ORIGINAL ARTICLE

Efficacy of Chloroquine as a first line agent in the treatment of uncomplicated malaria due to Plasmodium vivax in children and treatment practices in Pakistan: A Pilot study

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Abstract

Objectives: To ascertain the efficacy of chloroquine as first line agent in treatment of uncomplicated malaria - caused by Plasmodium vivax in children---and to determine its current treatment practice in Pakistan.

Methods: This pilot study was conducted at the Paediatrics Department of Combined Military Hospital (CMH), Lahore, Pakistan. Forty-eight children between six months and twelve years of age having positive blood film for Plasmodium vivax were included. They were treated with chloroquine as a drug of - choice. Efficacy of chloroquine was assessed by clinical response, absence of parasitaemia on day seven and twenty-eight after initiation of therapy. A survey was also conducted to determine the first line therapeutic choice of Paediatricians in the treatment of uncomplicated Plasmodium vivax malaria in children in Pakistan.

Results: The results showed 100% efficacy of chloroquine in treating uncomplicated malaria caused by Plasmodium vivax in children. Artemisin was preferred by 74.28% Paediatricians' in combination therapy as 1st line treatment.

Conclusions: Guidelines proposed by Malaria Control Programme Pakistan (MCPP) in collaboration with World Health Organization (WHO) are comprehensive but not being adhered to. The recently reported resistance of Plasmodium vivax to artemisin should urge measures to implement WHO guidelines.

Keywords: Vivax malaria, chloroquine, Pakistan, WHO. (JPMA 66: 30; 2016)

Introduction

Malaria kills a large number of children each year.[1] In 2012,482,000 children under the age of five died from Malaria worldwide.[1] While 90% of these deaths occurred in Sub-Saharan Africa, malaria also poses a significant threat to children in Pakistan where it is endemic.[2] According to WHO, Plasmodium vivax (P vivax) and Plasmodium falciparum (P falciparum) causes 75% and 25% of malaria in Pakistan respectively.[3] In 2011, 319,592 confirmed cases of malaria were reported.[4] As only 71% of the population uses public sector hospitals, the total disease burden in general and in children specifically is likely to be much higher.[5]

Chloroquine sensitive P.vivax is the major causative parasite of malaria in children and adults in Pakistan. WHO recommends chloroquine as a first line therapy for uncomplicated vivax malaria. However, doctors seldom comply to WHO's guidelines and artemisinin (ACTs) based combinations are used for its management.[6]

Although Pvivax remains the leading cause of malaria in Pakistan (67%), its resistance pattern has not been characterized.[7] Many studies have assessed the treatment of malaria in children from various small districts and localities of Pakistan but there is no recommendation for the use of ACTs across the board here. Though some cases of resistance to chloroquine in P vivax have been reported from Bannu,[8,9] (a small district in North Western Province of Pakistan) and some anecdotal isolated cases reported from Sind and Baluchistan province, WHO still recommends chloroquine as a first line therapy.[4] ACTs are only recommended for malaria in parts of Latin America and isolated pockets of East Asia where P vivax is resistant to chloroquine. Currently Pakistan and Afghanistan are not amongst regions with comparable or high resistance pattern.[10,11] Furthermore, Khattak et al have shown with molecular markers that in Pakistan chloroquine resistance to Pvivax has not yet surfaced but some mutations may pose future risk[7] which may be compounded with unjustified treatment of malaria by non-adherence to WHO guidelines.[7]

Our study re-emphasizes the need to treat uncomplicated Pvivax malaria with chloroquine in accordance with the guidelines proposed by the MCPP and WHO. We feel that unnecessary use of ACTs could contribute to possible emergence of artemisinin resistant strains of Pvivax.

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Patients and Methods

A quasi experimental pilot study was carried from April 2013 to October 2013 in the Paediatrics department of CMH Lahore (a tertiary care hospital in Pakistan).

The study was approved by the ethical committee of CMH Lahore Medical College; (an accredited medical college by WHO). Verbal consent was taken from parents of the children. Records were kept strictly confidential.

Sixty-five children presenting to the outpatients paediatric department of the hospital with a history of fever and clinical features of malaria were screened for the presence of malarial parasite by examining a thick and thin blood smear.

Children included were between the age of 6 months to 12 years, had fever for 48 hours before recruitment, parasitaemia for P vivax mono-infection and were willing to participate in the study.

Children with severe malnutrition, concomitant febrile illness that could interfere with follow-up, known allergy and/or intolerance to chloroquine, infection with other plasmodium species, and who had taken anti-malarial drugs in last 4 weeks, were excluded.

Sixty-five children with suspicion of malaria were included. Fifty-two having P vivax parasitaemia, without evidence of severe disease according to WHO criteria[12] were enrolled for a 28 day follow up. Forty-eight completed the follow up while 4 were lost to follow up.

Samples from the admitted children were collected for complete blood count, thick and thin smear for malarial parasite, blood culture, C reactive protein, liver and renal function tests, examined daily by a 4th year — Paediatric registrar or consultant and given Syrup Chloroquine (25 mg/kg of body weight per day for 3 days) in accordance with the MCPP and WHO's recommendation.[4] They were discharged on resolution of symptoms and asked to return for examination and assessment of parasitaemia on day 7 and day 28 from initiation of treatment. Efficacy of chloroquine was determined by the absence of fever and parasitaemia on completion of treatment and on days 7 and 28 of commencement of therapy.

During the study telephonic interviews were performed with 50 Paediatricians selected by non-probability sampling, working in tertiary and secondary hospitals in different parts of Pakistan. Of these, 35 agreed to participate. A verbal survey enquiring, place of duty, health care facility and appointment along with following questions were asked:

1. What is your first line treatment option for a suspected case of vivax malaria?

2. What is your first line of treatment for a confirmed case of vivax malaria?

3. What is your choice of treatment if the first line therapy fails for a confirmed case of vivax malaria i.e. non-resolution of clinical symptoms?

Statistical analysis was performed using SPSS version 20.

Results

Forty-eight children range 6 months — 12 years (mean 5.42±3.36 years) with confirmed Pvivax malaria were treated with chloroquine. Efficacy of 100% was evidenced by resolution of fever and parasitaemia. Mean time for resolution of fever was 38±15 (range 8-64) hours and a mean of 45±21 (15-69) hours for clearance of parasitaemia. None had clinical or laboratory evidence of malaria on day 7 and 28 of analysis.

Table: Trends of Paediatricians'practice for the treatment of vivax malaria.

Designation of Paediatricians	No of Pediatricians using ACTs for suspected vivax malaria	No of Paediatricians using ACTs for confirmed vivax malaria	No of Pediatricians using Chloroquine for suspected vivax malaria	No of Pediatricians using Chloroquine for confirmed vivax malaria	No of Pediatricians using Fansidar for suspected malaria
Professor	01	-	-	01	-
Associate Professor	01	02	-	02	-
Assistant Professor	05	02	-	-	01
Senior Registrars	13	02	-	05	-
Total	20	06	-	08	01

Demographics and analysis of paediatricians practice in treating uncomplicated P vivax malaria is shown in Table. Twenty six (74.28%) used ACTs as first line, Only 8(22.85%) adhered to MCPP/WHO's guidelines.

Discussion

With 627,000 deaths globally due to malaria in 2012[3] and 1.6 million suffering from malaria annually in Pakistan,

including 300,000 confirmed cases,[5] the MCPP and WHO have a responsibility not only to minimize the spread of malaria by vector control but to assure implementation of their guidelines. Efforts to control malaria in Pakistan started in 1960s in collaboration with the WHO, USAID and regional organizations. In 1998, with emerging chloroquine resistance, many experts realized that measures to eradicate malaria were inadequate. Consequently, a comprehensive malaria roll back programme was launched by the WHO, UNICEF, UNDP and other malaria control organizations. Pakistan became a signatory, leading to greater partnership, technical assistance and funding between the WHO and MCPP. In 2003, national treatment guidelines for malaria were launched and subsequently revised in 2006, emphasizing to treat P vivax malaria with chloroquine, discouraging ACTs. Despite P vivax remaining 100% sensitive to chloroquine in Pakistan, uncomplicated vivax malaria in children is not being treated in accordance with guidelines of the WHO and MCPP. Our survey reveals a large percentage of paediatricians' particularly and worryingly those in training (senior registrars; Table) chose to treat uncomplicated vivax malaria with ACTs without considering chloroquine as a first-line.

Our pilot study provides evidence that Pvivax malaria can be simply, cheaply and adequately treated with chloroquine. Whilst it is heartening to know that P vivax still remains fully sensitive to chloroquine, it is disturbing to know that WHOs and local MCPP guidelines are not being adhered to. Similar apprehensions have been highlighted by Malik et al and Khattak et al.[6,7] These are worrying findings as unnecessary treatment of Pvivax with ACTs can cause resistance to chloroquine and even ACTs (e.g. Latin America and far East Asia), an angst communicated by Khattak et al[7] also. A similar survey in Islamabad (capital of Pakistan), has highlighted that malaria is being treated irrationally in Pakistan[6] possibly due to lack of antimalarial stewardship, inadequate training of health professionals, poor diagnostic facilities, and failure of MCPP in implementing guidelines.[6]

Data from other countries with a high burden of Malaria is very similar to ours. In Combodia 68%,[13] whereas in Ghana only 9% prescriptions from private and 54% from public sector were according to standard guidelines.[14] India contributes to 70% of malaria in South East Asia and their guidelines recommend chloroquine as a first line drug.[15] Valecha et al[16] have shown that P vivax in India remains sensitive to chloroquine, it is not known how many practitioners truly adhere to guidelines.

Our findings and data from Malik et al[6] indicates that MCPP has not achieved its objectives to educate practitioners. Whilst we have not determined the reasons for this failure which could possibly be interplay of factors as lack of funds, social apathy, administrative discordance or political unwillingness, we suggest a national/ multicenter regional study steered by WHO be planned to ascertain the level of compliance and knowledge amongst paediatricians and general practitioners treating children.

Limitations of our study are its small sample size of both the cohort and the number of practitioners surveyed. Never the less our pilot project highlights the urgent need for a larger study requiring support and funding involving multiple regions of Pakistan.

Conclusion

It is recommended that WHO and MCPP ensure that uncomplicated vivax malaria in children is treated in accordance with their guidelines. Secondly, a national study should be carried out to determine the sensitivity of P vivax to chloroquine and ascertain national current practice.

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