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Short Communication

Comparison of artesunate and quinine in the treatment of Sudanese children with severe *Plasmodium falciparum* malaria

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ABSTRACT

Sixty-six children presenting to Singa hospital, Sudan with different manifestations of severe *Plasmodium falciparum* malaria were randomly divided into two well-matched groups (33 in each arm) to receive either intravenous artesunate 2·4 mg/kg at 0, 12, and 24 hours, then daily, or intravenous quinine 20 mg/kg initially then 10 mg/kg three times a day. There was no significant difference in the fever, parasite clearance, and coma resolution times. Three patients died, one in the artesunate and two in the quinine groups. One patient developed hypoglycaemia following quinine infusion. Thus, artesunate can be used for the treatment of severe falciparum malaria.

1. Introduction

Severe malaria is a medical emergency with high mortality especially when there is multiple organ dysfunction.[1] Until recently, the standard treatment of severe malaria was intravenous quinine.[1] However, adverse effects, and reports of limited clinical efficacy in some *Plasmodium falciparum* malaria–endemic areas, including Sudan, preclude its usefulness.[2] Artesunate, a water-soluble artemisinin derivate is considered safe and highly efficacious in the treatment of severe *P. falciparum* malaria in South-East Asian adults.[3] Recently, World Health Organization (WHO) recommended artesunate as the first-line treatment in adults with severe malaria, [4] however, currently, the drug is not widely used outside Asia. We could find no published randomized controlled trials comparing quinine and artesunate in African children, thus the current study was conducted in Singa hospital in central Sudan, which is characterized by unstable malaria transmission.[5] Such data is fundamental for both care givers and health planners and to add to our ongoing research on treatment of severe falciparum malaria in Sudanese children.[6]

2. Material and Methods

This was an open randomized comparison of intravenous artesunate and quinine in children admitted to Singa hospital in central Sudan with severe *P. falciparum* malaria during August-September 2009. Children who had been admitted to the hospital with slide-confirmed, severe *P. falciparum* malaria[1] were recruited after written informed consent was obtained from their parent or guardian. Blood films were prepared, stained with Giemsa and 100 oil immersion fields were examined. The parasite density was counted against 200 leucocytes, assuming 8000 leucocytes/μl. All the slides were double-checked blindly and only considered negative if no parasites were detected in 100 oil immersion fields. Individuals were randomized (by computer generated

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numbers which were sealed in individual envelopes and securely stored) to receive either intravenous artesunate 2.4 mg/kg body weight given at 0, 12, and 24 h, and then daily, or intravenous quinine (Shanghai, China) as 20 mg/kg loading dose infused over 4 h then 10 mg/kg infused over 2–4 h three times a day. Each 60 mg vial of artesunic acid (Guilin, Pharmaceutical Factory, Guangxi, People's Republic of China) was dissolved in 1 mL of 5% sodium bicarbonate to form sodium artesunate and then mixed with 5 mL of 5% dextrose. Oral medication of artesunate sulfadoxine/pyrimethamine or quinine tablets were given, once the children tolerated the tablets, to complete treatment.

Resuscitation and supportive management was given in accordance with the WHO guidelines, e.g., hypoglycaemia was corrected with 10% glucose, convulsions were terminated with intravenous diazepam if persisting for more than three minutes. Paracetamol was given every 6 h until defervescence. Those with severe anaemia (haemoglobin < 5 g/dl) and respiratory distress were transfused with blood screened for hepatitis and HIV. Vital signs and coma scale were measured every 15 min for the first hour, and then every 2 h until 24 h, thereafter every 6 h until parasite clearance. Blood films were investigated and repeated every 4 hours. Parasite clearance time was defined as the interval between the start of treatment and the time of the first of two sequential negative thick films. Fever clearance times were measured from the start of antimalarial treatment to the time at which the axillary temperature first dropped below 37.5 °C and remained below 37.5 °C for 24 h. Coma recovery time (for patients with a Glasgow coma score <11 [of 15] on admission) was measured from the start of antimalarial treatment to the time at which the score reached 15. Blood glucose levels were measured every 6 hours. Base-line investigations were performed for every patient on admission and repeated when clinically indicated. They included: haemoglobin level, serum urea and creatinine, serum bilirubin and white blood cells.

2.1. Statistical analysis

Data were entered using SPSS software version 13.0 (SPSS, Chicago, IL, USA) and double checked before analyses. Continuous and categorical data were compared by Student t-test and X^2 test, respectively. $P < 0.05$ was considered significant.

3. Results

Seventy-eight children presented with severe *P. falciparum,* out of which 66 fulfilled the inclusion criteria and were enrolled in the study (33 in each arm). The two groups were well matched in the basic clinical and biochemical characteristics. Convulsions, severe anaemia and hyperparasitaemia were the predominant manifestations of severe malaria in this setting, Table 1. While 9 (27.2%) vs. 11 (33.3%) patients presented with severe anaemia alone, 15 (45.4%) vs.13 (39.3%) patients presented with hyperparasitaemia alone in the artesunate and quinine groups, respectively. Three patients died, one of them in the artesunate and two in the quinine groups.

The mean (SD) of fever clearance time: 16.2 (8.9) vs. 18.2 (10.5) hours, $P = 0.4$ and parasite clearance time: 19.7 (7.1) vs. 20.8 (9.2) hours, $P = 0.4$ were not significantly different between the artesunate and quinine groups, respectively. In comatose patients, (four and five patients in the artesunate and quinine groups, respectively) there was no difference in coma resolution time (8.1 vs. 9.1 hours, $P = 0.4$). Following quinine infusion, 12 patients developed tinnitus and one hypoglycaemia. Abdominal pain and nausea were observed in three and four patients in artesunate and quinine groups, respectively.

4. Discussion

We think this is the first published data comparing artesunate with quinine in the treatment of children with

Table 1
Clinical and biochemical characteristics of the patients with severe *Plasmodium falciparum* malaria on admission to Singa Hospital, Sudan

Variables	Artesunate group		Quinine group		*P*
	n = 33	%	*n* = 33	%	
Female gender	15	45	14	42	0.9
Number of children with:					
Repeated convulsions	13	39	14	42	0.8
Cerebral malaria	4	12	5	15	0.9
Severe anaemia	12	36	15	45	0.4
Bleeding	1	3	0	0	0.7
Jaundice	2	6	1	3	0.5
Hyperparasitaemia	21	64	18	55	0.3
More than one manifestation	12	36	10	30	0.7
Mean/SD of:	Mean	SD	Mean	SD	
Age, years	4.4	2.6	4.6	3.4	0.7
Weight, kg	13.5	4.7	14.6	7.5	0.5
Height, cm	98.4	20.5	101.9	21.8	0.4
Temperature, °C	38.2	1.2	38.6	1.0	0.1
Haemoglobin, g/dl	8.5	3.0	9.0	2.9	0.5
White blood cells, μ/dl	6282.3	3180.4	7187.5	4492.0	0.6
Parasitaemia, geometric mean parasite/μ/l	240.7		258.7		0.7
Blood glucose, mg/dl	144.9	80.8	131.2	57.4	0.5
Creatinine, mg/dl	0.8	0.3	0.5	0.1	0.1
Bilirubin, mg/dl	1.7	0.8	2.1	0.4	0.5

severe *P. falciparum* malaria in an African setting. There was no significant difference in the fever and parasite clearance time between the two arms of the study. In this study the parasite clearance time (20 hours) in both arms was very low compared to other studies outside Africa (68 hours).[3] Previously, we observed that fever clearance time and parasite clearance time (16.0 vs. 22.4 hours) were shorter when intramuscular artemether was compared with quinine in the treatment of Sudanese children with severe *P. falciparum* malaria.[6] However, artesunate is likely to be superior to artemether in the treatment of severe malaria. Artesunate, unlike artemether, can be administered intravenously, and it is absorbed rapidly after intramuscular injection, whereas intramuscular artemether is absorbed erratically.[7,8] Furthermore, artesunate and its metabolite dihydroartemisinin have higher in vitro antimalarial activities than the activity of artemether.[9] Previous studies showed that artesunate was safe, highly efficacious and had a lower mortality rate when compared with quinine in the treatment of severe *P. falciparum* malaria.[3,10] However, our results should be compared with previous studies of severe malaria cautiously because in our study the group would appear to represent a milder spectrum of disease e.g. severe anaemia and hyperparasitaemia. Although, this is an open, randomized, small sample sized study, these descriptive data may inform the use of artesunate in African children with severe malaria. Moreover, quinine can induce hypogylcaemia[6] and has declining efficacy.[2] Further research is needed to investigate artesunate in African children using larger sample studies.

Authors' contributions: HGE and IA designed the study; AAO and AAM carried-out the clinical work and analysis and interpretation of these data. All authors shared in drafting, revising and all of them approved the final manuscript. HGE and IA are guarantors of the paper.

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Conflicts of interest: The authors have no conflicts of interest concerning the work reported in this paper.

Ethical approval: The study received ethical clearance from the Research Board at the Faculty of Medicine, University of Khartoum, Sudan.

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