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Role of Clindamycin In Complicated Falciparum Malaria

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ABSTRACT

Background: The emergence and rapid extension of Plasmodium falciparum resistance to various anti-malarial drugs has gradually limited the potential malaria therapeutics available to clinicians.

Methodology: We conducted a clinical trial on 43 admitted paediatric patients with complicated malaria dividing them into 3 groups. Group A received artesunate. Group B received artesunate plus quinine. Group C received artesunate plus quinine plus clindamycin.

Results: 74% having convulsions and 48.8% having unconsciousness at the time of presentation. On examination all 100% had splenomegaly, 93% had hepatomegaly, 23.2% had signs of meningeal irritation and 46.5% had signs of dehydration. Out of 8 patients in group A, 2 died. Out of 19 patients in group B, 3 died while there was no mortality in group C.

Conclusions: Clindamycin in addition to artesunate and quinine reduces the mortality in complicated malaria but larger studies need to be carried out to warrant the same.

KEYWORDS : clindamycin, malaria.

Introduction:

Malaria, a parasite vector-borne disease, is one of the largest health threats in tropical regions, despite the availability of malaria chemoprophylaxis and the use of repellents and insecticide-treated nets [1]. The prophylaxis and chemotherapy of malaria remains a major area of malaria research, and new molecules are constantly being developed prior to the emergence of resistant parasite strains. Artemisinin-based combination therapy (ACT) is the recommended standard of care in the treatment of uncomplicated falciparum malaria [2,3]. The adoption of combination therapy -the simultaneous administration of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite - is thought to improve treatment efficacy and to delay the emergence of drug resistance to the individual components of the combination [4,5]. ACT resistance has been described and global efforts are underway to contain the evolution of artemisinin resistance [6,7]. Alternative combinations to ACT are necessary and should be assessed for efficacy and safety. Clindamycin plus quinine is a potential non-ACT combination recommended by World Health Organization (WHO)[3]. No study has been done till date to show result of clindamycin plus quinine plus artesunate therapy in complicated malaria patients and hence we did the clinical trial to see if this is effective.

Methodology:

We conducted a clinical trial on 43 admitted patients who showed plasmodium falciparum positive in peripheral smear in the department of paediatrics in a tertiary hospital from 1st January, 2016 to 29th February, 2016. All patients below 12 years of age having high fever and a peripheral smear positive for plasmodium falciparum were included in the study. The patients were divided into 3 groups i.e. Group A who received only artesunate, Group B who received artesunate plus quinine and Group C who received artesunate plus quinine plus clindamycin. Mortality as an outcome was studied and compared using appropriate statistical tests.

Results: A total of 43 paediatric patients were studied with all of them fever, 74% having convulsions and 48.8% having unconsciousness at the time of presentation. On examination all 100% had splenomegaly, 93% had hepatomegaly, 23.2% had signs of meningeal irritation and 46.5% had signs of dehydration.

Table 1: Clinical presentation and laboratory investigations in total 43 patients.

	No. of patients (n=43)	Percentage (%)
Symptoms: Fever Present Absent	 43 0	 100 0
2. Convulsions Present Absent	 32 11	 74 26
3. Unconsciousness Present Absent	 21 22	 48.8 51.2
Signs: 1. Splenomegaly Present Absent	 43 0	 100 0
2. Hepatomegaly Present Absent	 40 3	 93 7
3. Signs of Meningeal irritation* Present Absent	10 33	23.2 76.8
4. Dehydration Present Absent	 20 23	 46.5 53.5

***CSF analysis was within normal limits.**

All 43 had a peripheral smear positive for plasmodium falciparum, 44.2% had a heavy parasitemia and 95.3% tested positive for malarial antigens. 4.7% had WBC count below 10,000, 48.8% had it between 10,000 to 15,000, 20.9% had it between 15,000 to 20,000 while 25.6% had it above 20,000. 79% had platelet count below 50,000 and 83.7% had hemoglobin levels below 5gm/dl.

Table 2: Laboratory investigations of the patients.

Laboratory investigations	No. of patients (n=43)	Percentage
Peripheral Smear Positive Negative	 43 0	 100 0
2. Heavy parasetemia Present Absent	 19 24	 44.2 55.8
3. Rapid diagnostic test for malarial antigens Positive Negative	 41 2	 95.3 4.7
4. WBC count <10,000 10,000-15,000 15,000-20,000 >20,000	 2 21 9 11	 4.7 48.8 20.9 25.6
5. Platelet count <50,000 >50,000	 34 9	 79 21
6. Hemoglobin <5gm/dl >5gm/dl	 36 7	 83.7 16.3

8 patients were assigned to group A which received only artesunate 2.4mg/kg among which 25% died. 19 patients were assigned to group B which received both artesunate and quinine among which 15.8% died and 16 patients were assigned to group C which received artesunate plus quinine plus clindamycin and showed no mortality. When applied Fisher exact test to the groups there was no significant difference between group B and group C i.e p value= 0.2336 as well as between group A and group C i.e. p value=0.1.

Discussion: Malaria is prominent public health problem in the developing countries and it becomes of even more importance in the forest adjoining areas like our city where the prevalence of malaria is predominant. The emergence and rapid extension of Plasmodium falciparum resistance to various anti-malarial drugs has gradually limited the potential malaria therapeutics available to clinicians. In this context, macrolides and associated antibiotics based on similar mechanism of action like lincosamides constitute an interesting alternative in the treatment of malaria. Here, we studied role of clindamycin along with ACT and quinine.

Clindamycin is a lincosamide having a 90 % digestive absorption. Characterized by slow but thorough anti-malarial activity, clindamycin presents a remarkably short plasma half-life (2–4 h) [8]. With respect to the effect on Plasmodium, clindamycin slowly accumulates in parasites [9].

Clindamycin is a major antibiotic for the treatment of anaerobic bacterial infections [10]. This drug also presents antimicrobial activity against Plasmodium, Toxoplasma,Babesia and Pneumocystis spp. Moreover, clindamycin is the drug of choice for treatment against toxoplasmic chorioretinitis in newborns and one of the treatments recommended in the babesiosis with Babesia microti and B. divergens [11]. Associated with pyrimethamine or primaquine, clindamycin is a treatment of second intention against toxoplasmosis and pneumocystosis [12].

The antiplasmodial indication of clindamycin was managed according to various therapeutic regimens. The WHO did not ultimately recommend clindamycin treatment when used alone as an anti-malarial treatment, as parasite clearance might be deleterious in cases of significant parasitaemia in fragile subjects (children and pregnant woman) [2]. However, clindamycin is now recommended for pregnant women in the first trimester with uncomplicated malaria, in association with quinine or artemisinin-based combination therapies or oral artesunate for 7 days.

The combination of clindamycin with other rapidly acting drugs is essential for the optimization of treatment. Clinically documented associations essentially involve the combination of clindamycin with quinine or chloroquine.

Quinine, showing a rapid onset and short half-life, is the ideal partner. In vitro studies have also shown a synergistic effect when the two molecules are associated [8, 13]. The bioavailability of the two drugs, when co-administered, remains unchanged [14]. A methodology and satisfactory post-treatment follow-up in approximately ten clinical trials with a wide number of patients have been published [15]. The duration of combination therapy remains controversial. While most studies consider that the administration of quinine for at least 7 days and clindamycin for at least 5 days is needed, treatments conducted for 3 days in African studies were effective [13, 16]. Short-duration treatment is justified for obtaining adequate compliance and fear of side effects with quinine. Parasite clearance has been correlated with parasitaemia in children treated for 4 days [17, 18]. In areas of multidrug resistance, such as Thailand, 5–7 days are needed to cure malaria.

One clinical trial combining artesunate with clindamycin for the treatment of uncomplicated P. falciparum malaria in Gabonese children was reported in 2005 [8].

Out of 43 patients of plasmodium falciparum positive malaria we had, we gave only artesunate to 8 patients and off which 2 had died. 19 patients were assigned to group B which received both artesunate and quinine among which 15.8% died and 16 patients were assigned to group C which received artesunate plus quinine plus clindamycin and showed no mortality. There was no significant difference between group B and group C i.e p value= 0.2336 as well as between group A and group C i.e. p value=0.1.

Conclusions:
The addition of clindamycin to artesunate and quinine in the treatment of complicated falciparum malaria reduces mortality in children but larger studies are required to validate the results.

Table 3: Mortality of patients in various groups:

Study Group	No. of patients in the group	No. of patients died	Percentage(%)
*Group A	8	2	25
**Group B	19	3	15.8
Group C	16	0	0

Applying fisher exact test between group C with group A and group B,

*p=0.1 and **p=0.2336.

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