



Comparative efficacy and safety of AL, ASAQ and ASAQ plus chlorpheniramine (Artemoclo™) for acute uncomplicated malaria in Nigerian children



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Objectives



- To evaluate the comparative efficacy and safety of artemether-lumefantrine (AL), artesunate-amodiaquine (ASAQ) and artesunate plus amodiaquine plus chlorpheniramine (AQC) in the treatment of acute uncomplicated malaria in Nigerian children.



Methods (1)



- *Study site:*
 - University College Hospital & Abanla PHC Ibadan, SW Nigeria. Malaria transmission is holo-endemic in SW Nigeria
- *Study design:*
 - Open label randomized clinical trial.
- *Inclusion criteria:*
 - Children of both sexes aged 6 months -12 years with clinical features consistent with symptomatic acute uncomplicated malaria
 - Confirmed *P. falciparum* asexual parasite density ≥ 1000 /microlitre of blood
 - Provision of written informed consent by the parent or guardians of the prospective study participant
- *Exclusion criteria:*
 - History of hypersensitivity to any of the study drugs i.e. Artemisinins, lumefantrine and amodiaquine
 - Clinical features of severe malaria, treatment with any antimalarial drug apart from chloroquine and sulfadoxine-pyrimethamine within 2 weeks of enrolment
- *Withdrawal criteria:*
 - violation of study protocol, - Withdrawal of consent
 - Serious adverse event, - progression of disease to severe malaria



Methods (2)



- Ethical approval:
 - UI/UCH ethical review committee provided ethical approval for the study
- Enrolment procedure:
 - Thorough physical examination.
 - Study participants were randomized to one of three groups to receive AL - Coartem™ (6-dose regimen), ASAQ (AS – 4mg/kg daily, AQ – 10mg/kg daily) or AQC - Artemoclo™ (AS-100mg. AQ - 300mg & CP 4mg/tablet) at standard doses for 3 days
 - All drugs were administered supervised
- Follow up
 - Daily days 0-3, then, days 7, 14, 21 & 28. Day 42 day follow up encouraged.
 - History, physical examination, TESS, blood smears, blood spots on filter paper and PCV at each follow up day
- Efficacy assessment
 - WHO 2003 criteria for assessment and monitoring of antimalarial drug efficacy – ETF, LPF, LCF and ACPR
 - Cure rates at days 7, 14, 28 & 42; gametocyte carriage rate
 - Mean parasite and fever clearance rates



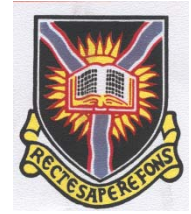
Table 1: Baseline characteristics



Characteristics	AL (N= 53)	ASAQ (N= 53)	AQC (N= 53)	ρ -value
Sex M:F	28 : 25	30 : 23	25 : 28	0.62
Age (months) M ± sd Range	49.3 ± 35.4 6 - 144	51.0 ± 32.8 7 - 126	51.6 ± 31.0 7b -243	0.90
Weight (Kg) M ± sd Range	14.4 ± 5.7 4 - 35	14.8 ± 5.5 3 - 30	14.7 ± 5.8 2 -25	0.93
Temp (°C) M ± sd Range	37.7 ± 1.2 35.5 – 40.2	37.7 ± 1.1 36.0 – 39.9	37.4 ± 1.2 38.5 -	0.51
PD(/μL) Geo-mean Range	13, 524 1115 -244,157	15, 817 1000 –230,793	15, 045 1109 –151259	0.56
Hematocrit (%) M ± sd Range	30.1 ± 4.3 18 - 37	30.2 ± 6.2 18 -40	30.7 ± 3.8 20 - 38	0.83



Table 2: Response to treatment of Per protocol population



Efficacy criteria	AL [N (%)]	ASAQ [N (%)]	AQC [N (%)]	ρ -value
D14 ACPR (%)	45 (100%)	50 (100%)	49 (100%)	
D 28 ACPR (%)	43 (93.3)	49 (96)	49 (100)	0.486
LPF (%)	1 (2.2)	2 (4.0)	2 (4.1)	
LPF (%)	3 (6.7)	2 (4.0)	0 (0)	
Day 42 ACPR (%)	27/38 (71.1)	32/40 (80)	32/37 (86.5)	0.843
Proportion wt parasite D2	27.3 %	14.9%	6.3%	0.022
“ “ D3	2.1%	0%	0%	
Fever Clearance T (d)	1.21± 0.51	1.19 ± 0.45	1.16 ± 0.38	0.94
Range FCT	1 - 3	1 - 3	1 - 2	
Parasite Clearance T (d)	2.0 ± 0.77	1.82 ± 0.66	1.72 ± 0.57	0.122
Range PCT	1 - 4	1 - 3	1 - 3	
Hematocrit (%) D2	29.2 ± 4.9	27.4 ± 4.4	30.0 ± 4.8	0.018
“ “ D14	32.3 ± 3.2	32.5 ± 4.2	33.0 ± 3.2	
Serious adverse event	1 (seizure)	NIL	NIL	



Conclusions



1. All three ACTs – AL, ASAQ and AQC (AS + AQ +CP) were effective and safe for the treatment of acute uncomplicated malaria
2. AQC gave non-significant higher ACPR than AL and AQC on days 28 and 42.
3. AQC also gave a significantly better hematological recovery and parasite clearance on day 2 compared to AL and ASAQ



Discussions and Future perspectives



- Amodiaquine (AQ) plus artesunate (AS) is one of the preferred ACTs.
- Chlorpheniramine (CP) has been reported to enhance the efficacy of amodiaquine.
- The better hematological recovery and parasite clearance with AQC on day 2 compared to AL and ASAQ may be a fine indication of the enhancement ASAQ effect by chlorpheniramine.
- The addition of chlorpheniramine as a resistance modulating agent may serve to prolong the clinical useful life of ASAQ and other ACTs especially in the face of emerging artemisinin resistance even if only as a stop gap while research on newer antimalarial drug discovery continue.