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Original Research Article

Chloroquine Vs Co-Artemether in Uncomplicated Malaria

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Abstract: The objective of this paper was to compare the efficacy of chloroquine and co-artemether in uncomplicated malaria cases. It was a prospective interventional study. The subjects included children with PBF proven uncomplicated Malaria (n=49) admitted in Department of Pediatrics of a tertiary care hospital of Northern India over a period of one year. Children with uncomplicated malaria (PBF proved) were given either chloroquine (n=24) or lumefantrine+artemether combination (n=25) according to random table. Therapeutic response to antimalarial drugs was assessed by fever defervescence time, parasite clearance time, spleen regression time and adverse reactions of the drug. Out of 49 cases chloroquine was given in 24 cases and co-artemether in 25 cases. The mean duration of fever was 42.5+29.81 & 36.00+12.96 hrs, splenic regression time was 5.08+1.04 & 4.92+1.21 days, parasitic clearance time was 1.83+0.76 & 1.48+0.58 days and the cure rate observed was 95.83% & 96.00% for chloroquine and co-artemether respectively and the difference was statistically insignificant ($p>0.05$). We concluded that there was no significant difference observed in cure rate with chloroquine (95.83%) and co-artemether (96%), but the cost of treatment 7-8 times increases with the use of co-artemether. No side effects are seen with both the antimalarial drugs. So based on our study we concluded that chloroquine is still the drug of choice for uncomplicated malaria cases in our setup because of its cost effectiveness.
Keywords: Malaria, Chloroquine, Co-artemether, Drug resistance

INTRODUCTION

Inspite of all developments, malaria remains an enormous international medical issue with 300- 500 million cases reported annually, resulting in 1.5- 2.7 million deaths. In absolute terms, malaria kills 3000 children aged less than 5 years every day[1]. According to world malaria report 2009,an estimated 243 million cases of malaria occurred in 2008 causing an estimated 863,000 deaths[2], mostly among African children. In India, 1.52 million malaria cases and 935 deaths were reported in 2008[3].

Chloroquine was the preferred drug for management of uncomplicated malaria for decades. But, for some time now there are reports of increasing resistance to chloroquine from different regions of world. Resistance has arisen to all classes of antimalarials except, as yet, to the artemisinin derivatives. This has increased the global malaria burden and is a major threat to malaria control. Widespread and indiscriminate use of antimalarials places a strong selective pressure on malaria parasites to develop high levels of resistance.

The foci of multidrug resistant strains of P.falciparum malaria are enlarging in tropical countries and this has arisen an urgent need to develop new efficacious drugs. Artemether-lumefantrine combination has been recently introduced to overcome this problem. It is indicated for the treatment of uncomplicated falciparum malaria, including multidrug resistant malaria[4]. It has been reported that Artemisnin derivatives are more rapidly acting in terms of parasite clearance, fever defervescence time, splenic regression time and are safer[5].

In their study, Krudsood *et al.;* [6] reported 100% cure rate with chloroquine and 97.4% cure rate with co-artemether in Thailand and Kshirsagar *et al.;* [7] reported cure rate of 19.7% with chloroquine and 95.4% with co-artemether in Mumbai (India). However, chloroquine seems to be quite effective in our day to

day practice, So we have undertaken this study to compare the efficacy of chloroquine and co-artemether.

METHODS

The present study was conducted in Department of Pediatrics of a tertiary care hospital of northern India over a period of one year. Children who had uncomplicated malaria according to WHO criteria[8, 9] and proved positive for malarial parasite on PBF were included in the study. The study was approved by ethical committee of Medical College.

Total 49 patients were enrolled for the study, out of them 24 patients received chloroquine (10mg/kg stat, 5mg/kg after 6 hours then 5mg/kg once a day for 2 days) and rest 25 patients received co-artemether (5-15kg 2.5ml, 15 to 24 kg 5ml, 25 to 40 kg 7.5 ml BD for 3 days, 5ml contains 20mg artemether & 120 mg lumefantrine). Chloroquine or lumefantrine+artemether combination (co-artemether) was started according to random table in child with uncomplicated malaria. All patients were hospitalized for a minimum of 7 days and thereafter each case was evaluated on 14^{th} day and on 28^{th} day. Detailed symptom evaluation, general physical examination, vital monitoring and complete systemic examination was done with particular reference to splenic size on first 7 days.

In every enrolled patient routine hematological investigation like hemoglobin, total and differential white cell count and platelets count were performed on day 0 and day 4. Liver function tests including serum bilirubin (total and direct), SGPT and renal function tests namely blood urea and serum creatinine were estimated on day 1 and day 7. Blood sugar was done to rule out hypoglycemia.

Among parasitological investigation peripheral blood film examination for parasite was done daily for first 7 days and then on 14^{th} and 28^{th} day. Thick and thin smears were prepared from the blood obtained by finger prick in all the study subjects on a slide and examined under microscope. Percent parasite count was recorded after calculation with the help of following formula. Percent parasite count = (Parasitized RBC/2000 RBC scanned) × 100

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Chloroquine or lumefantrine+artemether combination (co-artemether) was started according to random table. Primaquine was given in all cases at the end of treatment for its gametocytocidal action in P. falciparum and for radical cure in P. vivax malaria.

Therapeutic response to antimalarial drugs was assessed by

1. Fever clearance time – defined as the time from the day of drug administration till the patient became afebrile i.e. temperature < 100˚F.
2. Parasite clearance time – parasite clearance time is defined as the time from the day of drug administration till no asexual malaria parasite are detectable in peripheral blood smear. (considered to be an important measure of antimalarial drug efficacy)
3. Regression of spleen – pattern of splenic regression was noted daily for first 7 days after starting antimalarial.
4. Adverse reactions of the drug – clinical signs and symptoms were recorded from day 1 to day 7 to see for any side effect. Also, hematological and biochemical parameters were evaluated pre and post drug to see for any derangement, if any.

Detailed history, general physical examination and systemic examination was done with particular reference to recurrence of fever, reappearance of parasite in peripheral blood, presence of spleen and side effects of drug used. Follow up was done by repeating peripheral blood film and parasite density was calculated on 14^{th} and 28^{th} day.

Statistical Analysis

The statistical analysis was performed by using student's "t" test and Chi square test to find out the significance of difference in mean between two variables.

RESULTS:

Baseline characteristics of subjects and clinical manifestations of cases are depicted in Table 1 and 2.

Table-1: Base line characteristics of Patients

Age Group	Male n (%)	Female n (%)	Total n (%)
	Uncomplicated malaria		
<1 year	9 (18.37)	5 (10.20)	14 (28.57)
1-5 year	19 (38.78)	7 (14.29)	26 (53.06)
5-10 year	4 (8.16)	1 (2.04)	5 (10.20)
>10 year	2 (4.08)	2 (4.08)	4 (8.16)

Table-2: Clinical Manifestations of Malaria Cases

Symptoms	**Uncomplicated malaria**	**Complicated malaria**
	n=49 %	**n=13 %**
Intermittent Fever	47 (95.92)	12 (92.31)
Fever with Rigors	28 (57.14)	10 (76.92)
Pallor	25 (51.02)	11 (84.62)
Fever without Rigors	21 (42.86)	3 (23.08)
Cough	20 (40.82)	1 (7.69)
Nausea / Vomiting	11 (22.45)	6 (46.15)
Diarrhoea	06 (12.24)	1 (7.69)
Continuous Fever	02 (4.08)	1 (7.69)
Headache	02 (4.08)	0 (0)
Abdominal Pain	02 (4.08)	0 (0)
Body ache	01 (2.04)	2 (15.38)
Puffiness	01 (2.04)	1 (7.69)
Yellowish discoloration of eyes or body	0 (0)	10 (76.92)
Anorexia	0 (0)	3 (23.08)
Altered consciousness	0 (0)	4 (30.77)

Uncomplicated malaria is a disease of protean and varied clinical manifestations. Fever was the most common presenting symptom which was present in 100% children. The other clinical manifestations observed in order of frequency were pallor (51.02%), cough (40.82%), vomiting (22.45%) and diarrhoea (12.24%) (Table 2). Splenomegaly and hepatomegaly were present in 100% and 36.73% patients respectively (Table 3). Severe anaemia was present in 20.41% of cases.

Table-3: Hepatosplenomegaly & its size

	Uncomplicated Malaria	**Complicated Malaria**
Spleen Size	**n=49 (%)**	**n=13 (%)**
Not palpable	0 (0)	0 (0)
<1cm	19 (38.78)	5 (38.46)
1-3cm	20 (40.82)	3 (23.08)
>3cm	10 (20.41)	5 (38.46)
Mean+SD cm	**1.37+0.96**	**1.88+1.33**
Liver size		
Not palpable	31 (63.27)	2 (15.38)
<1cm	2 (4.08)	0 (0)
1-3cm	16 (32.65)	6 (46.15)
>3cm	0 (0)	5 (38.46)
Mean+SD cm	**0.44+0.16**	**1.92+1.32**

Table -4: Identification of the Parasitic Species

Species	**Uncomplicated Malaria**	
	n=49	**(%)**
Vivax	34	69.39
Falciparum	14	28.57
Vivax + Falciparum	01	2.04
Others	0	0

Most common parasitic species identified in uncomplicated malaria patients was plasmodium vivax which was present in 34 (69.39%) patients while Plasmodium falciparum was present in 14 (28.57%) patients. Both P. vivax and P. falciparum were present in 1 (2.04%) patient (Table-4).

Table 5: Comparison of efficacy of chloroquine and co-artemether in uncomplicated malaria

	Chloroquine (A)	**Co-artemether (B)**	**A vs. B**
	Mean+SD	**Mean+SD**	**χ^2 `p`**
Fever defervescence time (hrs)	42.5+29.81	36.0+12.96	0.16 >0.7
Splenic regression time (<7 days)	5.07+1.04	4.92+1.21	0.01 >0.9
Parasitic clearance time (days)	1.83+0.76	1.48+0.58	0.27 >0.7
Cure rate	95.83%	96%	0.001 >0.95
Cost of treatment(15 kg child)	16/-	114/-	
Side effects	Nil	Nil	-

We used two drugs chloroquine and co-artemether according to random table and compared their efficacy in uncomplicated malaria patients. The mean duration of fever was 42.5+29.81 hrs in chloroquine group and 36.00+12.96 hrs in co-artemether group and p value was >0.7 which was statistically insignificant. Therapeutic response in the form of splenic regression time showed mean values for splenic regression were 5.08+1.04 and 4.92+1.21 days for chloroquine and co-artemether respectively (p>0.9) (table-5).

The mean duration for parasitic clearance was 1.83+0.76 days and 1.48+0.58 days for chloroquine and co-artemether respectively (p>0.7). The cure rate observed in uncomplicated malaria was 95.83% and 96.00% with chloroquine and co-artemether respectively (p>0.95) (table-V). Nonresponse to chloroquine was present in 4.17% patients in the form of persistence of parasitemia (P.vivax) and to co-artemether in 4% patients in the form of reappearance of parasites (P.vivax) in peripheral blood at 28th day.

DISCUSSION

Resistance to antimalarial drugs is proving to be a challenging problem in malaria control in most parts of the world. Since early 60s the sensitivity of the parasites to chloroquine, the best, safe and most widely used drug for treating malaria, has been on the decline. Newer anti-malarials were discovered in an effort to tackle this problem, but all these drugs are either expensive or have undesirable side effects. Moreover, after a variable length of time, the parasites, especially the falciparum species, have started showing resistance to these drugs also.

We compared chloroquine and co-artemether in patients with uncomplicated malaria. Fever defervescence time, splenic regression time and parasitic clearance time for chloroquine and co-artemether were 42.5+29.81 & 36.0+12.96 hours, 5.07+1.04 & 4.92+1.21 days and 1.83+0.76 & 1.48+0.58 days respectively. The differences were statistically insignificant. The cure rate was 95.83% for chloroquine and 96% for co-artemether with no significant statistical difference; however the cost of treatment was 7-8 times (114/- Vs 15.70/-) more with the use of co-artemether. No side effects were seen with both the drugs.

In some other studies, Krudsood *et al.;* [6] reported 100% cure rate with chloroquine and 97.4% cure rate with co-artemether in Thailand and Kshirsagar *et al.;* [7] reported cure rate of 19.7% in chloroquine group and 95.4% in co-artemether group from Mumbai (India). This difference in cure rate in different part of the world are seems to be due to development of varying degree of resistance by plasmodium species for chloroquine in different geographical areas.

No significant difference was observed in fever defervescence time, splenic regression time and parasitic clearance time with co-artemether and chloroquine. Finally it can be concluded that there was no significant difference in efficacy of chloroquine and co-artemether in uncomplicated malaria but the cost of treatment increases significantly with the use of co-artemether.

Moreover, chloroquine is a time tested drug, against which the resistance has developed after its use for many decades; there are chances that resistance may develop early to co-artemether if it is used widely in uncomplicated malaria. In a developing country like India, cost of treatment is also a very important factor. Due to large number of poor people in our country and considering the efficacy and side effects, we recommend that still chloroquine is the drug of first choice for uncomplicated malaria, in our setup.

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