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Original Research

An Observational Study on the Effect of Chlorthalidone Therapy on Blood Pressure in Advanced Chronic Kidney Disease Patients

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ABSTRACT:

Patients with advanced chronic kidney disease (CKD), hypertension is a significant risk factor for cardiovascular disease (CVD) and CKD both. The effectiveness and safety of chlorthalidone, a thiazide-like diuretic, in treating hypertension in patients with advanced CKD were assessed in present study. 150 patients in all were randomized to get any one of chlorthalidone or placebo. Systolic and diastolic blood pressure (BP) were significantly lower after chlorthalidoneadministration than after a placebo (38.05/13.3 mmHg vs. 4.2/2.55 mmHg, respectively). Tolerability was acceptable, with manageable adverse effects. These findings highlight chlorthalidone's potential as a critical therapeutic option for hypertension in CKD patients. More study is required to optimize dosing and evaluate long-term outcomes.

Keywords: Advanced CKD, Blood Pressure, Chronic kidney disease, Chlorthalidone, Hypertension

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INTRODUCTION

Hypertension is a significant risk aspect for CVD and chronic renal disease both, is commonly not properly treated, especially in people with severe CKD.[1] Drugs that lower BP in people with important hypertension include thiazide or thiazide-like diuretics.[2] Chlorthalidoneis a thiazide-like diuretic that lowers cardiovascular mortality and morbidity, including the risk of heart failure and stroke.[3-5] Little is known about its effectiveness and safety in people with advanced chronic renal disease.[6] Numerous studies propose that these drugs may be helpful in controlling hypertension in people with chronic renal disease.[7,8] based on early indications that individuals with chronic renal disease experience an impact on their blood pressure.[9]

Spironolactone is the recommended treatment for resistant hypertension in general population.[10] However, compared to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (May be both), spironolactone quintupled the incidence of gynecomastia and doubled the risk of hyperkalemia, according to a meta-analysis.[11] Spironolactone was used inrandomized trial of individuals with resistant hypertension whose estimated glomerular filtration rates ranged from 25 to ≤45 mL/min/1.73 m^2, courtesy to the potassium binding polymer Patiromer.[12]

About 8 million people in the US are thought to have moderate-to-severe CKD who are not getting dialysis.[13]The pathophysiology of hypertension in these patients is significantly influenced by volume expansion.[14] As per current standard, diuretics should be used to manage hypertension in the majority of individuals with chronic kidney disease.[15]

As mentioned earlier, chlorthalidone is stored in erythrocytes and has a half-life of 45–60 hours, with a 72-hour influence on blood pressure.[16]Agarwal's trial's long-lasting effects on blood pressure and fluid volume attest to chlorthalidone's prolonged duration of action.[12] Since renal excretion primarily eliminates chlorthalidone as an unaltered molecule, the drug's longer half-life in individuals with kidney insufficiency may be a factor in its long-lasting hypotensive effect in CKD subjects.[17]

Changes in eGFR were most likely caused by lower blood pressure, as was the case in earlier BP-lowering experiments. In fact, these alterations were thought to be of minimal clinical significance and were completely reversible following drug withdrawal. Therefore, those randomly assigned to chlorthalidone in Antihypertensive and Lipid-Lowering treatment to prevent heart attack trial were at same threat of renal failure as those randomized to amlodipine or lisinopril.[18]

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Both male and female hypertensives with impaired kidney function are at significant risk for CVD and renal disease.[19,20] BP management is essential to the treatment of chronic renal disease, as per renal Disease: Improving Global outcomes guidelines from 2012.[21] A very powerful thiazide-like diuretic is chlorthalidone.[22]

Large-scale studies involving hypertensives with impaired renal function have examined the long-term effects of a treatment plan based on hydrochlorothiazide and chlorthalidone.[23] Because the design of both studies sought to effectively control hypertension and permitted the sequential addition of additional medications in addition to the diuretic under examination, it is challenging to assess the anti-hypertensive effects of the diuretics per se in those two trials. Small studies on hydrochlorothiazide demonstrated short-term effects on reduced renal function.[12]

MATERIALS AND METHODS

Study Design

Participants were enrolled who meet inclusion criteria in this study, after obtaining informed consent. Relevant demographic, clinical and laboratory information were collected at baseline and regular intervals for patients receiving either the study drug (Chlorthalidone) or placebo. When compared to the placebo group, advanced chronic kidney disease patients receiving chlorthalidone showed variations in their SBP and DBP. The study had 150 patients in all, who were randomized 1:1 between the two groups.

Study Population

Patients with advanced CKD stages (4^{th} and 5^{th}, defined as an [eGFR] <30 mL/min/1.73 m^2) were enrolled based on following norms:

Inclusion Criteria

- Adult patients aged ≥18 years.
- Diagnosed with advanced CKD.
- Uncontrolled hypertension despite current antihypertensive treatment.

Exclusion Criteria:

- Known hypersensitivity patients to chlorthalidone.
- Pregnant or breastfeeding women.
- Patients with significant electrolyte imbalances (e.g., severe hypokalemia or hyperkalemia).
- Recent history of acute kidney injury or dialysis dependence.
- Use of other diuretics in the last 2 weeks.

Outcome Measures

The primary effect was altered in systolic BP and diastolic BP from baseline [Time points; 1-month, 3-months, etc.]. Secondary outcomes included:

- The incidence of adverse effects, such as electrolyte disturbances (e.g., hypokalemia, hyperuricemia).
- Changes in serum creatinine and eGFR levels.
- Tolerability of chlorthalidone therapy.

Data Collection

Baseline clinical characteristics and demographic including sex, age, BMI, duration of CKD, comorbidities (e.g., diabetes, cardiovascular disease) and baseline blood pressure, were recorded. Blood pressure was measured using a calibrated sphygmomanometer following standard protocols (average of three readings, seated position, 5-minute rest). Serum electrolytes, creatinine, and eGFR were measured at baseline and at follow-up visits.

Follow-up visits were conducted at 2-weeks, 1-month and 3-months intervals. At each visit, blood pressure was measured, and patients were assessed for adverse effects. Medication adherence was monitored using patient self-reports and pill counts.

Statistical Analysis

Continuous variables, including changes in SBP and DBP were presented as mean ± SD and compared using paired t-tests. Categorical variables were presented as frequencies and percentages and analysis using chi-square for *p-value* (<0.05) was considered statistically significant using SPSS software.

RESULTS

Cholthalidone treatment

75 patients were enrolled in chlorthalidone group, comprising 48 males and 27 females. Most patients had a baseline SBP >160 mmHg and DBP >80 mmHg. Following treatment with chlorthalidone, the absolute mean reduction in SBP was 38.05 mmHg and DBP was 13.3 mmHg. In comparison, the placebo group showed a significantly lower absolute mean reduction in SBP, with 4.2 mmHg and DBP with 2.55 mmHg (Table 1).

Placebo Treatment

Study was conducted to evaluate the effects of a treatment on BP reduction in a group of diseased subjects. A total of 75 participants were enrolled in the study, comprising 48 males (64%) and 27 females

Table 1: Effect of cholthalidone before and after treatment.

S.No.	Number of patients	Percent age	Gender	Mean age	BP (systolic & diastolic) before treatment (mean value)	BP (systolic & diastolic) after treatment (mean value)	Difference from baseline (mean value)
1	48	64	Male	38.9	161.7 / 95.7 mmHg	123.3 / 81.3 mmHg	38.4 / 14.4 mmHg
2	27	36	Female	37.4	161.3 / 94.8 mmHg	123.6/ 82.6 mmHg	37.7 / 12.2 mmHg

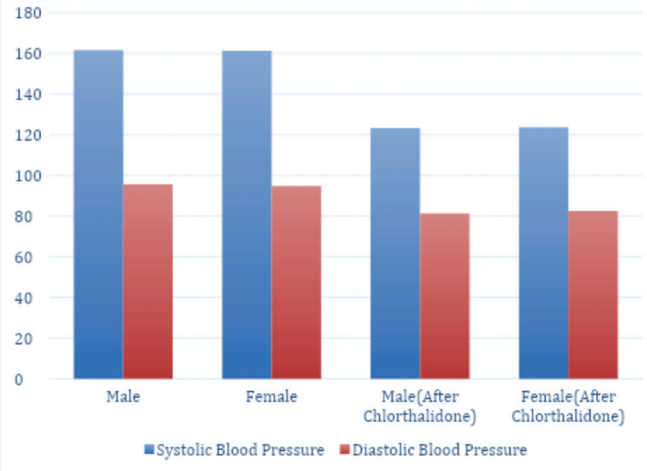

Figure 1: Bar-graph showing effect of cholthalidone treatment in male and female.

(36%). The mean age of the male group was 38.9 years, while that of the female group was 36.9 years. The BP measurements were recorded as systolic and diastolic values before and after treatment. In males, the mean SBP and SBP before treatment were 161.5 and 94.5 mmHg, respectively. Following treatment, these values reduced to 156.9 mmHg (systolic) and 91.08 mmHg (diastolic). The differences from baseline were 4.6 mmHg for systolic and 3.4 mmHg for diastolic pressure, indicating a modest reduction in BP levels after treatment. Similarly, in females, the mean systolic and diastolic BP before treatment was 160.9 and 94.4 mmHg, respectively. After treatment, the mean systolic and diastolic BP decreased to 157.1 and 92.7 mmHg, respectively. This represented a reduction of 3.8 mmHg in SBP and 1.7 mmHg in DBP from baseline. Overall, the data suggests that the treatment resulted in a measurable decline in SBP and DBP among the participants, with males showing a slightly greater reduction compared to females (Table 2).

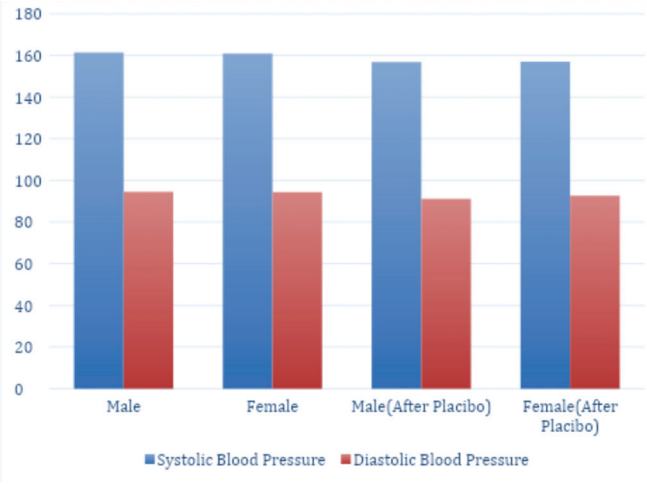

Figure 2: Graph showing effect of placebo treatment in male and female.

DISCUSSION

The study highlights the effectiveness of chlorthalidone in reducing BP among patients with baseline hypertension. A significant absolute mean reduction of 38.05 mmHg in SBP and 13.3 mmHg in DBP was noted in chlorthalidone group, compared to the placebo group, which showed minimal reductions (4.2 mmHg systolic and 2.55 mmHg diastolic).

Although males exhibited slightly greater reductions (4.6/3.4 mmHg) compared to females (3.8/1.7 mmHg) in systolic and diastolic values, the overall decrease in both genders indicates the treatment's efficacy. However, the modest decrease in systolic and diastolic BP reported within this specific dataset raise the question of additional factors influencing response to treatment, such as dosage, adherence, or baseline variability.

According to the blood pressure changes' time course, the majority of the blood pressure drop happened four weeks after beginning treatment with 12.5 mg of chlorthalidone (In addition to other antihypertensive drugs).[24] The regimen was dropped. 53% of the peak weight loss observed at conclusion of 12-week therapy duration and 44% of the reduction in seated clinic SBP persisted two weeks after the cessation of chlorthalidone therapy. According to reports, chlorthalidone has a half-life of 45 to 60 hours and an even longer time frame of action, lasting 48 to 72 hours.[25] Chlorthalidone's lengthy period of action or a modifying influence on kidney disease are consistent with the drug's long-lasting effects on blood pressure and weight loss. Given that chlorthalidone is 3 times as effective as hydrochlorothiazide, significant drop in blood pressure is probably what happened.[26,27] Better blood-pressure control, as seen in earlier trials, is likely the cause of reversible alterations in the projected GFR that took place in the chlorthalidone set.[28,29]

The projected GFR rebounded to around the baseline value two weeks after the cessation of chlorthalidone medication, indicating the extra participation of tubuloglomerular feedback, while the blood pressure didn't rise above the starting point.[30,31] In long-term, phase-3 experiment (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack experiment [ALLHAT]), kidney failure outcomes for patients randomly assigned to chlorthalidone were similar to those observed for patients treated to amlodipine or lisinopril.[32] There was no clinically significant rise in the danger of mortality, dialysis or severe, long-lasting decline in kidney function, according to observational follow-up in ALLHAT. Our trial's other side-effects were comparable to those seen in prior trials where

Table 2: Effect of placebo before and after treatment.

S.No.	Number of patients	Percent age	Gender	Mean age	BP (systolic & diastolic) before treatment (mean value)	BP (systolic & diastolic) after treatment (mean value)	Difference from baseline (mean value)
1	48	64	Male	38.9	161.5/ 94.5 mmHg	156.9/ 91. 08 mmHg	4.6/ 3.4 mmHg
2	27	36	Female	36.9	160.9 / 94.4 mmHg	157.1/ 92.7 mmHg	3.8 / 1.7 mmHg

chlorthalidone was administered to participants without chronic renal disease.[33,34] Within four weeks of starting the regimen, the degree of albuminuria decreased in chlorthalidone group, which might be attributed to either a haemodynamic effect or a diuretic-induced potentiation of the antialbuminuric effect of renin-angiotensin system inhibitors.[35] Rise in urine albumin-to-creatinine ratio between the end of chlorthalidone treatment and two weeks later indicates that haemodynamics plays a role in the mechanism of decline in the severity of albuminuria. Chlorthalidone may offer cardiovascular and kidney protection to individuals with CKD as evidenced by the drug's consistent improvement in the degree of albuminuria.[36] Chlorthalidone may be particularly helpful in lowering cardiovascular problems in persons without chronic renal disease, according to some evidence.[37–40]

CONCLUSION

Patients with advanced CKD who were treated with chlorthalidone for the management BP had considerable reduction in BP compared to placebo. The data confirms that chlorthalidone effectively reduces blood pressure, outperforming placebo and offering measurable benefits for managing hypertension in both male and female populations. Further research may be warranted to explore individualized responses and optimize therapeutic outcomes.

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Conflict of Interest-No

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