Original Article

Efficacy of Oral Chloroquine in Uncomplicated Vivax Malaria in children

Salma Shaikh, Shazia Memon and Chetan Das

ABSTRACT

Objectives: To assess the efficacy of Chloroquine in treatment of uncomplicated vivax malaria.
Study Design: Observational study
Place and Duration of Study: This study was conducted at the Pediatric Outpatient Department, LUMHS, Jamshoro, Sindh from March to December 2016.
Materials and Methods: All the patients from 6 months to 15 years presented with febrile illness with no any cause for fever and not severely malnourished were screened for malaria by doing slide microscopy. We had included 100 children confirmed on microscopy as cases of vivax malaria as our sample for complete follow up protocol upto 42 days for scheduled slide microscopy (3,7,14,21,& 42). They were treated with oral chloroquine in outpatient department, under supervision of research officer for first three days and follow up continued for 42 days to assess clinical and parasitological response. Our Primary Outcome was Adequate Clinical and Parasitological Response (ACPR) while our Secondary Outcomes were early treatment failure and late parasitological failure.
Results: From 100 mono-infected patients with Plasmodium vivax, 92 cases responded to chloroquine by day 3, while 8 cases cleared parasitemia by day 7. By day 7 response to treatment was 100%. 5 were lost to follow up on day 14 and3cases on day 21.
Conclusion: CQ remains safe and effective therapy for uncomplicated Vivax malaria, such studies on larger scale should be continued for early detection of resistance.
Key Words: Vivax Malaria, Chloroqiune Efficacy, Uncomplicated Malaria, Children.

Citation of article: Shaikh S, Memon S, Das C. Efficacy of Oral Chloroquine in Uncomplicated Vivax Malaria in children. Med Forum 2017;28(4):148-151.

INTRODUCTION

Malaria is one of major health problems in Pakistan where 19% of all malaria cases of EMRO region occurs and Plasmodium Vivax is responsible for 88% of cases.[1] Vivax malaria requires more attention not only for being the predominant species and its association with anemia and poor pregnancy outcomes but also has now been documented to cause severe malaria and deaths in many countries including Pakistan.[2] Chloroquine remains drug of choice for Vivax malaria, but resistance has been reported from Asia, south America and eastern Africa.[3]

Globally 2.48 billion people are at risk of Vivax infection with almost 67% cases occurring in south east Asia[1]. Plasmodium vivax is responsible for nearly 80 million cases every year mainly in Asia, western pacific, middle east and Americas[4].

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Received: January 10, 2017; Accepted: February 15, 2017

One of the strategies to control malaria is timely provision of effective anti-malarials to infected individuals. Resistance to anti-malarials is a major challenge for effective malaria control. There is a need for routine monitoring of efficacy of the antimalarial drugs every two years in all malaria endemic countries. ACT is recommended treatment for Falciparum by our national malaria control program but Chloroquine remains drug of choice for Vivax Malaria. Though vivax in most countries is sensitive to chloroquine but resistance has been reported from Asia, south America and eastern Africa.[5] Therefore, monitoring the dynamics of anti-malarial drug resistance could help detect emerging resistant strains early. Vivax has many important biological differences from P. falciparum, like the development of dormant liver stages and the emergence of gametocytes before the onset of clinical symptoms which result in recurrences and greater transmission risk[5]. Chloroquine has good oral absorption with bioavailability of 80 to 90%, it has a long terminal elimination time of one to two months. Studies from Pakistan have showed good response to chloroquine and it remains a safe and cost effective treatment but we need to conduct such studies periodically as recommended by WHO[1] to assess the efficacy and safety of different anti-malarial drugs to provide scientific evidence to physicians and to guide national malaria control program for future treatment policies.

This prospective, observational follow up study assessed the therapeutic efficacy of CQ, which remained a drug of choice for the treatment of P.vivax mono-infection. So purpose of this study was to assess the effectiveness of the chloroquine in children with P-vivax malaria.

MATERIALS AND METHODS

This observational study was conducted from March to Dec 2016 at pediatric out-patient department LUMHS. Inclusion criteria of our study were the children from 6month to 15 years presented with fever and positive for Plasmodium vivax, able to swallow oral medication; and willingness to comply with the protocol for the duration of the study. Patients with severe malnutrition and clinical feature of severe complicated malaria and those who have taken ant malarial in last 8 weeks, having mixed infection with P. falciparum.

All the patients who fulfilled the inclusion criteria (from 6 months to 15 years with fever or history of fever for 48 hours) were examined thoroughly and M.P was done by preparing thick and thin films and reported by 2 separate trained technicians. Total 100 confirmed cases of vivax malaria were enrolled for complete follow up protocol of scheduled slide microscopy upto day 42 as Our estimated sample size. It was calculated based on the WHO revised protocol for anti-malarial drug efficacy surveillance[1] and prevalence of around 5% treatment failure rate reported in different studies of Pakistan [5] with 95% confidence level, 5% margin of error and 25% contingency (expected loss to follow-up rate). Our sampling technique was Non-probability purposive. Informed consent was taken from parents. They were assured that their identity will be kept confidential.

They were treated with oral chloroquine in outpatient department 25mg/kg over 3 days (on day 0 (10 mg base/kg body weight), day1(10 mg base/kg body weight), and day2 (5 mg base/kg body weight). Drug administration was done under observation of research officer daily and all the patients were observed for 30 minutes for vomiting. When vomiting took place, the patient was treated with a same full dose of drug.

The follow-up included a fixed schedule on (day 1, 2, 3, 7, 14, 21, and 28 and 42 days). Assessment and monitoring of parasitological and clinical outcome was made for each patient until day 42. Day 0 was defined as the day on which the case was enrolled and received the first dose of CQ. The study subjects were asked to come back to health center immediately showed any signs of danger (as unable to drink or breastfed (if child), vomiting, presenting with convulsions, lethargic or unconscious, unable to sit or stand, difficult breathing). Auxiliary temperature, body weight and clinical conditions were recorded during the follow up period. Patients were labeled as lost to follow-up whenever they did not come to the clinic as scheduled.

Our Primary Outcome was Adequate Clinical and Parasitological Response (ACPR) while our Secondary Outcomes were fever clearance and gametocyte clearance

RESULTS

During this study around 3822 patients presenting with fever were screened for malaria infection by doing slide microscopy test (male 2145/female 1660). Around 267 were positive for malaria. Regarding the species 226 patients were positive for vivax infection. Frequency of species with their age and gender distribution is given in table 1 and 2.

Table No.1. Frequency of plasmodium species

Species	<5	>5	Total	%
Vivax	116	110	226	84.4
Falciparium	17	15	32	12.2
Mixed	3	6	9	3.4
Total	136	131	267	100

Table No. 2: Age And Gender Distribution Among MP Positive Cases

Age Group	<5		>5		Total
Gender	Male	Female	Male	Female	
Vivax	66	50	58	52	226
Falciparium	9	8	8	7	32
Mixed	2	1	3	3	9
Total	77	59	69	62	267

Regarding the parasite clearance time from 100 mono-infected patients with Plasmodium vivax, 92 cases responded to chloroquine by day 3, while remaining 8 cases were cleared by day 7. By day 7 response to treatment was 100% as given in table #3.

Table No. 3: Time frame for the clearance of parasites.

Day of enrollment	MP Positive	MP Negative	Percentage %
Day-0	100		
Day-1	40	60	60%
Day-3	8	92	92%
Day-7	00	100	100%

Table No.4: Outcome of 92 patients who completed 42 days follow up

Outcome	No. of patients	Percentage
Number of enrolled patients	92	
Early treatment failure	0	
Late clinical failure	0	
Late parasitological failure	2	2.1%
Adequate clinical and parasitological response	90	97.9%

The lost to follow up rate in our study was 8%(5 cases on day 14 and 2 cases on day 21) while the adequate clinical and parasitological response rate and relapse rate were 97.9% and 2.1% respectively. The result of 92 patients who completed 42 days follow up is shown in Table # 4.

DISCUSSION

This observational prospective study was conducted from March to December 2016, to assess the effectiveness of oral chloroquine in children from 6 month to 15 years of age. This study has shown vivax as the most prevalent species as shown in other studies as well[10] Clinical drug efficacy against P.vivax is difficult to interpret due to inability to differentiate reliably between relapse, recrudescence, or re-infection. Primary outcome was ACPR which shows 97.9% response, which is similar to other studies nationally[8] and internationally where chloroquine sensitive vivax prevails.[9]

The secondary outcome of our study were fever clearance time and parasite clearance time. This study shows a fast clearance rate of both parasitemia and fever following CQ mono therapy. Around 68% patients presented with fever, more than 80% became fever free within36—48hrs and 100% by day 3. Regarding the parasite clearance rate in 60%patients the MP was negative on day1 while 92% on day 3 and 100% by day7. Some studies have shown higher failure rates in children and suggested to increase dose from 25mg/kg to 30mg/kg to maintain therapeutic levels on weight basis.[12] We did not measure drug levels but clinical response on 25mg/kg was seen in almost 98% in our population. Only 2/100 children vomited but tolerated repeated dose after 30 minutes on first day of treatment, no adverse events were reported on follow up.

Timely effective treatment to control infection and reduce transmission is one of the main steps in 3T strategy of malaria control program.[10] Though testing for malaria is recommended in all countries by WHO through microscopy or RDT, both are not available in many of our public health facilities. Appropriate treatment can only be prescribed after confirming species as ACT is given for falciparum and Chloroqine for vivax in Pakistan according our national guidelines.[11] According to experts a unified treatment policy for malaria of gives significant individual, public health, and operational benefits in regions co-endemic for P. falciparum and P. vivax, and this approach has been adopted by some countries where vivax is sensitive to chloroquine.[13]

This study shows clinical efficacy of CQ in routine outpatient setting, the limitations of study are lack of confirmation by PCR, plasma drug levels or study of gene polymorphism which are available in few centers in Pakistan. The policy makers are urged to establish such facilities at least at provincial level for future operational research on other antimalarials effective against vivax, along with drug quality control mechanism to control Plasmodium vivax malaria by effective treatment and to contain resistance.

Few studies conducted in Ethiopia so far indicated an alarming levels of CQR. In the current study, a three-dose regimen of CQ was safe and well tolerated anti-malarial drug. In our study no adverse effects were noted except 2% has developed vomiting. In other studies adverse effects of CQ and more than one adverse effect per individuals were rarely reported.

CQ efficacy studies have shown good results in most local studies in the range of 80-90% …. to …(ref),but some recent case reports and study on molecular genetic analysis of strains of P. vivax from Pakistan have shown possiblility of chloroquine resistance in future.

In view of our findings, the risk of treatment failure to three-dose regimen of CQ therapy for vivax malaria is low. A significant improvement in clinical and parasitologic parameters was as well as minimal adverse events were recorded. However, given conflicting reports indicating alarming levels of treatment failures from other sites, there remains a need to monitor the emergence of chloroquine-resistant vivax malaria across the nation to obtain an adequate representation in different ecological and epidemiological settings.

CONCLUSION

CQ remains safe and effective therapy for uncomplicated Vivax malaria, such studies on larger scale should be continued for early detection of resistance. It is suggested that HEC , PMDC and PMRC in collaboration should make operational research on National issues like Nutrition, Tuberculosis and Malaria mandatory for research degrees like PHD in medical Universities by providing funds and technical support to produce reliable local scientific data for guiding national policies. It is also recommended strongly that government should provide RDT in open market on subsidised rates to encourage all practitioners to confirm malaria diagnosis before prescribing treatment.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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