

An open randomized controlled trial to compare the efficacy of two fixed dose combinations of artemisinin based combinations for uncomplicated falciparum malaria in Bangladesh

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Abstract

National Malaria Control Program (NMCP) of Bangladesh has introduced Artemisinin Based Combination (ACT), Coartem^(R) (Artemether-Lumefantrine (AL), fixed dose combination, in the confirmed cases of uncomplicated *P. falciparum* malaria since 2004. Despite the reduction of mortality due to malaria, the development and spread of anti-malarial drug resistance worldwide posing a threat to the health services and will make it difficult to control malaria in Bangladesh in future. We need to have an alternative to Coartem which could be Artesunate-amodiaquine (AA) in a fixed dose combination (FDC), a cheaper alternative not yet evidenced to be effective and safe to our population. In this study we compared the efficacy and safety of Artemether + Lumefantrine (FDC, Coartem^(R)) with Artesunate +Amodiaquine tablets (100/270 mg FDC) for the treatment of uncomplicated *P. falciparum* malaria in three high risk multi-drug resistant malaria prevalent areas of Bangladesh. It was an open label randomized controlled trial conducted between December 2008 and November 2009 in 4 upazillas in patients over the age 12 to 60 years diagnosed as a case of uncomplicated *P.falciparum* malaria. The outcome of the cases were measured as clinical response, parasitological response, defervescence time and parasite clearance time. Drug safety was assessed by comparing the adverse events. A total of 252 cases were randomized to receive Artesunate + Amodiaquine (AA group, 147 cases) and Artemether + Lumefantrine (AL group, 106 cases), one lost to follow up at day 28 in AA group. The distribution of the cases was comparable by age, sex and study sites. Treatment success⁷ response was observed 100% in the AL group and AA group had 99%, two failures with AA were late treatment failures and the difference was not statistically significant ($p>.1$). The parasitological sensitive (S) response was observed in 97% of cases in AL group and 95% in the AA group, and was not a statistically significant difference. There was no significant difference in defervescence time and parasite clearance time between two groups of cases. No serious adverse events were observed. The frequencies of minor adverse events were insignificantly different between the two treatment groups. The two ACT regimen, AA and AL had no significant difference in efficacy and safety for treatment of Uncomplicated Malaria in Bangladesh. However, there were few more failures with AA regimen compared to AL regimen, which was not statistically significant. Both these regimens can be used alternatively by the NMCP of Bangladesh as first-line treatment option.

Introduction

Bangladesh has updated the treatment regimen and guidelines of malaria with artemisinin based combination, Coartem^(R) (artemether and lumefantrine) for diagnosed cases of uncomplicated *P. falciparum* malaria as the first line drug replacing CQ since 2004¹. In Bangladesh, malaria transmission is restricted to the hilly districts in the eastern and northern border areas. The majority of malaria cases are found in three districts of the Chittagong Hill Tracts (CHT)².

Emergence of drug resistance in *P. falciparum* was a serious problem to malaria control in Bangladesh. Resistance (RII+RIII) to chloroquine (CQ) has increased from 10% in 1979 to 45% in 1987 and 57% in 1992³. The failure to CQ and sulphadoxine-pyremethamine (SP) was first documented in the country between 1968 and 1970⁴. Thereafter, scanty data are available from the government's Malaria and Parasitic Disease Control unit (unpublished), showing in-vivo cure rates sensitive/resistance (S/RI) from various falciparum endemic areas until 1993 of 41% (466/1149) for

CQ, 56% (283/508) for SP and 100% (328/328) for Quinine. In vitro sensitivity testing over the same period showed sensitivity (S) in 161/1049 (15%), 215/343 (63%), 284/284 (100%) and 884/884 (100%) for CQ, SP, Quinine and Mefloquine respectively. After 1993, no systematically collected sensitivity data were available. Guidelines for treatment were available periodically, but not uniformly implemented. Few small-scale studies showed the existence of clinical and parasitological failures to CQ, CQ+SP and SP⁵⁻⁷.

More recent trials showed >70% resistance to CQ⁸. High levels of in vitro mefloquine resistance also been reported in the area, despite the fact that this drug was not part of the national drug policy⁹. Several antimalarial drug combinations have subsequently been tried in the region¹⁰. The fixed combination artemether/lumefantrine was proven to be highly effective for the treatment of uncomplicated falciparum malaria in the area, with a 92.4% cure rate and excellent tolerability¹¹. Based on the findings of this study as well as the high levels of resistance to other antimalarials, the Government of Bangladesh changed the recommended firstline treatment of parasitologically confirmed uncomplicated falciparum malaria to the artemisinin-based combination therapy (ACT) artemether/lumefantrine, Coartem^(R)¹.

ACT is also recommended for use in the whole of sub-Saharan Africa. Fifteen out of 43 Sub-Saharan African countries have already adopted AA as first-line drug and the rest are at various stages of preparation for changes to the same regimen or to AL^{12,13}.

It has been proven that efficacy of artemether/lumefantrine for the treatment of uncomplicated falciparum malaria in Bangladesh is still high¹⁴. As emergence and spreading drug resistance is a serious problem worldwide puts on pressure for constant change of drug policy according to local evidences on sensitivity.

Every drugs for infectious diseases, especially anti-malarials has exhibited a therapeutic life span and efficacy declines over time. The current recommended AL regimen for Bangladesh is also expected to have a decline in efficacy over time. The evidence on the efficacy of alternative ACTs should be available for Bangladesh especially as FDC as alternative first line anti-malaral drug. Also the cost of AL regimen is about 2.5 USD compared to the of AL regimen about 1.5 USD per treatment course. The other ACT Artesunate plus Mefloquine is about 4.5 USD and may not be suitable for Bangladesh on cost consideration at present.

This study was an attempt to evaluate and compare the efficacy of the current first line agent (Artesunate-Lumefantrine) with that of a relatively cheaper alternative (Artesunate-amodiaquine) fixed dose regimen for use by NMCP.

Materials and Methods

Place and period of study: An Open randomized controlled trial was conducted between December 2008 and November 2009 in 4 upazillas of 3 high prevalent districts of Bangladesh. The areas were Naikhongchari, Kawkhali & Kaptai and Matiranga Upazila Health Complexes of Banderban, Rangamati and Khagrachari Hill Districts respectively. Each of the UHCs serves as the lowest level in-patient facility for about 200,000 populations. Multi-drug resistant falciparum malaria has been documented from all these areas.

Sample size: Sample size was calculated as 132 (66 in each treatment group) cases in each District to detect a difference in efficacy of 25%, with alpha error .05 and beta error .02 with 80% power and 95% confidence. The study cases were attending the out-patient (OPD) department passively.

Inclusion criteria: The inclusion criteria consisted of a) febrile patients with temperature >100⁰F or a history of fever in last 48 hours. b) Blood slide positive for asexual forms of *P. falciparum* with a parasite density between 500-250,000/cmm, c) age between 12 and 60 years and d) agreed to Sign the informed consent to take part in the investigation and e) agreed to remain in hospital for 3 days and attend for follow up on days 7, 14 & 28 day.

Exclusion criteria: The exclusion criteria consisted of a) pregnant and lactating women b) presence of any of the severe manifestations of malaria c) suspected or proven co-existence of other febrile illness d) co-infection with *P. vivax* e) known hypersensitivity to artesunate, lumefantrine and amodiaquine or to the excipients and f) history of taking any of these drugs over the last four weeks.

Randomisation procedure: A computer-generated simple randomization scheme was prepared in advance. Allocated treatments were kept in sealed opaque envelopes. After completion of formal enrolment procedures, allocated treatments were administered by project nurses.

Treatment allocation: Artemether + Lumefantrine (FDC, Coartem^(R)) 24 tablets in six doses (>35 Kg adult) were used manufactured by Novartis^(R) pharmaceuticals, Basel, Switzerland was administered at 0 and 8 hours on the first day, and then twice daily for two subsequent days.

Artesunate+Amodiaquine tablets (100/270 mg FDC) 2 tablets single dose daily (>35 Kg adult) in three doses, manufactured in China, donated to the NMCP, were administered.

The dosages for children and adults weighing <36 kg appropriate FDC doses were applied as per WHO recommendation and adult doses were administered for all cases weighing >36 kg. Administration of each treatment dose of the drug were supervised by a team nurse and observed for one hour thereafter for vomiting. The total dose was replaced for vomiting within one hour of ingestion.

Follow up:

Subjects were followed-up on days 1, 2, 3, 7, 14 and 28 for clinical recovery or deterioration, side-effects of drugs and new complaints if any by a study physician. Patients were modestly compensated for hospital stay and attendance (actual travel expenses) for follow-ups.

For microscopic examination of malarial parasite, Giemsa-stained blood films were examined by a trained laboratory technician in the public lowest level in-patient facility. 100 film fields of oil-immersion lens were examined for at least 15 minutes for the negative slides. Density of parasite were calculated by counting number of parasites per 200 leucocytes considering average white cell count of 8000/cmm for all patients. 5% of the positive slides and 10% of the negative slides were cross-examined by quality assurance microscopist and were found in agreement.

The outcomes of the cases were measured as clinical response, parasitological response, defervescence time and parasite clearance time and were defined as follows:

A. Clinical Response:

Early Treatment Failure: Study subjects with parasitaemia and persistent fever on day 3, as well as those whose condition has worsened before day 3.

Late Treatment Failures: Study subjects with initial clearance of fever (body temperature <100⁰F) on Day 3 but with persistent/recurrent parasitaemia and recurrent fever (body temperature >100⁰F or history of fever) at a later time, with or without other symptoms.

Treatment success: The remainder (excepting those withdrawn because of a change of diagnosis). However some of the treatment successes might have asymptomatic persistent/recurrent parasitaemia.

B. Parasitological Response:

R III: Density on day 2 more than 25% of density on day 0 or alternative antimalarial therapy was required on or before day 2.

R II: Positive on day 2, with a density not more than 25% of density on day 0, and either positive on day 7 or alternative antimalarial therapy was required on any of days 2 to 7.

R I: Negative or positive (<25% of day 0) on day 2, negative on day 7 and positive anytime thereafter (within 28 days).

S: The remainder including those positive on day 2 with density less than 25% of day 0 and negative thereafter.

C. Defervescence Time and Parasite Clearance Time: Defervescence (<100⁰F) time was calculated from the six hourly temperature chart and parasite clearance time was calculated from the daily blood slide examinations.

Data Collection, Processing and Analysis: Individual patient's data were recorded on a printed questionnaire, entered, cleaned and analyzed using the software SPSS 10.0. Continuous variables were compared by t-test and by non-parametric methods. Discrete variables were compared either by χ^2 test or Fisher's exact test where appropriate. 95% confidence interval for the cure rates were described.

Ethical consideration: Institutional ethical clearance was obtained from Ethical review committee of Chittagong Medical College. Patients were enrolled after taking consent from the patient/guardian. All the findings were recorded in semistructured questionnaire. Modest amount of compensation for wage loss due to hospital stay for patient/ guardian were compensated. Exact amount of travel cost were repayed for each follow up or unscheduled visit.

Results

A total of 252 cases were randomized to receive Artesunate +Amodiaquine (AA group, 147 cases) and Artemether Lumefantrene (AL group, 106 cases). The recruited numbers were less than target by site (66 in each group) because of not findings enough cases over the time period of the study and there was asymmetry in randomization between sites, e.g., Kawkhali upazilla used only AA regimen because of logistic supply problem. Hence the data was analyzed on total numbers (in all sites) for assessing comparative efficacy.

The distribution of the cases was comparable by age, sex and study sites are shown in Table-I. The asymmetry in enrolled numbers between the two regimens was due to non-availability of AL drug at the Kawkhali site (a protocol violation).

‘Treatment success’ response was observed in all cases (100%) in the AL group and the AA group had 144/146 (99%, one lost to follow up) and the difference was not statistically significant ($p>.1$). The two failures with AA were late treatment failures (Table II).

The parasitological sensitive (S) response was observed in 97% of cases in AL group and 95% in the AA group, and the difference was not significant statistically. All parasitological resistance types R-I through R-III was observed in AA group compared to only R-III response in the AL group (Table III). However the difference was not statistically significant.

There was no significant difference in defervescence time and parasite clearance time between two groups of caes (Figure 1 & 2).

The frequency of adverse events was insignificantly different between the two groups of treatment (Table V). There was also no significant difference in response between different study sites.

Table I: Distribution of Age, sex and study site for study subjects

		Artesunate + Amodiaquine n=147	Artemether + Lumefantrine n=106
Age	Median (range)	20 years	20 years
	Range	2 - 60 years	1 -60 years
Sex	Male	105 (71.4)	71 (67.0)
	Female	42 (28.6)	35 (33.0)
Site	Ramu	26 (17.7)	24 (22.6)
	N Chari	25 (17.0)	29 (27.4)
	Kaptai	23 (15.6)	16 (15.1)
	Matiranga	34 (23.1)	36 (34.0)
	Kawkhali	39 (26.5)	01 (0.9)

Table II: Comparison of clinical response

Clinical Response (AA) category	Artesunate+ Amodiaquine		Artesunate + Lumefantrine (AL)	
	Frequency	Percent	Frequency	Percent
ETF	0	0.0	0	0.0
LTF	2	1.37	0	0.0
Success	144	98.63	106	100.0
Total	146*	100.0	106	100.0

*1 patient was lost to follow up

ETF (Early Treatment Failure): Study subjects with parasitaemia and persistent fever on day 3, as well as those whose condition has worsened before day 3.

LTF (Late Treatment Failures): Study subjects with initial clearance of fever (body temperature <1000F) on Day 3 but with persistent/recurrent parasitaemia and recurrent fever (body temperature > 10000F or history of fever) at a later time, with or without other symptoms.

Success (Treatment success): The remainder (excepting those withdrawn because of a change of diagnosis). However some of the treatment successes might have asymptomatic persistent/recurrent parasitaemia.

Table III: Comparison of parasitological response

Parasitic response category	Artesunate + Amodiaquine (AA)		Artesunate + Lumefantrine (AL)	
	Frequency	Percent	Frequency	Percent
R III	02	01.4	03	02.8
R II	04	02.7	00	00.0
R I	02	01.4	00	00.0
S	139	94.6	103	97.2
Total	147	100.0	106	100.0

R III: Density on day 2 more than 25% of density on day 0 or alternative antimalarial therapy was required on or before day 2.

R II: Positive on day 2, with a density not more than 25% of density on day 0, and either positive on day 7 or alternative antimalarial therapy was required on any of days 2 to 7.

R I: Negative or positive (<25% of day 0) on day 2, negative on day 7 and positive anytime thereafter (within 28 days).

S: The remainder including those positive on day 2 with density less than 25% of day 0 and negative thereafter.

Table IV: comparison of hematological response through paired comparison

Measurement point pair	Artesunate+ Amodiaquine (AA)		Artesunate + Lumefantrine (AL)	
	Paired mean difference	P Value	Paired mean difference	P Value
HB0 vs HB14	-.71 (.66)	P <.001	-.63 (.58)	P <.001
HB0 vs HB28	-.86 (.77)	P <.001	-.78 (.63)	P <.001
HB14 vs HB28	-.16 (.34)	P <.001	-.16 (.37)	P <.001

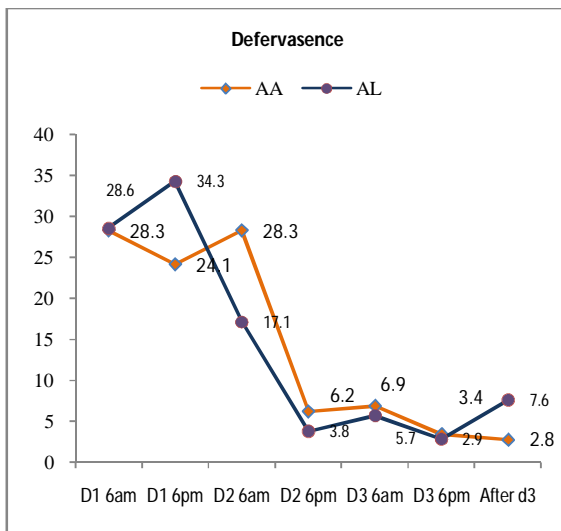
Haematological response was observed by hemoglobin estimation by colour matching method. It was observed in all patients on days 0, 14, 28. HB0=Hb concentration at baseline, HB14=Hb concentration at day 14, HB28=Hb concentration at day28

Table V: Comparison of adverse even and unscheduled visit

	Artesunate+ Amodiaquine (AA)		Artesunate + Lumefantrine (AL)	
	Frequency	Percent	Frequency	Percent
Adverse event				
Yes	1 ^a	.7	1 ^b	.9
No	146	99.3	105	99.1
Total	147	100.0	106	100.0
Unscheduled visit				
Yes	27 ^c	18.4	23	21.7
No	120	81.6	83	78.3
Total	147	100.0	106	100.0

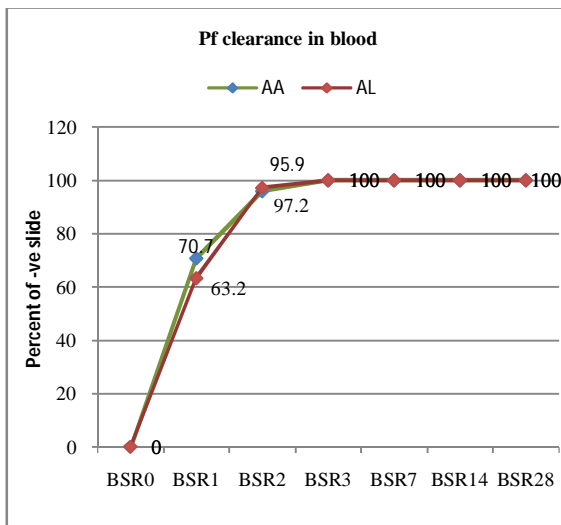
- a. One patient experienced severe weakness
- b. One patient experienced weakness and vomiting

Fig. 1: Defervescence time



Defervescence (fever clearance) time was calculated from the six hourly temperature chart.

Fig. 2: Plasmodium falciparum clearance



Parasite clearance time was estimated from the daily blood slide examinations. Both the treatment group showed similar parasite clearance in blood over time.

Discussion

Overall the two artemisinin-based combination Therapy (ACT) regimens, Artemether-Lumefantrine (AL) and Artesunate-amodiaquine (AA) applied in Fixed Dose Combinations (FDC), have high cure rates and had no significant difference in efficacy and safety in uncomplicated falciparum malaria (UM) in Bangladesh. However, there was few more treatment failures with AA compared to the AL regimen, which was not statistically significant. Both these regimens can therefore be used alternatively as first line treatment option for UM by the NMCP of Bangladesh.

The study on the efficacy of Artemether-Lumefantrine (AL), in the area dates from 2003¹¹, showing a slightly lower efficacy of 92.4% PCR-corrected parasitological cure rate at Day 42. Based on the findings of the study, level of resistance, financial implications and policy, the NMCP of Bangladesh introduced ACT AL as the 1st line antimalarial for uncomplicated falciparum malaria.

Emergence of drug resistance is posing a serious problem in Bangladesh. The degree of resistance of *Plasmodium falciparum* to CQ has increased tremendously. CQ resistance increased from 10% in 1979 to 45% in 1987 and 57% in 1992 (RII+RIII)⁷. Few trials showed more than 70% resistance of CQ against *Pf*⁸. Increasing trend of resistance was observed against all antimalarials in use in Bangladesh. Even mefloquine, an antimalarial which was never used by NMCP, was available temporarily in the private sector also showed relatively high degree of resistance against *Pf*⁹. Several studies carried out to update the antimalarial drug regimen specially to identify a suitable first line drug, MSF-Holland (NGO) in collaboration with Government of Bangladesh carried out a study to measure the efficacy of several drug combinations including artemether plus lumefantrine (Coartem®). The study documented overall efficacy of 92.4% of artemether-lumefantrine against¹¹. Based on the findings of the study, level of resistance, financial implications and policy, the Government of Bangladesh has updated the treatment regimen and guidelines of malaria with artemisinin based combination-Coartem (artemether and lumefantrine) as the first line drug replacing CQ since 2004.

The efficacy of alternative ACT, AA given as a FDC is supported by findings of clinical studies performed in locations throughout sub-Saharan

Africa^{15,16}. The most widely adopted ACT regimens in Africa are artemether/lumefantrine (AL) and amodiaquine/artesunate (AA), each of which is first-line for uncomplicated *P. falciparum* malaria¹⁷. Democratic republic of Congo and Senegal are among the countries which included by AA as 1st line regimen^{18,19}. Additionally it is worth to mention that AA, a user friendly (3day 3 doses) regimen is quite economic in comparison to AL regimen²⁰.

There were serious limitations in the conduct of the study, being limited in time, could not achieve desired sample size and the randomization process was not followed in one out of five sites and the comparison was unequal in recruited numbers. PCR corrected failure rates could not be performed.

The present study results substantiate the information on continued high efficacy of the 1st line agent AL and its justification of continued use as the current 1st line treatment option. The study also demonstrate non-inferiority of AA in terms of both safety and efficacy compared to AL applied in FDC formulation and hence may be considered an alternative 1st line agent for the national malaria control program.

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