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THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND/OR ANGIOTENSIN RECEPTOR BLOCKERS VERSUS CALCIUM CHANNEL BLOCKERS ON PROGRESSION OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH HYPERTENSION IN SUDAN

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ABSTRACT

Background: Chronic kidney disease (CKD) is a worldwide disease with a prevalence rate of 10% to 13%. Hypertension (HTN) is closely associated with CKD and it has the highest prevalence among the major non-communicable diseases in Sudan. The Sudan Guidelines for the Management of HTN in adults recommend that the first line drug of pharmacological intervention is to start with a diuretic or one of the long-acting calcium channel blockers (CCBs). This is based on the notion that African groups have low renin levels and therefore may not respond well to angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Yet, many physicians in Sudan start their hypertensive patients on ACEIs or ARBs and claim that they get good control of the HTN. One of the important objectives of good control of HTN in CKD patents is to prevent/ slow down progression to end stage renal disease (ESRD). This study aimed to assess the effect of ACEIs and ARBs drugs versus CCBs on hypertensive CKD patients regarding control of blood pressure (BP) and the effect on progression to higher classes of CKD. **Methods:** This is a prospective cohort study on 240 patients with

CKD and HTN who were treated by their respective physicians in three major hospital in Khartoum, Sudan, The patients were divided into two groups according to their medical records: those who were treated with ACEIs or ARBs on the one hand (Group 1) and those treated with CCBs on the other hand (Group 2): The medical records were reviewed by one of researchers and the patients were interviewed. BP measurements and personal and laboratory data were recorded. The same patients were called upon about one year later and reevaluated to assess their BP control and state of CKD progression. **Results**: Overall the effect of ACEIs/ARBs and CCBs on the degree of control of BP were comparable up to one year of follow up (FU), there being no statistically significant differences between the mean SB P2 and mean DB (P1-P2) of the two groups by the end of the study. The mean serum creatinine, however, was consistently lower in Group 1 compared to Group 2 at the beginning of the study and after one year of FU. However, the estimated glomerular filtration rate (eGFR) was not significantly different between the two groups during the first assessment, but was significantly higher in Group 1 compared to Group 2 by the end of one year FU (P=0.021). The urinary protein excretion (grams / day) was significantly lower in Group 1 by the end of the study. Overall, 28.5% of patients in Group 1, compared to 55.5% of patients in Group 2 progressed to higher classes of CKD (P <0.001). When stratified by the class of CKD, more patients progressed from CKD1 to CKD2 in the CCBs group compared to ACEIs/ARBs group by the end of FU. This effect was also found, though to a lesser degree in higher classes of CKD. **Conclusion:** The results showed that the BP was fairly well controlled in both groups using either regimen of medications up to one year of FU. However, more patients progressed to higher classes of CKD, and proteinuria was more pronounced in the CCBs group. Serum potassium levels were significantly higher in the ACEIs/ARBs group but the potassium levels were within the acceptable normal range up to the end of the study.

KEYWORDS: ACEI; ARBs; CCB; CKD; Hypertension; Progression of Chronic Kidney Disease.

1. INTRODUCTION

Chronic kidney disease (CKD) is defined as either measured Estimated glomerular filtration rate (eGFR) abnormality or evidence of kidney damage (e.g., albuminuria), or both, for a minimum of three months.[1] CKD is a worldwide problem with a prevalence rate varying between 10.5% and 13.1% in different countries.[2] Screening surveys of representative

samples of the whole population performed in the US, Australia, Japan and Europe have identified between 6% and 11% as having some degree of CKD.[3-6] Unfortunately, there are no reliable statistics on CKD from most African countries. However, there is a general impression that it is at least three to four times more frequent than in developed countries.[7] In Sudan, for example, there is no national registry for renal patients and the knowledge about epidemiology of CKD is very limited.[8] The high incidence of CKD among African due to rising prevalence of risk factors diabetes mellitus (DM), hypertension, and other social and economic factors.[7] Hypertension has the highest prevalence among the major non-communicable diseases in Sudan, with a prevalence rate of 23.6 in Khartoum state.[9] One of the most important goals of management of CKD is to slow progression to end stage kidney disease (ESKD); and when CKD is associated with hypertension, good control of blood pressure is a major step to help in slowing progression to ESKD.[10] The Sudan Guidelines for the Management of Hypertension (SGMH) in adults recommend that the first line drug of pharmacological intervention in hypertension is to start with a diuretic or one of the long-acting calcium channel blockers (CCBs).[10] This is based on the notion that African groups have low renin levels and therefore may not respond well to angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).[10] This notion is not based on any local studies in Sudan, rather it is adopted from the British Hypertension Society recommendation.[11] The aim of this study was to compare the effect of ACEIs and/or ARBs versus CCBs as used by physicians treating CKD patients who also had hypertension, on progression of CKD in Sudanese patients.

2. METHODOLOGY

Study design and study area

This is a prospective cohort study, to measure the effect of ACEIs and/ or ARBs versus CCBs on progression of CKD in Sudan. The study groups were CKD patients who were designated for regular follow-up (FU) at three major hospitals in Khartoum: 'Ahmed Gasim Cardiac surgery and Renal Transplantation Center', 'Ibn-Sina Specialized Hospital', and Omdurman Teaching Hospital; during the period January 2018- January 2020.

Inclusion criteria

1. Adults patients (aged 18 years or more), who were diagnosed to have CKD stages 1 to 4; and who had high blood pressure (BP) that was treated by pharmaceutical agents by their

respective physicians, were identified from the specialized clinics in the three hospitals named.

2. Patients on ACEIs and/or ARBs, with or without any other antihypertensive agent other than CCBs were identified as Group one,
3. Patients on CCBs with or without any other antihypertensive agent other than ACEIs or ARBs were identified as Group two.

Exclusion criteria

1. Patients diagnosed as having ESKD (CKD stage 5 or on a dialysis modality).
2. Patients on combination antihypertensive medications that included both ACEI/ARB and CCBs groups.
3. Patients not on regular follow-up or incomplete data records,

The main outcome points

To measure progression of CKD (from one CKD stage to another up to stage CKD5 or need for dialysis) during the FU period.

Ethical approval

Was obtained from State Ministry of Health Research Department, and from respective hospital authorities. Recruited patients signed informed consent forms

Sample size

The required sample size was estimated using the formula.[12]

$(n = \frac{z^2 pq}{d^2})$

Where (n) is sample size, (z) the normal standard deviate (z =1.96), (p) the frequency of occurrence of CKD patients on antihypertensive = 0.8, (q) the frequency of non occurrence CKD patients on antihypertensive (1- p) =1-0.8= 0.2 and (d) is level of precision (0.05).

n = 1.96x1.96x 0.8x0.2 / 0.05/ 0.05 = 245.86 ≈246

Thus, the sample size needed was 123 patients for each limb of the study (groups one and two), total estimated sample size 246 adult patients. An increment of 25% (about 60 patients) was added to account for dropouts: total required sample 300 patients (150 for each group).

Data collection and follow-up

Personal interview, checklist and review of hospital data results were used for assessment the effect of ACEIs and/or ARBs therapy on the one hand, versus patients using CCBs as

antihypertensive drugs on the other hand, during the study period (January 2018 to January 2020).

Medical history was obtained by direct interview in all patients. Cigarette smoking was determined by self-report (non smoker, passive smoker, slight, or moderate to heavy smoker).

Measurements of height (Cm), weight (Kg), and BP using a mercury sphygmomanometer after 5 min in a seated position was obtained during each clinical examination. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation (mL/minute/1.73m^2). Albuminuria or proteinuria, creatinine and electrolyte measurements were measured using standard hospital methods.

Main dependent variables were: BP readings, serum creatinine, eGFR and proteinuria. Independent variables were: ACEIs/ ARBs drugs versus CCBs in hypertensive patients with CKD stages 1 to 4.

Statistical analysis

Data collected personally and manual coding to checked any error in coding. Double checked of entering data to prevent potential data entry error. The study conducted all statistical tests at a confidence level of 95%. Also used SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc., Chicago, IL, USA) for statistical analyses, and represented numerical data as mean and standard deviation and categorical data as frequency (count) and relative frequency (percentage). To compare categorical data, we performed a chi-square test. We made comparisons between quantitative variables using the Student t-test. We considered P values less than 0.05 as statistically significant.

3 RESULTS

Patient's characteristics and antihypertensive drugs

Out of 320 CKD patients approached, 300(94%) agreed to participate in the study and responded for the first follow-up interview and data collection. The second evaluation was done after completion of one year time from the first evaluation. Almost all patients were approached to respond to the second interview and data collection. By the end of 16months from the first visit 240 (80%) of the patients were able to attend both visits and the data was analyzed.

Of the 240 patients who completed the study, 130 (54%) were from Group 1 (treated with ACEIs and/or ARBs drugs) and 110 (46%) were from Group 2 (treated with CCBs). Almost half (50%) of patients interviewed in both groups were female, employed, and reported that they are not smokers during the study period. Table 1: shows the demographic characteristics of both groups. There were no significant differences between the two groups in terms of gender distribution, employment or smoking habits.

Table 1: Comparison between some demographic characteristics and smoking habits between the two study groups (Group 1: patients treated with ACEs /ARBs; Group 2 patients treated with CCBs). Statistics chi-square (n=240).

Parameters	Subgroup	Group1 (n =130)	Group2 (n=110)	p-value
		ACEIs / ARBs n (%)	CCBs n (%)	
Gender	Male	66 (58.4)	47 (41.6)	0.133
	Female	64 (50.4)	63 (49.6)	
Employment	Employed	47 (52.2)	43 (47.8)	0.369
	Not-employed	83 (55.3)	67 (44.7)	
Smoking habits	Non smoker	110 (54.2)	93 (45.8)	0.864
	Passive smoker	15 (51.7)	14 (48.3)	
	Smoker	5 (62.5)	3 (37.5)	

ACEIs = angiotensin converting enzyme inhibitors.
ARBs=angiotensin receptor blockers.
CCBs = calcium channel blockers.

Differences between the two groups in various study variables

Table 2: shows comparison between the two groups in measurements in various parameters during the first visit in the study (P1) and the second visit (P2) that occurred after at least one year from the first visit. Values that reached statistical difference are highlighted in *italic and bold.*

Table 2: Comparison between various variables between the two groups.

Parameter	ACEIs / ARBs Group		CCBs Group		p -value
	Mean	SD	Mean	SD	
Follow up period (Mons)	16.05	3.03	15.39	2.69	0.081
Age (years)	54.16	16.05	54.29	14.31	0.948
Height (Cm)	166.89	10.05	165.89	7.5	0.999
Weight (Kg) P1	85.09	19.87	80.3	17	0.458
Weight (Kg) P2	81	15.2	82	13.8	0.895
SBP P1	138.29	17.96	146.22	18.45	0.001
SBP P2	144	18.7	140	16	0.11
DBP P1	80.77	9.55	77	10	0.188
DBP P2	83.5	10.38	81.5	9	0.118
emoglobin P1	11.15	1.52	10.64	1.84	0.022
Hemoglobin P2	10.97	1.66	10.53	1.96	0.066
Serum creatinine P1	1.98	0.98	2.42	1.35	0.005
Serum creatinine P2	2.37	1.08	2.89	1.39	0.001
eGFR P1	59.82	28.66	55.73	30.59	0.287
eGFR P2	52.11	27.68	43.75	27.9	0.021
Serum K P1	4.3	0.596	4.1	0.595	0.01
Serum K P2	4.26	0.6	4.12	0.629	0.084
Total Cholesterol P1	137.05	32.43	144.28	31.28	0.08
Total Cholesterol P2	137.74	33.99	149.24	34.47	0.01
Urine protein (g/day) P1	3.4	1.4	4.98	1.84	0.001
Urine protein (g/day) P2	3.79	1.49	5.09	1.69	0.001

Abbreviations: **ACEIs** = angiotensin converting enzyme inhibitors; **ARBs**=angiotensin receptor blockers; **CCBs** = calcium channel blockers; **DBP**= diastolic blood pressure; e**GFR**= estimated glomerular filtration rate; **K** = potassium; **P1**= first presentation to the study; **P2**=second presentation to the study; **SBP** = systolic blood pressure.

There were no significant differences between in the mean follow-up period, age distribution, weight or height of patients in the two groups (Table 2). The mean systolic blood pressure (SBP) was significantly lower in Group 1 (ACEI/ARBs Group) compared to Group 2 (CCBs Group) in the first visit assessment (P1) (P=0.001); but this did not extend to the mean SBP in the second assessment period (P2) or to the mean diastolic blood pressure (DBP) in both assessment periods (P1 and P2). The mean serum creatinine, however, was consistently lower in Group 1 compared to Group 2 in both periods of assessment, P1 and P2. The eGFR was not significantly different between the two groups during P1, but during P2 the eGFR was significantly higher in Group 1 (P=0.021). The serum potassium was higher in Group 1 during P1 (P=0.01), but this difference was not maintained during P2 (P=0.084). The total serum cholesterol was not much different between the two groups in P1, but became

significantly lower in Group 1 in P2 assessment (P=0.01). The urinary protein excretion (grams / day) was significantly lower in Group 1 during both P1 and P2 (P=0.001).

The results of Sodium level (Na), Calcium level (Ca), Phosphate level (Po4)
And Parathyroid hormone, showed no significant differences between ACEIs/ARBs and CCBs groups during follow-up.

Progression of CKD after a mean follow up period of 16.05 and 15.39 months in the respective study groups

Of the 240 patients who completed the study, 130 (54%) were from Group 1 (treated with ACEIs and/or ARBs drugs) and 110 (46%) were from Group 2 (treated with CCBs).Each of the two study groups was divided to four subgroups according to stages of CKD (stages 1 to4), (Table-3).

Table 3: Distribution of Stages of chronic kidney disease (CKD) in the two groups of the study (n=240).

Stage of CKD (eGFR mL/minute/1.73m^2)	Antihypertensive drugs		p-value
	Group 1: ACEIs-ARBs (n = 130) n (%)	Group 2: CCBs (n=110) n (%)	
Stage1 (>90)	20 (57.1)	15 (42.9)	0.360
Stage2 (60 – 89)	30 (50)	30 (50)	0.274
Stage3 (30 -59)	45 (60)	30 (40)	0.093
Stage4 (15 – 29)	35 (50)	35 (50)	0.336
Total	130 (100)	110 (100)	0.560

There were no significant differences between the two groups in the distribution of the stages of CKD at the start of the study (Table 3).

By the end of the study 99 of the 240 patients (41.2%) showed evidence of progression of their kidney disease as measured by the stage of the CKD.

Table 4: shows comparison between the two groups in progression of CKD from one stage to the other over the study period.

Table 4. Progression of CKD. Comparison between the study groups. n = 99 of 240 patients (41.2%)

Stages of CKD progression	Anti hypertensive drugs		p-value
	ACEI/ARBs n (%)	CCBs n (%)	
Stage 1 to Stage 2	1(10)	9 (90)	0.005
Stage 2 to Stage 3	9(42.9)	12(57.1)	< 0.001
Stage 3 to Stage 4	13(52)	12(48)	0.413
Stage 4 to Stage 5	13(37.1)	22(62.9)	0.023
Stage 2 to Stage 4	0 (0)	3(100)	0.095
Stage 3 to Stage 5	1 (20)	4(80)	0.137
Total of patients progression	37 (37.4)	62 (62.6)	<0.001

✓ P-value less than 0.05 were considered statistically significant

Overall, 37 of 130 (28.5%) of patients on ACEIs/ARBs (Group 1) and 62 of 110 patients (55.5%) of patients on CCBs (Group 2) progressed to more advanced CKD stage over the follow up period. The difference between the two groups was statistically highly significant (P < 0.001) (Table 4). Progression to higher stages of CKD was more pronounced in the earlier stages of CKD. Thus in ten patients who progressed from stage 1 to stage 2, nine of them were in the CCBs group, and only one in the ACEIs/ARBs group (P=0.005). Similarly more cases of Group 2 progressed from Stage 2 to stage 3 compared to cases in Group 1 (Table 4).

4. DISCUSSION

Although the Sudan Guidelines of management of HTN recommend the use of CCBs as first choice drugs in HTN, whether associated with CKD or not[10] yet in practice many doctors start off with ACEIs or ARBs in the drug treatment of HTN. This is because the Sudan guidelines recommendations were not based on local studies; rather they were based on the British Guidelines[11] and surely biased by the reports from USA about Black African Americans and their less favourable response to renin-angiotensin-aldosterone system (RAAS) blockade in the drug management of HTN.[11] In a previous study in Sudanese patients for the effectiveness of ACEI/ARBs as mono therapy in controlling high blood pressure, found that 79% of the population involved in the study had a controlled blood pressure.[9] The sample size in that study consisted of 95 adult patients and no comparison was held with CCBs use.[9] Sudanese Population has clear genetic variability. There are groups who could be grouped together as populations originally from the northeastern parts of the Country (North-Nubians, mixed Arab-African decedents residing in North and Central Sudan, and the Beja tribes mostly in Eastern Sudan). Another broad group would be

populations originally from the west and south Sudan (Nilotic tribes, Darfur and South-Kordofan populations). This differentiation is mainly caused by a large Eurasian ancestry component of the northeast populations likely driven by migration of Middle Eastern groups followed by admixture that affected the local populations in a north-to-south succession of events.[13] Genetic evidence points to an early admixture event in the Nubians, concurrent with historical contact between North Sudanese and Arab groups.[13]

In this study the investigators picked up CKD patients with hypertension who were being followed in three major hospitals in Khartoum by their respective physicians, irrespective of the possible genetic differences of the patients.

The results of this study show that the effect of ACEIs/ARBs on the degree of control of BP were comparable to the effects of CCBs up to one year of follow up, there being no statistically significant differences between the mean SBP2 and mean DB(P1-P2) of the two groups by the end of the study (Table 2). However, there was evidence of more damage to the kidneys over one year in patients who were on CCBs as compared to those who were on ACEIs or ARBs. This was indicated by:

a. Overall, 28.5% of patients in Group 1, compared to 55.5% of patients in Group 2 progressed to higher classes of CKD by the end of one year FU (P <0.001). When stratified by the class of CKD, more patients progressed from CKD1 to CKD2 in the CCBs group compared to ACEIs/ARBs group by the end of the study. In fact 90% of those who progressed from stage 1 to stage 2 where from the CCBs group. A similar, but less dramatic difference was seen in patients who progressed from stage 2 to stage 3; and in those who progressed from stage 4 to stage 5 (see Table 4).
b. There was also significantly more proteinuria in the CCBs group compared to the ACEI/ARBs group from the start of the study, and this continued up the end of the FU period of about one year (Table 2).

Several studies have shown that[14,15,16,17,18] First study: Shown ACEI (Ramipril) decline renal progression in patients with hypertensive renal disease and proteinuria.[14] Second study: Suggested Antihypertensive therapy that included ACE inhibitors was more effective than therapy without ACE inhibitors in slowing the progression of non diabetic renal disease.[15] Third study: Recommended the renoprotective effects of angiotensin converting enzymes and angiotensin-receptor blockers independent of their effect on blood pressure control are uncertain.[16] Fourth study: was found Angiotensin converting enzyme inhibitors appear to be

more effective than b-blockers or dihydropyridine calcium channel blockers in slowing GFR decline.[17] Fifth study was shown ARBs (losartan) treatment decreased albumin excretion in hypertensive patients with non-diabetic nephropathy comparing to CCB (amilodipine).[18]

There was also more hypercholesterolemia in the CCBs group compared to the ACEIs/ARBs group by the end of the study. This may have some implications on causing more damage to the vascular system in the CCBs group over the follow-up period because of the known association of hyperlipidemia with atherosclerosis, in previous study targeting of lipoproteins may be important to decrease CVD in CKD patients, other study of Japanese adults were indicated that high cholesterol level significantly associated with prevalent CKD.[19-20]

This risk of side-effects associated with RAAS blockade, such as hyperkalemia, that may be exaggerated by decrease GFR.[21] did not seem to be a big concern in this study as the mean serum Potassium remained within the acceptable range (4.26 mmol/L +/- 0.60) in the RAAS blockade group compared to 4.12 mmol/L +/- 0.629) in the CCBs group.

We conclude that ACEIs or ARBs when used to treat HTN associated with CKD, had effective control on BP comparable to the use of CCBs. However, ACEIs/ARBs had a clear protective effect on the kidneys in CKD patients in all the stage 1 to 4 and were associated with delay of progression to more advanced stages of CKD compared to CCBs used for the same purpose. This was reflected by more stable eGFR and less proteinuria in the ACEIs/ARBs group compared to the CCBs group over one year of follow-up.

Hyperkalemia is a known complication of ACEIs/ARBs treatment in CKD patients, in previous research[22] was recommended it should be monitored for closely in such patients. However, in this cohort of patients it did not cause significant clinical concern up to one year of follow up.

It seems important to have another study on the same subject with considerations of the ethnic groups in Sudan.

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