COMPARATIVE COST-BENEFIT OF ANTIMALARIA THERAPY

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ABSTRACT

Background: Antimalaria combination therapy is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets on malaria parasites. Presently, 90% of global episodes of clinical malaria and malaria mortality occur in sub-Saharan Africa. Malaria control efforts in the region were greatly affected by the emergence and spread of chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) resistant plasmodium species. Artemisinin-based combination therapies (ACTs) was shown to improve treatment efficacy and curtailed drug resistance. The study aimed at comparing the post-treatment protection period as benefit with cost of procuring antimalarial drugs by consumers.

Method: The University Health Center, Uyo was selected for the study by convenience sampling. Ethical approval was obtained from the Center. Case notes of 118 patients on antimalaria prescriptions attending the Center for treatment of uncomplicated malaria from January 1st 2004 to December 31st 2013 were surveyed. Information such as age, sex, names and time of prescribed antimalarial drugs were collated. Protection period was measured by time interval between two antimalarial prescriptions. Statistical analysis was computed by using SPSS version 21 software packages. Statistical significance level was set at p=0.05.

Result: A total of one thousand three hundred and sixty-five (1365) antimalarial prescriptions were collated among patients of different age groups ranging from 0 to 79 years. Four hundred and eighty-four (484) and eight hundred eighty-one (881) antimalarial prescriptions were received by male and female patients respectively. Antimalarial single therapy (558, 40.87%) was prescribed mostly in 2004 while ACT (443, 32.45%) and other combination therapies (323, 23.66%) were used predominantly after 2004. SP (208, 37.27%) and Artemether +

Lumefantrine (AL) (309, 69.75%) were the most frequently prescribed antimalarial single therapy and approved ACT respectively. The protection period of antimalarial single therapy was highest for Artesunate (233.75±31.92days). The protection period of antimalarial combination therapy approved as ACT was highest for Artesunate + Amodiaquine (AA) (192.51±24.28days).

Conclusion: This study showed that none of the recommended artemisinin-based combination therapies produced protection period as when artesunate was used alone. AA was shown to have the best cost-benefit among all the four recommended ACTs.

Key words: Artemisinin-based Combination Therapies, Sulphadoxine-Pyrimethamine, Chloroquine, Cost-benefit, Protection Period

Introduction

Over 3.2 billion people in 107 countries were at risk of malaria attack[1]. Over 80% of deaths associated with malaria occurred in Africa. Malaria infects about 219 million people annually and caused about 438,000 deaths which are mostly African children[2]. Ninety per cent of malaria deaths occur in Africa, where malaria accounts for about 10% of under-five deaths[2]. Malaria infection during pregnancy is associated with severe anaemia which caused low birth weight of newborn infants[3]. Anaemia is one of the leading risk factors for infant mortality, growth and development in Africa[2].

Malaria has strong economic impacts in Africa such as slowing economic growth, development and propelling the vicious cycle of poverty[4]. Malaria is a disease associated with poverty because it afflicts primarily the poor who live in malaria-endemic rural areas where houses offer little barriers to mosquitoes[3].The implication of malaria burden on economic growth indicated 1.3% annual reduction in Nigeria's economic growth[5]. Malaria scourge has compounded both national economy and household poverty as a result of loss of productive time due to malaria attack and death. Growing resistance to cheap antimalarial drugs necessitated the need for more expensive artemisinin-based combination therapy (ACT)[6]. In 2001, WHO recommended that both SP and CQ should be replaced by ACT as first line therapy[7]. The Federal Ministry of Health (FMOH) in Nigeria had a summit in 2004 to develop principles of adopting ACT as part of National Antimalaria Treatment Policy[8]. ACT has shown more therapeutic advantages over CQ and SP. ACT has been proved to reduce treatment failure

and recurrence of new malaria episodes[9]. However, ACTs are more expensive than SP and CQ[10].

Combination therapy with antimalarial drugs is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite. Multiple-drug therapies that include a non-antimalarial drug to enhance the antimalarial effect of a blood schizontocidal drug are not considered combination therapy. Antimalarial drugs that fit the criteria of synergistic fixed-dose combinations are operationally considered as single products when none of the individual components would be given alone for antimalarial therapy such as sulfadoxine-pyrimethamine[7].

Access to ACTs in malaria-endemic countries has led to remarkable success in reducing the global malaria burden. No alternative antimalaria medicine is currently available offering the same level of efficacy and tolerability as ACTs. In Africa there is evidence that the spread of antimalarial drug-resistance coincided with increases in child mortality and morbidity[2].

All ACTs contain an artemisinin derivative combined with a partner drug. There are currently five ACTs recommended by World Health Organisation (WHO). The role of the artemisinin compound is to reduce the main parasite load rapidly during the first days of treatment; the role of the partner drug is to eliminate any remaining parasites. A high proportion of patients infected with artemisinin-resistant strains of Plasmodium falciparum, are still parasitaemic 72 h after the beginning of treatment; however, patients are currently still cured if they are treated with an ACT containing a partner drug that is still effective in the geographical area. If resistance to artemisinins exists, it is more likely that resistance to the partner drugs will also develop, and vice versa. Consequently,

resistance to ACT partner drugs is also an important concern, and must be monitored carefully[2].

Soe *et al.* emphasized the importance of protection from clinical malaria after administration of antimalaria drug regimens especially in hyperendemic environment[11]. WHO reported the use of SP as intermittent preventive treatment of malaria in both pregnant women and infants. WHO also recommended amodiaquine + SP as monthly chemopreventive treatment in children below 6 years old in sub-Sahel region of Africa[12].

This study aimed at generating systematic evidence on the consumer's cost and post-treatment benefits of antimalarial therapy by assessing and comparing the cost and protection period of ACTs and monotherapy such as SP and CQ in uncomplicated malaria patients attending secondary healthcare facility.

Method

This study was designed to assess data on consumers' cost of malaria treatment and their derived benefit of protection period from further attacks of malaria in a secondary healthcare facility. According to Soe *et al.*, an individual residing in a malaria hyperendemic region is assumed to be clinically protected when the individual has no episode of clinical malaria over a period of time[11]. Convenient sampling was used to select University Health Center, University of Uyo for the study. Case notes of patients attending the University Health Center for treatment of uncomplicated malaria from January 1st, 2004 to December 31st, 2013 were surveyed and relevant information such as age, sex and drug regimen and time of prescription were documented. The case notes of one hundred and eighteen (118) patients consisting of forty-nine (49) males and sixty-nine (69) females were surveyed for malaria treatment. In this survey, the period that

patients did not present at the clinic for malaria treatment were assumed as period of no clinical malaria and were regarded as protection period. This study used the average of protection periods derived by all individuals receiving a particular antimalarial agent. Also, the case notes showed laboratory test results indicating presence of malaria parasites before commencement of malaria treatment by the Clinicians. The cost of malarial drug per episode of malaria attack and period in between malaria attacks (protection period) after use of antimalarial drugs were determined for each antimalarial agent and compared with other antimalarial agents. The retail prices of antimalarial drugs in 2013 were used to calculate the cost of documented drug regimen. The cost of antimalarial drug regimen at the time of the study, NGN 170.00 was equivalent to US$1.00.

In order to evaluate the cost-benefit of antimalarial drug regimens, the consumer's cost and protection period for antimalarial drug regimens were compared. The year different antimalarial therapies were used was not taken into consideration in this study because same patients that used the single antimalarial therapy were the ones that used the combination therapy. This study intended to look at the benefits derived by these patients after their exposure to different antimalaria therapies in this period of review.

Data were analysed by using SPSS version 21 software package. Descriptive statistics were used in result presentation. Test statistics used were t-test and ANOVA. Significance level was set at $p=0.05$.

Results

A total of one thousand three hundred and sixty-five (1365) antimalarial prescriptions were collated among patients of different age groups ranging from 0 to 79 years who attended the clinic during the ten years of review. Four

hundred and eighty-four (484) antimalarial prescriptions were received by male patients while eight hundred and eighty-one (881) were received by the female patients (Table 1) within the period of review. Among the documented antimalarial therapies used by the selected patients, single therapy (558, 40.87%) was prescribed most frequently within the early period of review followed by ACT (443, 32.45%) and other combination therapies (323, 23.66%) respectively. SP (208, 37.27%) was the most frequently prescribed antimalarial single therapy followed by Chloroquine (105, 18.81%) and amodiaquine (83, 14.87%) respectively. The most frequently prescribed antimalarial combination therapy approved as ACT was AL (309, 69.75%) followed by AA (75, 16.93%) and DP (30, 6.77%) respectively (Table 2).

Table 1: Demographic parameters

S/N	PARAMETERS	FREQUENCY
1	Sex	
	Male	49 (41.53%)
	Female	69 (58.47%)
	Total	**118**
2	Antimalaria prescriptions per age group (in years)	

	0-19	377 (27.62%)
	20-39	317 (23.22%)
	40-59	507 (37.14%)
	60-79	164 (12.01%)
	Total	**1365**
3	Antimalaria prescription per gender	
	Male	484 (35.46%)
	Female	881 (64.54%)
	Total	**1365**

Table 2: Pattern of antimalarial prescriptions

Antimalarial therapy	**Number of prescriptions**	**Combination therapy**	**Number of prescriptions**
ACT	443 (32.45%)	Artesunate + Mefloquine (AM)	29(6.54%)
OCT	323 (23.66%)	Artemether + Lumefantrine (AL)	309(69.75%)
ST	558 (40.87%)	Artesunate + Amodiaquine (AA)	75(16.93%)

Others	41 (3.00%)	Dihydroartemisinin + Piperaquine (DP)	30(6.77%)
Total	**1365**	**Total (ACT)**	**443**
Single therapy (ST)	**Number of prescriptions**	**Other combination therapy (OCT)**	**Number of prescriptions**
Amodiaquine	83(14.87%)	SP + Amodiaquine (SPA)	84(26.00%)
Artesunate	79(14.15%)	SP + CQ (SPQ)	17(5.26%)
SP	208(37.27%)	CQ + Artemether (CQA)	6(1.85%)
Chloroquine	105(18.81%)	Artesunate + SP (ASP)	194(60.06%)
Halofantrine	19(3.4%)	Artemether +Amodiaquine (ArA)	6(1.85%)
Artemether	36(6.45%)	Artesunate + CQ (ACQ)	5(1.54%)
Dihydroartemisinin	23(4.12%)	Artemether + SP (ArSP)	8(2.47%)
Arteether	5(0.89%)	Halofantrine + CQ (HCQ)	3(0.92%)
Total	**558**	**Total (OCT)**	**323**

The protection period of antimalarial single therapy was highest for artesunate (233.75±31.92days) followed by amodiaquine (228.22±32.94days), SP (211.02±17.28days), halofantrine (192.00±37.34days) and chloroquine (181.22±23.10days) respectively. The cost of procuring single antimalarial drug was highest for arteether (NGN1,716.66±343.91) followed by halofantrine (NGN1,497.00±79.29) and artemether (NGN658.10±36.22) respectively (Table 3). The protection period of antimalarial combination therapy approved as ACT was highest for AA (192.51±24.28days) followed by AM (166.0±34.66days), DP (137.19±33.15days) and AL (137.02±8.75days) respectively. The cost of antimalarial combination therapy approved as ACT was highest for AM

(NGN916.66±53.62) followed by AL (NGN880.74±18.21) and DP (NGN468.06±58.12) respectively (Table 4).

The protection period of antimalarial single therapy showed that SP was varied significantly from artemether (p=0.000) while the cost of procuring SP was varied significantly from all the other antimalarial single therapy (p=0.000). The protection period of CQ was varied significantly from dihydroartemisinin (p=0.003) while the cost of procuring CQ was varied significantly from all the other antimalarial single therapy (p=0.000).

The protection period of DP was shown to be significantly lowered than SP (p=0.000). The cost of procuring antimalarial combination therapy approved as ACT was significantly higher than SP. Only AL (p=0.007) among antimalarial combination therapy approved as ACT had protection period which was significantly lower than that of CQ. The cost of procuring AM (p=0.009) and AA (p=0.003) were significantly higher than that of CQ. Among other antimalarial combination therapy, ArA (p=0.001) showed a significantly higher protection period over SP.

Table 3: ANALYSIS OF SINGLE THERAPY IN MALARIA TREATMENT

S/N	SINGLE THERAPY	WEIGHT (KG) Mean±SEM	AGE (YEARS) Mean±SEM	PROTECTION PERIOD (DAYS) Mean±SEM	COST (NGN) Mean±SEM	COST (US DOLLAR) Mean±SEM
1	Amodiaquine	49.66±11.69	31.83±1.95	228.22±32.94	173.09±3.79	1.01±0.02
2	Artesunate	45.80±15.31	41.11±2.12	233.75±31.92	326.87±6.22	1.91±0.03
3	SP	26.4±3.47	35.47±3.01	211.02±17.28	135.31±7.23	0.79±0.04
4	Chloroquine	16.07±5.03	30.18±2.30	181.22±23.10	185.90±8.77	1.08±0.05
5	Halofantrine	19.67±6.97	22.05±4.70	192.00±37.34	1497.00±79.29	8.80±0.46
6	Artemether	14.0±2.04	20.59±3.91	142.27±25.66	658.10±36.22	3.86±0.21
7	Dihydroartemisinin	NA	39.62±3.38	138.75±26.03	479.58±25.59	2.81±0.15
8	Arteether	NA	11.50±6.27	90.0±45.16	1716.66±343.91	10.09±2.02

Table 4: ANALYSIS OF COMBINATION THERAPY IN MALARIA TREATMENT

S/N	COMBINATION THERAPY	WEIGHT (KG) Mean±SEM	AGE (YEARS) Mean±SEM	PROTECTION PERIOD (DAYS) Mean±SEM	COST (NGN) Mean±SEM	COST (US DOLLAR) Mean±SEM	Remark
1	Artesunate + Mefloquine (AM)	NA	45.80±3.38	166.0±34.66	916.66±53.62	5.39±0.31	ACT
2	Artemether + Lumefantrine (AL)	26.18±1.71	35.70±1.26	137.02±8.75	880.74±18.21	5.18±0.10	ACT
3	Artesunate + Amodiaquine (AA)	27.8±1.71	36.34±2.31	192.51±24.28	440.39±12.92	2.58±0.07	ACT
4	Dihydroartemisinin + Piperaquine (DP)	NA	39.87±3.31	137.19±33.15	468.06±58.12	2.74±0.34	ACT
5	SP + Amodiaquine (SPA)	32.43±8.08	31.67±2.32	176.82±20.61	292.23±7.08	1.71±0.04	OCT
6	SP + CQ (SPQ)	NA	23.05±5.29	211.66±55.80	277.22±18.93	1.62±0.11	OCT
7	CQ + Artemether (CQA)	11.00±3.00	51.42±10.78	742.85±152.52	4.36±0.89	0.92±0.34	OCT
8	Artesunate + SP (ASP)	22.38±3.17	42.14±1.38	180.77±18.43	423.94±4.31	2.49±0.02	OCT
9	Artemether + Amodiaquine (ArA)	NA	13.85±6.39	287.14±155.03	665.71±138.52	3.91±0.81	OCT
10	Artesunate + CQ (ACQ)	NA	33.50±11.53	180.0±109.81	508.33±132.64	2.96±0.77	OCT
11	Artemether + SP (ArSP)	NA	2.0±0.72	126.66±53.09	713.33±100.52	4.19±0.59	OCT
12	Halofantrine + CQ (HCQ)	7.5±0.5	9.93±9.35	105.0±51.23	1312.50±437.50	7.71±2.57	OCT

13	Artesunate + Artemether (AAr)	NA	0.5±0.5	90.0±90.0	525.0±525.0	3.08±3.08	OCT
14	Arteether + SP (AtSP)	NA	4.0±2.30	250.0±206.63	1500.0±750.0	8.82±4.41	OCT

Protection period of AL showed significant correlation with age (p=0.007). Protection period of AA showed significant correlation with weight (p=0.022) and age (p=0.000). Protection period of DP showed significant correlation with weight (p=0.000). Protection period of SPA showed significant correlation with weight (p=0.021). Protection period of ASP showed significant correlation with weight (p=0.009), age (p=0.001) and cost (p=0.008).

Discussion

Protection period is a derived benefit after administration of a particular antimalarial drug regimen which clears malaria parasites from the systemic circulation. The consumer of antimalaria drug regimen is therefore protected from clinical malaria until a particular period that clinical malaria emerges[11]. In this study, more females were found to attend clinic than males because they tended to show care for health issues than males as reflected by the number of prescriptions for antimalarial treatment received. Earlier reports had indicated that more females attended hospitals for treatment than their male counterparts[13,14]. The effectiveness of antenatal clinic for pregnant women is also an important factor for ensuring that more women assess their health needs. In the ten year review of antimalarial treatment, fifty-nine percent of the antimalarial drugs used were combination therapy indicating widely acceptability of the artemisinin-based combination therapy thereby supporting previous

report[15]. This was due to universal recommendation of artemisinin-based combination therapy for treatment of uncomplicated malaria[16] and advocacy for Home Management of Malaria in underserved rural communities[17,18]. The most widely used antimalarial single therapy was SP followed by Chloroquine suggesting their high tolerability and availability to consumers which justified their use as first line in treatment of malaria prior to adoption of ACT as first line by Federal Ministry of Health[8]. AL was the most commonly prescribed antimalarial combination therapy. Previous report had indicated AL as the most widely used of artemisinin-based combination therapy[7].

Artesunate among the single therapy had the longest protection period, which implied that the period in-between malaria attacks indicated its benefit after treatment of malaria. The benefit of artesunate could be attributed to its earlier confirmed superior bioavailability above other artemisinin derivatives and other antimalarial drugs[19]. Amodiaquine was close to artesunate in protection period which also indicated its benefit to consumers after malaria treatment. Both SP and Chloroquine had their protection period below that of artesunate suggesting that they were of less benefit to consumers after treatment of malaria. The cost of procurement of antimalarial single therapy was highest for arteether, halofantrine and artemether though were not among the top three single antimalarial drugs with highest derived benefit. This probably suggested that the cost of procurement of these three antimalarials was not commensurate with the benefit derived by the consumers.

The protection period of antimalarial combination therapy approved as ACT was highest in descending order for AA, AM, DP and AL suggesting the decreasing order of their benefits to the consumers. The artemisinin component of ACT was reported to rapidly clear parasites from the blood, active against sexual stages of

parasites that mediate onward transmission to mosquito while the longer acting partner drug clear the remaining parasites and provide protection against resistance[12]. Partner drugs with longer elimination half-lives also provide a period of post-treatment prophylaxis[12]. In a previous report, it was indicated that AA had a complete cure rate (100%) and better performance than AL after 28 days of follow-up after administration of the ACTs among under-five children[9]. This might be responsible for the benefit of AA because it might take a longer period before clinical malaria can emerge after complete clearance of plasmodium species. This finding was in contrast to the report of Bretscher *et al.*, whose observation from a meta-analysis study indicated that DP had better protection period after malaria treatment than AA and AL respectively[20]. This variance could be due to different genetic factor and antimalarial drug resistance.

None of the recommended ACT had protection period up to that of antimalaria single therapy, when artesunate or SP was used alone suggesting that this derived benefit did not match that of artesunate. However, use of single therapy artesunate is not encouraged because of emergence of resistance. SP is presently used as intermittent prevention of malaria in pregnancy, the benefit of SP resulted in reduction of severe maternal anaemia[21], low birth weight[22] and perinatal mortality[23]. Intermittent preventive treatment in infants with SP was reported to provide protection against clinical malaria and anaemia in first year of life[24]. Apart from AA, no other antimalaria combination therapy approved as ACT had protection period up to that of CQ. This probably suggested that combination of artesunate with other antimalarias such as amodiaquine, mefloquine, piperaquine and lumefantrine were not with high benefit as when artesunate was used alone. This observation might be due to in vivo interaction between other antimalarial drugs and artesunate or its derivatives. Winthrop had reported that artesunate derivative, dihydroartemisinin was statistically

significantly reduced by 47% when artesunate was concomitantly used with amodiaquine[25]. In recent times, there had been repeated use of artemisinin-based combination therapy because of lack of immediate response to treatment which might be an indication of emerging resistance[26]. Hence, there will be low derived benefit from the use of any artemisinin-based combination therapies with low clearance of plasmodium species. The artemisinin-based combination therapy with the highest benefits, AA, also had the lowest cost of procurement. Among the ACT, AA suggested to be best cost-benefit artemisinin-based combination therapy to the consumers as observed in this study.

The comparative analysis in this study indicated that SP had protective advantage over artemether and cost advantage over other single antimalarias. Similarly, CQ had protective advantage over dihydroartemisinin and cost advantage over other single antimalarias. Among the recommended ACTs, DP had protective period which was significantly lower than that of SP suggesting that DP did not offer better benefit after treatment of malaria than SP. The protection period of AL was significantly lowered than that of CQ suggesting that AL did not offer better benefit after treatment of malaria than CQ. This probably suggested that the cost of procuring ACTs by patients did not produce a commensurate benefit of protection from further attack of malaria better than CQ and SP. This support the findings of a previous study conducted in Uganda which suggested the cost of ACTs was yet to be justified in the treatment of uncomplicated malaria[27]. WHO apparently appreciated the cost implication of using ACTs and had advocated for involvement of all stakeholders at improving cost-effectiveness of ACTs at curbing the menace of malaria in the endemic regions of the World[7].

Among other antimalaria combination therapy which were not recommended for ACT, ArA had protection period which was significantly higher than that of SP suggesting that it offered a better benefit after treatment of malaria than SP. It also had a better benefit than those of the recommended artemisinin-based combination therapy suggesting that its recommendation as ACT might be very helpful in the treatment of malaria.

The protection period of AL was significantly correlated with age suggesting that age of consumers would determine the extent of protection period. AA was significantly correlated with age and weight suggesting that the protection period would depend on weight and age of the consumers. Protection period of DP was significantly correlated with weight suggesting that protection period would depend on the weight of consumers.

The limitation of the study included possibility of patients attending other clinics for treatment of malaria or using self-medication of which reports were not included in the folders of patients. Other malaria preventive control measures such as use of mosquito treated net and indoor or outdoor spraying which were not documented in the patients' folders could also affect the results of the study.

Conclusion

In conclusion, this study showed that none of the recommended artemisinin-based combination therapy (ACT) produced longer protection period as when either artesunate or SP was used alone. AA was shown to have the best cost-benefit among all the four recommended ACTs. ArA was shown to have protection period higher than all the recommended ACTs.

Recommendation

In vivo interaction of artesunate and its derivatives with other antimalaria drugs used in ACTs should be considered for further research. ArA should also be considered for recommendation as ACTs. Weight of patients intending to use antimalaria should be determined and documented before prescription of ACTs in hospitals.

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