AND IMPROVEMENT IN CARDIAC FUNCTION IN HYPERTENSIVE CHRONIC KIDNEY DISEASE PATIENTS ON HAEMODIALYSIS

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ABSTRACT

Introduction: Hypertension is common in hemodialysis patients and can often be difficult to control. Considering the high cardiovascular burden in hemodialysis patients, control of blood pressure is important to improve outcomes. First-line interventions for blood pressure control should focus on sodium restriction, adequate sodium removal during hemodialysis, and attaining an adequate "dry weight." Despite these interventions, adequate blood pressure control with thrice weekly hemodialysis typically requires the addition of pharmacologic agents.

Objectives of the study: The objectives of the study was to determine the efficacy of losartan in regression of left ventricular hypertrophy and improvement in cardiac function in hypertensive CKD patients on haemodialysis.

Material and Methods: Hypertensive CKD patients of 18-60 years of age on maintenance haemodialysis 3 per week through AV fistula were included in the study. All patients included in the study were be subjected to a uniform evaluation. Demographic data, history, detailed clinical examination will be recorded in a pro-forma. Informed written consent was obtained from all the patients at the time of enrolment. Laboratory evaluation of all patients included: Complete blood counts, Renal function test, Serum electrolytes (Na/K/Ca/Po4), Liver function test including serum protein and albumin, iPTH and Echo-cardiography (esp LA diameter, ejection fraction, left ventricular mass index, E/A) will be done in all patients. These patients were made dry by increasing ultra-filtrate on subsequent haemodialysis. Achievement of dry weight was defined by pre-dialysis BP less than 140/90 with 2or less anti-hypertensives without any clinical oedema. After achieving dry weight losartan treatment was started at a dose of 25 mg/day and increased after one week to a 50 mg/day dose that was maintained to the end of the study (6 months).

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 12, 2023

Result: LA size decreased from 3.30 ± 0.15 cm/m2 to 2.88 ± 0.18 cm/m2 in the losartan arm (n=27) and from 3.33 ± 0.18 cm/m2 to 3.30 ± 0.14 cm/m2 in the control arm (n=25). This change was statistically significant. (p <0.001) E/A decreased from 1.51 ± 0.11 to 1.35 ± 0.10 in the losartan arm (n=27) and from 1.55 ± 0.09 to 1.46 ± 0.12 in the control arm (n=25). This change was statistically significant. (p=0.003) EF% increased from 44.22 ± 4.26 to 56.91 ± 3.90 in the losartan arm (n=27) and from 44.48 ± 4.32 to 48.24 ± 3.74 in the control arm (n=25). This change was statistically significant. (p <0.001) LVMI decreased from 170.56 ± 9.19 g/m2 to 146.50 ± 7.54 g/m2 in the losartan arm (n=27) and from 171.16 ± 9.29 g/m2 to 166.0± 8.48 g/m2 in the control arm (n=25). This change was statistically significant. (p <0.001)

Conclusion: In conclusion, in our study, use of losartan improved cardiac parameters (e.g, LA size, E/A ratio, Ejection fraction and left ventricular mass index) significantly in the hypertensive chronic kidney disease haemodialysis dependant patients after our study period of 6 months.

Keywords: losartan, antihypertensive, dialysis, cardiac parameters, ejection fraction, left ventricular mass index and chronic kidney disease.

INTRODUCTION:

Cardiovascular disease is the most common cause of death in chronic kidney disease patients on maintenance haemodialysis. And it is particularly common among the hypertensive CKD patients. Hypertension affects 90% haemodialysis patients and is often poorly controlled. To improve blood pressure, there are various non-pharmacologic interventions like educating patients about limiting sodium intake (less than 2 gm/day), ensuring adequate solute removal during haemodialysis, and achieving target "dry weight". Even after achieving these they may need pharmacologic interventions. So during choosing drugs among different classes of anti-hypertensives, we have to select these drugs that not only improve hypertension but also improve cardiovascular outcome. Low ejection fraction and left ventricular hypertrophy (LVH) is frequently found at the initiation of dialysis in hypertensive CKD patients, and is highly predictive of future cardiovascular morbidity and mortality.

Normal systolic function is considered if LVEF >50%. Conversely, systolic dysfunction was defined as LVEF ≤50%. LVMI was calculated by Devereux′s formula considering the

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 12, 2023

diastolic measurements of left ventricular internal diameter (LVID), interventricular septal thickness (IVST) and posterior wall thickness (PWT).

LVMI (g/m2) = (1.04 [(IVST+LVID+PWT)3−LVID3]−14)/Body surface area. According to this formula, LVMI is increased if >134/m2 in men and >110 g/m2 in women. Although angiotensin receptor blockers (ARBs) reduce cardiovascular disease (CVD) events in patients with diabetes and chronic kidney disease, their effect in patients with CKD on HD therapy is not known.

OBJECTIVES OF THE STUDY: The objectives of the study was to determine the efficacy of losartan in regression of left ventricular hypertrophy and improvement in cardiac function in hypertensive CKD patients on haemodialysis.

MATERIALS AND METHODS:

a) STUDY AREA: The study was in the department of General Medicine in association with the Department of Nephrology at our tertiary care hospital.
b) STUDY DESIGN: This study was an open level randomised prospective interventional study
c) STUDY POPULATION: All patients who are on haemodialysis in HD unit of our tertiary care hospital.
d) SAMPLE SIZE: The number is 27 patients in the case arm and 25 patients in the control arm.
e) Method of randomization: Random number table

Inclusion criteria:

1. Patient of age within 18-60 year.
2. CKD stage 5 on haemodialysis.
3. On maintenance haemodialysis 3 per week.
4. A-V Fistula is used as haemodialysis access.
5. Haemoglobin level > 10gm%.
6. Echo-cardio graphic evidence of Left ventricular hypertrophy.
7. Pre dialysis BP > 140/90 on 2 occasions.
8. No contraindication to any of the medication used in the study.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 12, 2023

Exclusion Criteria

1. Life expectancy less than 6 months.
2. Pregnancy and unwilling to take contraception.
3. Patients with active infection.
4. Past history of allergy or side effects to losartan.
5. Contraindication to start losartan. Eg hyper k
6. Unwilling to give consent.

Interventions: Hypertensive CKD patients of 18-60 years of age on maintenance haemodialysis 3 per week through AV fistula were included in the study. All patients included in the study were be subjected to a uniform evaluation. Demographic data, history, detailed clinical examination will be recorded in a pro-forma. Informed written consent was obtained from all the patients at the time of enrolment. Laboratory evaluation of all patients included: Complete blood counts, Renal function test, Serum electrolytes (Na/K/Ca/Po4), Liver function test including serum protein and albumin, iPTH and Echo-cardiography (esp LA diameter, ejection fraction, left ventricular mass index, E/A) will be done in all patients. These patients were made dry by increasing ultra-filtrate on subsequent haemodialysis. Achievement of dry weight was defined by pre-dialysis BP less than 140/90 with 2or less anti-hypertensives without any clinical oedema. After achieving dry weight losartan treatment was started at a dose of 25 mg/day and increased after one week to a 50 mg/day dose that was maintained to the end of the study (6 months).

STATISTICAL ANALYSIS: All data gathered were tabulated on a master chart and analysed using charts, diagrams and application of standard statistical techniques using latest SPSS software. Level of significance of 0.05 was applied to all analysis.

RESULTS :

In the present study, a total 52 CKD 5D patients were enrolled. They were randomised in 1:1 ratio with random number table into two groups. 27 patients were taken as cases and 25 patients were taken into control group. 22 and 21 patients have completed the study in the case and control group respectively.

Table 1: Shows the Age-wise and gender-wise distribution of study participants

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 12, 2023

	Case	Control	P value
Age	39.3±9.10	37.84±7.66	0.515
21-30	5 (18.52)	4 (16)	0.70
31-40	9 (33.33)	12 (48)	
41-50	10 (37.04)	8 (32)	
51-60	3 (11.11)	1 (4)	
Female	13 (48.15)	12 (48)	0.991
Male	14 (51.85)	13 (52)	
Total	27 (100)	25 (100)	

Table 2: Shows Baseline ECHO findings in study participants

	Case	Control	P value
LA SIZE (cm/m2)	3.30±0.15	3.33±0.18	NS
E/A	1.51±0.11	1.55±0.09	NS
EF%	44.22±4.26	44.48±4.32	NS
LVMI (gram/m^2)	170.56±9.19	171.16±9.29	NS

Table 3: Shows the changes ECHO findings in study participants

	Case	Control	P value
LA SIZE (cm/m2)			
0 month	3.30±0.15	3.33±0.18	NS
3rd month	3.11±0.10	3.35±0.17	<0.001
6th month	2.88±0.13	3.30±0.14	<0.001
E/A Ratio			
0 month	1.51±0.11	1.55±0.09	NS

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 12, 2023

3rd month	1.46±0.10	1.55±0.09	NS
6th month	1.35±0.10	1.46±0.12	S
EF%			
0 month	44.22±4.26	44.48±4.32	NS
3rd month	50.5±4.31	46.18±3.55	S
6th month	56.91±3.90	48.24±3.74	S
LVMI (gram/m^2)			
0 month	170.56±9.19	171.16±9.29	NS
3rd month	158.95±8.45	167.14±9.06	S
6th month	146.50±7.54	161.52±8.48	S

DISCUSSION

Hypertension is common in hemodialysis patients and can often be difficult to control. Considering the high cardiovascular burden in hemodialysis patients, control of blood pressure is important to improve outcomes. First-line interventions for blood pressure control should focus on sodium restriction, adequate sodium removal during hemodialysis, and attaining an adequate "dry weight." Despite these interventions, adequate blood pressure control with thrice weekly hemodialysis typically requires the addition of pharmacologic agents. First-line pharmacologic agents for blood pressure control in hemodialysis patients should be RAAS inhibitors (either ACE-I or ARB) because of their documented benefit on left ventricular hypertrophy, pulse wave velocity, and potentially cardiovascular events. Second line agents include the addition of beta-blockers (particularly in patients with coronary artery disease), combined α- and β- blockers in patients with heart failure, CCBs, and alternative agents such as direct vasodilators. Most hemodialysis patients require a combination of antihypertensive agents to achieve adequate blood pressure control. Considering the high pill burden and high rates of noncompliance among hemodialysis patients, once daily (or thrice weekly) formulations should be used preferentially. Nocturnal dosing of once daily antihypertensive medications is favoured to control the nocturnal increase in blood pressure observed in many hemodialysis patients and to minimize the risk

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 12, 2023

of intradialytic hypotension. Newer antihypertensive agents, such as direct renin inhibitors, provide alternative choices for blood pressure control but need to be tested in hemodialysis patients to determine their safety and efficacy before being widely adopted [1].

Hypertension is a potent risk factor for cardiovascular disease in hemodialysis patients, as in the general population, whereas there is no association of hypertension with mortality. Active reduction in systolic blood pressure is important to minimize the occurrence of cardiovascular events [2].

In the present study, a total 52 CKD 5D patients were enrolled. They were randomised in 1:1 ratio with random number table into two groups. 27 patients were taken as cases and 25 patients were taken into control group. 22 and 21 patients have completed the study in the case and control group respectively. In this study we have analysed Angiotensin receptor blocker (ARB)-losartan in CKD 5 hemodialysis dependant patients and followed them up to 3 and 6 months in comparison to patients not on ARB. The objectives of the study was to determine the efficacy of losartan in regression of left ventricular hypertrophy and improvement in cardiac function in hypertensive CKD patients on haemodialysis.

LA size decreased from 3.30 ± 0.15 cm/m2 to 2.88 ± 0.18 cm/m2 in the losartan arm (n=27) and from 3.33 ± 0.18 cm/m2 to 3.30 ± 0.14 cm/m2 in the control arm (n=25). This change was statistically significant. ($p < 0.001$) E/A decreased from 1.51 ± 0.11 to 1.35 ± 0.10 in the losartan arm (n=27) and from 1.55 ± 0.09 to 1.46 ± 0.12 in the control arm (n=25). This change was statistically significant. ($p = 0.003$) EF% increased from 44.22 ± 4.26 to 56.91 ± 3.90 in the losartan arm (n=27) and from 44.48 ± 4.32 to 48.24 ± 3.74 in the control arm (n=25). This change was statistically significant. ($p < 0.001$) LVMI decreased from 170.56 ± 9.19 g/m2 to 146.50 ± 7.54 g/m2 in the losartan arm (n=27) and from 171.16 ± 9.29 g/m2 to 166.0± 8.48 g/m2 in the control arm (n=25). This change was statistically significant. ($p < 0.001$)

Davina J Tai et al [3] shows that ACEI or ARB use resulted in a statistically significant reduction in LV mass, with a MD of 15.4 g/m2 (95% CI 7.4 to 23.3; $P < 0.001$)There was no significant difference in the change in LV ejection fraction between the two groups over the study period with a WMD of 0.06% (95% CI −3.03 to 2.90; $P = 0.97$).

Shibashaki et al [4] shows after 6 months of treatment, losartan treatment significantly reduced the LVM index (-24.7 +/- 3.2%) than amlodipine (-10.5 +/- 5.2%) or enalapril (-11.2

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+/- 4.1%) therapy.

London G M et al [5] showed a decrease in LVM was observed only in patients receiving perindopril (from 317 +/- 18 to 247 +/- 21 g) (time-treatment interaction, P = .036). Nitrendipine had no significant effect on LVM (314 +/- 29 versus 286 +/- 32 g).

But Kanno Y et al [6] , Matsumoto Y et al [7] and Yu WC [8] et al showed no difference between case and control group.

CONCLUSION: In conclusion, in our study, use of losartan improved cardiac parameters (e.g, LA size, E/A ratio, Ejection fraction and left ventricular mass index) significantly in the hypertensive chronic kidney disease haemodialysis dependant patients after our study period of 6 months.

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