COMPARATIVE EFFECTIVENESS STUDY OF COMBINED ANTIHYPERTENSIVES FOR NIGERIAN PATIENTS

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ABSTRACT

Objective: The objective of the study was to compare the clinical and economic effectiveness of four combination antihypertensives recommended for Nigerians.

Methods: An open, randomized, controlled, and longitudinal double-blind trial of four groups of antihypertensives combinations: Telmisartan/chlorthalidone/amlodipine (TCA), TC, CA, and TA was conducted among hypertensive patients. The participants were recruited from three hospitals in Enugu, and randomly assigned to the study groups. The primary outcome for this study was blood pressure (BP) control, based on Joint National Committee-8 and cost per BP control. The secondary outcomes were cost per quality adjusted life years (QALY) and patients' self-reported health status. Descriptive and inferential statistics were used for statistical analysis.

Results: Of the 110 patients enrolled in the study, more than half were women (55.5%). The mean age of patients was 54.93±12.38. The enrollees had hypertension for over 9 years (9.17±8.40). About 77% of the patients completed the study in all the groups except for TA (66.7%). There was no difference in BP in all the groups at baseline and at end-of-study (p>0.050). However, the probability of BP control was highest in TCA group (0.37±0.01), followed by TC group (0.23±0.02). The TA group showed the most favorable cost per QALY, then CA, TC, and TCA in that order. The group with the most favorable cost per BP control was TCA (70.92±0.04), then TA (94.16±0.05).

Conclusion: The triple combination therapy of TCA had the best cost per BP control in the management of hypertensive patients. It demonstrated the highest probability of BP control.

Keywords: Antihypertensive medications, Combination therapy, Cost-effectiveness, Health status.

INTRODUCTION

Hypertension is still a global public health problem, and the financial cost associated with the disease continues to increase. It is estimated to affect over 1 billion people worldwide [1]. Sub-Saharan Africa (SSA) including Nigeria, account for approximately two-thirds of the global burden of hypertension. Hypertension is a major risk factor for the development of other cardiovascular diseases such as heart failure, stroke, and ischemic heart disease [2]. It is one of the leading causes of morbidity and mortality due to cardiovascular complications [3,4].

Nigeria presently has a population estimate of over 180 million, and thus the most populous country in Africa. In 2014, hypertension prevalence in Nigeria was estimated at 28.9% by the World Health Organization. However, in 2030, it is projected that the country will record 39.1 million cases of hypertension among its adult population, with a prevalence of 30.8% [5,6]. Therefore, Nigeria contributes significantly to the hypertension burden in SSA. The high prevalence of hypertension in Nigeria is probably the result of increasing aging population, rapid urbanization, high intake of processed food, tobacco, and alcoholic products [7]. In addition, treatment and control of hypertension are low in Nigeria and other countries in SSA. For instance, a study reported that only 25.4% of patients attending a hypertension clinic in a tertiary hospital achieved desired blood pressure (BP) control [8].

Research has demonstrated that it is usually difficult achieving BP control with a single antihypertensive medication [9,10]. Evidently,

about 75% of patients with hypertension would require two or more antihypertensive drug combination to ensure optimal BP control. This is because the specific cause of hypertension is rarely known and BP elevation is usually the product of multiple factors [9-11]. This makes it almost impossible to control BP with administration of a single antihypertensive medication.

Nevertheless, the Joint National Committee (JNC) on the prevention, detection, evaluation, and treatment of high BP (JNC-8), recommends monotherapy for initial treatment of hypertension in persons <60 years with BP above 140/90 mmHg, with or without diabetes, or chronic kidney disease (CKD). The BP target for patients aged 60 years and above was fixed at 150/90 mmHg. According to the guideline, failure to attain BP target with a single agent warrants the addition of one or more antihypertensive drugs with different mechanisms of action, after titrating initial therapy to a maximum dose, if necessary [12].

In general, hypertension is incurable. Hence, its treatment is lifelong. There are several available antihypertensive drugs for optimal BP control, with varying clinical effectiveness, cost implication, and side effect profile [13,14]. Some of the antihypertensive medications have proven efficacy, but are not affordable by majority of the populace.

However, there appears to be limited data comparing the efficacy and cost of antihypertensive combination therapies to determine the most suitable for black patients in Nigeria and sub-Sahara Africa in general. Therefore, this study aimed to compare the BP control and

cost-effectiveness of four different combinations of antihypertensive therapies recommended for black Africans [12,15,16].

METHODS

Study design
An open, randomized, controlled, longitudinal double-blind, and four-arm parallel prospective trial with 6 weeks patient follow-up. The four arms of the study were: (1) Amlodipine + Telmisartan (AT), (2) A + Chlorthalidone (TAC), (3) T + C, and (4) A + T + C.

Study setting
This study was conducted in three private hospitals in Enugu. The facilities used were the Redemption Clinic, Kenyatta Hospital, and Doctor-on-call Clinic.

Study population
The study participants consist of 110 hypertensive patients who are 18 years and above. The participants were recruited from the outpatient clinics of the study centers.

Patients' allocation
The patients were allocated to the four arms of the study through a mixture of cluster and random sampling techniques. The patients in each clinic who met the inclusion criteria were distributed into clusters based on their matching characteristics. Subsequently, they were allocated to any of the four study arms through simple random technique. The criteria for grouping patients into clusters were age (18–59 years, ≥60 years), sex (male, female), and severity/comorbidity (CKD and/or diabetes, no CKD nor diabetes). Thus, giving rise to eight independent clusters.

Eligibility criteria
The study participants were recruited based on the following inclusion criteria: (1) Patients who are 18 years and above, (2) patients with compelling indications to use a combination therapy, and (3) patients who accepted to visit the clinic weekly for BP measurement and medication refill. The study excluded pregnant women.

Study instruments
The patients' socio-demographic and clinical characteristics were obtained using a pro forma designed for such purpose. The socio-demographic data retrieved include patients' study group, age, sex, marital status, place of residence, occupation, monthly income, and educational level. The clinical variables were duration of hypertension since diagnosis, smoking and alcohol status, physical activity, use of herbal/traditional medicines, and adjuvant medications. Others are BP weekly readings, urine tests (e.g., urine protein, glucose, ketone, PH, nitrite, creatinine clearance, HCO_3, and Tc_a^{2+}), blood tests (e.g., packed cell volume, bilirubin, glucose, fasting blood sugar, creatinine, low-density lipoprotein, high-density lipoprotein, and triglycerides), and anthropometrics (e.g., height, weight, and hip circumference).

Data collection
The patients were assigned to four study groups. Each patient received a 6 weeks supply of antihypertensive drug combinations based on their group. Neither the physician nor the patients knew whether they received a triple combination antihypertensive or any of the three dual combinations. The patients were encouraged to take the medications daily and to monitor their BP. They were asked not to use any other antihypertensive medications throughout the study period of 6 weeks, and to report to the physician if there was a need to stop therapy. The patients were required to visit the clinic once a week, where the physicians examined their health status, measured, and recorded their BP and other clinical information.

The EQ-5D-5L English language version was used to measure patients' health status. The instrument was developed and validated by the EuroQol group. It is internationally accepted and recommended for use in economic evaluation studies. The previous studies have re-validated the instrument among Nigerian population [17]. The EQ-5D instrument consists of the descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system had five dimensions: Mobility, usual care, self-care, anxiety/depression, and pain/discomfort. Each dimension had five levels: "(1) No problem, (2) slight problem, (3) moderate problem, (4) severe problem, and (5) extreme problem." On the other hand, the EQ-VAS is a 20 cm scale with endpoints ranging from 0 to 100. The endpoints "0" and "100" signify "the worst health you can imagine" and "the best health you can imagine," respectively. A box for recording patients' self-rated health state was provided beside the scale.

Outcome measures
The primary outcome for this study was BP control based on JNC-8 guideline and cost per BP control, while the secondary outcomes were cost per quality adjusted life years (QALY) and patients' self-reported health status.

Statistical analysis
The patients' socio-demographic, clinical characteristics, and health status were presented using descriptive statistics (frequency, percent, mean, and standard deviation). Student t-test was employed in examining the mean difference between the pre- and post-tests continuous laboratory values assessed across various study groups. One-way ANOVA test was used to determine the mean difference in systolic BP and diastolic BP for the different study groups. QALY was calculated using the average utility valuation score for the study population. *p<0.05 was considered to be statistically significant.

Ethical considerations
Ethical Committee of University of Nigeria Teaching approved the protocol of study. The patients who are willing to participate were provided with additional written information and asked to sign the study consent form or thumb print for illiterate patients.

RESULTS

Table 1 shows the socio-demographic and clinical characteristics of the patients. Out of the 110 patients enrolled in the study, more than half were women (55.5%). The mean age of patients was 54.93±12.38. The majority of the patients were married (78.2%) and are urban dwellers (82.7%). Less than half of the participants had tertiary education (44.5%). On average, the enrollees have had hypertension for over 9 years (9.17±8.40).

Table 2 reveals the distribution of patients with controlled BP across the different study groups. At the end of study, patients on CA antihypertensive combination had the highest proportion of patients with BP control (83.3%), while enrollees on TA had the least BP control (54.2%).

Table 3 shows the probability of BP control and cost-effectiveness of a triple antihypertensive combination and three dual combinations. The results showed that patients' reported health status indices (EQ-VAS and EQ-5D index scores) were highest for CA group, followed by TCA group. The probability of BP control was highest in TCA group (0.37±0.001), while the least was the TA group (0.19±0.001). The TA group demonstrated the best cost per QALY, followed by CA, TC, and TCA in that order. However, the group with the most favorable cost per BP control was TCA (70.92 ± 0.04), followed by TA (94.16±0.05).

Figs. 1 and 2 shows the acceptability curves for the different interventions. TCA and TA had the best probabilities of being cost-effective at competitive willingness to pay values.

DISCUSSION

This study was the first that compared the effectiveness of combined antihypertensive medications in terms of the BP control and QALY among patients in Nigeria and SSA. Its major findings demonstrate that the probability of BP control was highest among patients on the triple

Table 1: Socio-demographic and clinical characteristics of the patients

Variable	Frequency (percent)				
	TCA	TC	CA	TA	Total
Age (years)	54.12±12.15	57.80±10.78	53.67±14.75	54.29±12.77	54.93±25.39*
Sex					
Male	19 (45.2)	13 (50.0)	6 (33.3)	11 (45.8)	49 (44.5)
Female	23 (54.8)	13 (50.0)	12 (66.7)	13 (54.2)	61 (55.5)
Marital status					
Single	4 (9.5)	2 (7.7)	1 (5.6)	0 (0.0)	7 (6.4)
Married	32 (76.2)	20 (76.9)	15 (83.3)	19 (79.2)	86 (78.2)
Widowed	5 (11.9)	4 (15.4)	2 (11.1)	5 (20.8)	16 (14.5)
Place of residence					
Urban	33 (78.6)	22 (84.6)	16 (88.9)	20 (83.3)	91 (82.7)
Rural	5 (11.9)	2 (7.7)	2 (11.1)	2 (8.3)	11 (10.0)
Occupation					
Unemployed	6 (14.3)	6 (23.1)	6 (33.3)	4 (16.7)	22 (20.0)
Employed	22 (52.4)	13 (50.0)	7 (38.9)	9 (37.5)	51 (46.4)
Retired	11 (26.2)	7 (26.9)	5 (27.8)	7 (29.2)	30 (27.3)
Student	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Educational level					
None	3 (7.1)	1 (3.8)	1 (5.6)	2 (8.3)	7 (6.4)
Primary	10 (23.8)	7 (26.9)	3 (16.7)	8 (33.3)	28 (25.5)
Secondary	12 (28.6)	3 (11.5)	3 (16.7)	5 (20.8)	23 (20.9)
Tertiary	16 (38.1)	14 (53.8)	11 (61.1)	8 (33.3)	49 (44.5)
Monthly income (naira)	47933±69733	75318±12697	27125±24879	35053±34858	49190±34858*
Duration of diagnosis	10.27±9.303	9.56±8.917	9.35±8.403	6.96±6.175	9.17±16.577*
Comorbidity					
Diabetes	0 (0.0)	4 (15.4)	2 (11.1)	2 (8.3)	8 (7.3)
Hyperlipidemia	4 (9.5)	1 (3.8)	1 (5.6)	1 (4.2)	2 (1.8)
Stroke	1 (2.4)	1 (3.8)	2 (11.1)	1 (4.2)	8 (7.3)
Others	5 (11.9)	1 (3.8)	1 (5.6)	2 (8.3)	9 (8.2)
Smoking status					
No	40 (95.2)	25 (96.2)	16 (88.9)	22 (91.7)	103 (93.6)
Yes	2 (4.8)	0 (0.0)	0 (0.0)	1 (4.2)	3 (2.7)
Alcohol status					
No	28 (66.7)	14 (53.8)	11 (61.1)	14 (58.3)	67 (60.9)
Yes	14 (33.3)	12 (46.2)	7 (38.9)	9 (37.5)	42 (38.2)
Herbal/traditional medicine status					
No	33 (78.6)	21 (80.8)	12 (66.7)	19 (79.2)	85 (77.3)
Yes	9 (21.4)	5 (19.2)	6 (33.3)	4 (16.7)	24 (21.8)
BP apparatus					
No	28 (66.7)	16 (61.5)	12 (66.7)	16 (66.7)	72 (65.5)
Yes	14 (33.3)	10 (38.5)	6 (33.3)	7 (29.2)	37 (33.6)
Physical activity					
No	10 (23.8)	5 (19.2)	5 (27.8)	9 (37.5)	29 (26.4)
Yes	31 (73.8)	20 (76.9)	13 (72.2)	13 (54.2)	77 (70.0)

*Mean±standard deviation. TCA: Telmisartan/chlorthalidone/amlodipine, TC: Telmisartan/chlorthalidone, CA: Chlorthalidone/amlodipine, TA: Telmisartan/amlodipine.
TCA: Telmisartan/chlorthalidone/amlodipine, TC: Telmisartan/chlorthalidone, CA: Chlorthalidone/amlodipine, TA: Telmisartan/amlodipine, BP: Blood pressure

Table 2: Blood pressures control across the different study groups

Study groups	BP control, n (%)	
	Uncontrolled	Controlled
Telmisartan+Chlorthalidone+Amlodipine	16 (38.1)	26 (61.9)
Telmisartan+Chlorthalidone	10 (38.5)	16 (61.5)
Chlorthalidone+Amlodipine	3 (16.7)	15 (83.3)
Telmisartan+Amlodipine	11 (45.8)	13 (54.2)

combination (TCA) therapy, followed sequentially by patients on TC, CA, and TA. It also showed that TCA had the most favorable cost per BP control followed by TA. Other findings showed that patients on TA combination had the best cost per QALY.

Acceptability curves were used to present the result of cost-effectiveness analysis. Acceptability curves illustrate the probability that any particular intervention is cost-effective conditional on the willingness to pay per QALY [18]. The curve also illustrates the degree of uncertainty in the estimates. The cost-effectiveness acceptability curve based on BP control showed that at willingness to pay above $40, TCA was the most cost-effective. At higher willingness to pay values, no other combination was a contender for cost-effectiveness with TCA. At willingness to pay below $40, TA was the most cost-effective.

The cost-effectiveness acceptability curve based of QALY showed that at willingness to pay below $600, TA was the most cost-effective. At willingness to pay above $600, CA and TCA were the most effective. Even at willingness to pay value above $2000, CA and TCA were most cost-effective. Although this values are high, they are still within the WHO threshold limit for cost-effectiveness [19,20].

The findings of this study were similar to those reported in a Greek study of the cost-effectiveness analysis of a triple combination of valsartan, A, and hydrochlorothiazide over its dual combinations [21]. In the study, Stafylas *et al.* found that the single triple combination therapy was more cost-effective compared to the dual combinations (valsartan and A, A and hydrochlorothiazide, and valsartan and hydrochlorothiazide). Even though the triple combination therapy was the most expensive, it is a cost-effective choice for patients with moderate to severe hypertension [21].

Table 3: Probability of BP control and cost-effectiveness of a triple antihypertensive therapy and 3 different dual combinations

Variables	Study group (mean±standard deviation)			
	TCA	TC	CA	TA
Cost of drugs per annum ($)	26.24±0.05	23.86±0.03	21.47±0.04	17.89±0.03
EQ-VAS score	71.60±14.09	65.47±20.53	71.30±11.10	66.22±11.05
EQ-5D index score (utility valuation)	0.78±0.10	0.74±0.12	0.80±0.13	0.69±0.11
Probability of BP control	0.37±0.01	0.23±0.02	0.21±0.01	0.19±0.01
QALY	0.128±0.0064	0.126±0.0073	0.130±0.0075	0.123±0.0058
Cost per QALY	205.00±8.69	189.37±9.35	165.15±7.14	145.45±7.1
Cost per BP control	70.92±0.04	103.74±0.06	102.24±0.03	94.16±0.05

TCA: Telmisartan+Chlorthalidone+Amlodipine; TC: Telmisartan+Chlorthalidone; CA: Chlorthalidone+Amlodipine, TA: Telmisartan+Amlodipine, BP: Blood pressure, QALY: Quality adjusted life years, EQ-VAS: EQ visual analogue scale
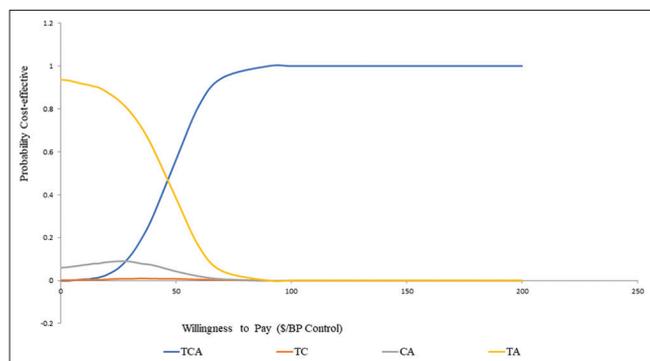
Fig. 1: Cost-effectiveness acceptability curve for the four interventions based on cost per blood pressure control
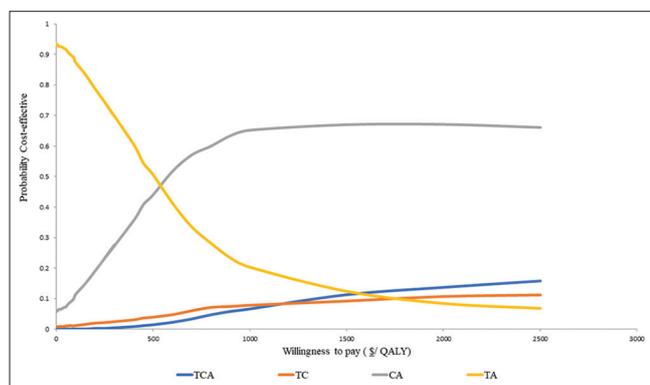

Fig 2: Cost-effectiveness acceptability curve for the four interventions based on cost per quality adjusted life years

Although diuretics generally appear to be the least expensive antihypertensive drug class, they are usually recommended as monotherapy for hypertensive patients without any compelling indication. Nevertheless, studies have shown that hypertensive patients require an average of three drugs for effective BP control [9]. The present study lends support to this notion. It has been suggested that in black patients who require more than one drug for BP control, a combination of renin-angiotensin-aldosterone system inhibitor, dihydropyridine-type calcium channel blocker, and diuretic should be recommended.

In this study, the triple combination was the most cost-effective in terms of BP control. The probability of achieving target BP control was about 2 times higher for patients on triple combination compared to those taking dual combinations. Nevertheless, T and A combinations should be reserved as an alternative considering that patients benefitted more from the combination in terms of cost per QALY gained. Hence, in cases where the quality of life of the patient is of paramount importance, T, and A combination should be considered as the first option. Furthermore, patients who are unable to afford the triple combination therapy can equally benefit from the TA dual combination as it is the least expensive.

Furthermore, the current treatment guidelines advocate for the use of single fixed dose combinations for patients requiring more than one antihypertensive drug to attain optimal BP control [10]. This is because of the high prevalence of poor medication adherence often seen among patients on multiple medications. The use of fixed dose combinations improves medication adherence with resultant better BP control and reduction in cardiovascular risks associated with hypertension [14,22].

In addition, inappropriate antihypertensive combination or poor drug selection is thought to be responsible for low BP control in many countries. A large proportion of patients present to the hospitals or clinics with resistant hypertension, thus giving a unique challenge to the clinician regarding the best drug combination to prescribe bearing in mind patient's characteristics and financial strength. Thus, there is need for fixed dose combinations.

The parameters of the laboratory tests (pre and post) carried out showed that the drug combinations had no significant effect on the electrolytes and other key parameters.

The findings of the present study would serve as possible guide for clinical practitioners in Nigeria; regarding the clinical and economic efficacies of commonly recommended antihypertensive drug combinations for the Black population.

Limitations

One major limitation of this study was that we used a small sample size from three settings in one town. Using a larger population and more centers are recommended in future studies.

Furthermore, extra laboratory tests would have given us a clearer effect of some pharmacodynamic properties of the different drug combinations, for example, liver function test and platelet count. There is growing evidence that thiazides and thiazide-like diuretic reduces platelet aggregation. However, the extent is still unknown and investigations are still ongoing [23,24]. Conducting platelet count test would have provided information about their effect on platelet count.

CONCLUSION

The triple combination therapy of TCA had the best cost per BP control followed by TA combination in the management of hypertensive patients. Furthermore, triple combination therapy demonstrated the highest probability of BP control. Therefore, this study provides valuable information to guide clinicians in decision-making regarding appropriate antihypertensive drug selection in the management of hypertensive patients. However, there is a need to further validate the study findings using larger population.

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