Over prescribing and resistance to chloroquine

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ABSTRACT

Malaria is a major health concern in the developing world including India. Overdiagnosis and overprescribing of malaria may lead to increase morbidity, mortality and increases risk of resistance to antimalarial drugs and hence increase the economical burden to health care system. The present study was carried out to determine the actual cases of malaria and extent of chloroquine resistance at Civil Hospital Ahmedabad, a tertiary care teaching hospital in Gujarat, India. After Institutional Ethics Committee approval, adult patients of either gender, presenting with a history of fever at the Out Patient Department (OPD), diagnosed to be suffering from malaria and prescribed chloroquine were included in the study. Peripheral thick blood smear test and OptiMAL-rapid diagnostic test (RDT) were carried out. RDT was performed in these patients on day 0 before the start of chloroquine treatment and after completion of the 3 day chloroquine treatment. They were again subjected to RDT on day 4. The positive cases on RDT on day 4 were considered as resistant to chloroquine. During the study period of 12 months, out of the 250 clinically suspected cases of malaria who were prescribed chloroquine, 80 (31%) cases (35 cases of P. vivax and the 45 of P. falciparum) were positive for malaria (by the peripheral smear and the Rapid Diagnostic Test (RDT) OptiMAL test). Thirty out of the 35 cases of P. vivax malaria, responded to the three- day chloroquine treatment. Out of the 45 cases of P. falciparum malaria, 30 responded to chloroquine while 15 patients (35%) continued to be OptiMAL positive on 4th day and required change of treatment. It suggests that an early diagnosis, definitive treatment and avoiding overprescribing could delay drug resistance and reduce the morbidity and mortality due the disease.

Keywords: Malaria, chloroquine, overprescribing, resistance.

INTRODUCTION

The outcome of treatment in malaria depends on the right diagnosis, selection of the right drug and its efficacy, correctness of the advice given to the patient and compliance of the patient (NIMR and NVBDCP, 2011). Chloroquine (CQ) is the first drug of choice for among the available antimalarial drugs (National drug policy on malaria, 2008) and widely used as self-medication for presumptive treatment of malaria despite the existence of parasite resistance to the drug (Picot et al, 1997). Resistance to antimalarial drugs is on the rise and has become a major factor in deciding the choice of antimalarial drugs. For instance, as per estimates in the past decade, 50% of the strains of P. falciparum are resistant to chloroquine (Garg, 1999) and resistant strains of P. vivax are also increasing in different parts of India (Kochar, 2007). A presumptive approach alone may result in overdiagnosis of malaria. Empirical treatment based on this approach may also result in unnecessary and irrational drug use with a consequent increased risk of morbidity, mortality, resistance to antimalarial drugs and increased cost of therapy (Plowe, 2003). It thus becomes imperative to detect the extent of presumptive diagnosis of malaria study was therefore conducted at Civil Hospital, Ahmedabad, a tertiary care teaching hospital in Gujarat, India, with an objective
to determine the actual cases of malaria out of such clinically diagnosed cases and to determine the extent of chloroquine resistance in this population.

**METHODS**

The study protocol was approved by the Institutional Ethics Committee (IEC) of Civil Hospital, Ahmedabad (CHA). Adult patients of either gender, above the age of 18 years and presenting with a history of fever at the Out Patient Department (OPD) were screened for the study. All those patients who are clinically diagnosed to be suffering from malaria and prescribed chloroquine were included in the study. Patients who had taken prior treatment for malaria and those with a history of vomiting were excluded from the study. Pregnant and lactating women, patients with a history of hypersensitivity to antimalarial drugs and those suffering from major illnesses like hypertension or severe diabetes mellitus were also excluded from the study (OptiMAL –IT kit was supplied by Doctor & Company, Ahmedabad : Morepan Laboratories, New Delhi, Manufactured by DiaMed AG Diagnostics and Medical Products, Switzerland).

Patients were informed about the aims and methods of the study and a written consent was obtained. Detailed history, clinical examination and treatment given were recorded in a case record form (CRF). Peripheral thick blood smear test and OptiMAL-rapid diagnostic test (RDT) were carried out for malaria in all patients that were included in the study. RDT was performed in these patients on day 0 before the start of chloroquine treatment.

The cases that showed positive microscopic examination and +ve RDT for malaria on day 0 were considered as true/actual cases of malaria either *P. vivax* or *P. falciparum*. These patients were advised to return on day 4 after the completion of the 3 day chloroquine treatment. They were again subjected to RDT on day 4. The positive cases on RDT on day 4 were considered as resistant to chloroquine.

**RESULTS**

During the study period, 250 cases of fever and clinically suspected cases of malaria, who were prescribed chloroquine were studied. Out of these, 80 (31%) patients showed a positive peripheral smear as well as positive RDT (OptiMAL test) for either *P. vivax* or *P. falciparum* malaria. Two false positive and one false negative cases were reported (cases where peripheral smear was positive for malaria parasites and RDT was negative were considered as false negative and vice versa). Therefore it was observed that 170 (68%) cases of fever presumptively diagnosed with malaria, were not actually suffering from this infection yet they were prescribed chloroquine. (Figure 1). Out of the 80 positive malaria cases, 35 cases were suffering from *P. vivax* malaria (44%) and the remaining 45 patients were suffering from *P. falciparum* (56%) (Table 1) Out of 35 cases of *P. vivax* malaria, 30 patients responded to chloroquine treatment while 5 patients (14%) were still positive on chloroquine after three days chloroquine treatment. They required alternate antimalarial drugs and were referred to the medicine consultant. Thirty out of 45 confirmed positive malaria cases, 35 cases were suffering from *P. falciparum* malaria (44%) and the remaining 15 cases were suffering from *P. falciparum* malaria (33%) (Table 1) Out of 35 cases of *P. vivax* malaria, 30 patients responded to chloroquine treatment while 5 patients (14%) were still positive on chloroquine after three days chloroquine treatment. They required alternate antimalarial drugs and were referred to the medicine consultant. Thirty out of 45 confirmed positive malaria cases, 30 cases were suffering from *P. falciparum* malaria (67.86%) showed a negative peripheral smear and negative RDT test for malaria.

We further observed that out of 80 cases detected to be positive for malaria by peripheral smear and RDT (OptiMAL) tests, 35 (44 %) were of *P. vivax* and 45 (56% ) were of *P. falciparum* malaria. Chloroquine was effective in 30 cases (86%) of *P. vivax* & 30 cases (67%) of *P. falciparum* origin. Resistance was therefore observed in 5 patients (14%) and 15 cases of (33%) *P. vivax* and *P. falciparum* of malaria respectively. There is therefore an evidence based of treatment on presumptive diagnosis alone, which may contribute to antimalarial drug resistance.

**DISCUSSION**

Outcome of treatment of malaria depends on the efficacy of the drug, right diagnosis, the treatment given and compliance of patient while presumptive use of anti malarial drugs may increase parasite resistance. Confirming the clinical diagnosis with microscopy or Rapid Diagnostic Tests (RDTs) may prevent overuse of antimalarial drugs and decrease the risk of drug resistance (ICMR, 2002).

In the present study, 250 patients of fever were prescribed chloroquine on the basis of a presumptive clinical diagnosis. However, only 80 cases were positive either for *P. vivax* or *P. falciparum* malaria on microscopy and RDT (OptiMAL) while 170 cases (67.86%) showed a negative peripheral smear and negative RDT test for malaria.

We further observed that out of 80 cases detected to be positive for malaria by peripheral smear and RDT (OptiMAL) tests, 35 (44 %) were of *P. vivax* and 45 (56% ) were of *P. falciparum* malaria. Chloroquine was effective in 30 cases (86%) of *P. vivax* & 30 cases (67%) of *P. falciparum* origin. Resistance was therefore observed in 5 patients (14%) and 15 cases of (33%) *P. vivax* and *P. falciparum* of malaria respectively. There is therefore an evidence based of treatment on presumptive diagnosis alone, which may contribute to antimalarial drug resistance.

Treatment based on presumptive clinical diagnosis alone is an accepted approach for management of most cases of malaria in areas with high rates of transmission e.g. in rural and remote areas of the healthcare system where laboratory facilities for definitive diagnosis may not be available. Patients in endemic areas are familiar with the symptoms and they frequently self-diagnose malaria and practice self medication with chloroquine and other antimalarial drugs. These drugs are easily available from pharmacies in India. Treatment based on presumptive clinical diagnosis alone may result in unnecessary and irrational drug use. In addition, overdiagnosis and overprescribing of malaria may lead to increase morbidity, mortality and increases risk of resistance to
antimalarial drugs and an increased economical burden to health care system of the country. Thus, the clinical diagnosis would benefit from laboratory confirmation by microscopy/Rapid Diagnostic Tests (RDTs) (Plowe, 2003).

Therapeutic efficacy and/or parasitological resistance may be measured by in vivo test. (Plowe, 2003) However, standard in vivo tests are expensive and time-consuming while in vitro methods for measuring drug resistance are not practical and have a limited scope. All available tests either do not give quick results to influence the therapeutic decisions or do not give results that are not interpretable in terms of individual patient treatment (ICMR, 2002). Alternatively, non-microscopic methods, rapid dipstick methods (like OptiMAL) based on the immunochromatographic detection of Plasmodium lactate dehydrogenase (pLDH) have the capacity to detect and distinguish infections caused by P. falciparum and P. vivax species (Ferro et al., 2002).

OptiMAL is the first RDT, approved on June 13, 2007 by the U.S. Food and Drug Administration (FDA) for use by hospital and commercial laboratories. This RDT utilizes a dipstick coated with monoclonal antibodies against the intracellular metabolic enzyme parasite lactate dehydrogenase (pLDH) and detects pLDH produced by viable parasites only. Its ability to follow its decline in sequential samples from that patients during treatment may be useful in evaluating clinical cases. (Palmer CJ et al., 1998, WHO, 2000) Thus, we have used this RDT as a tool for monitoring of antimalarial treatment. This diagnostic tests may provide rapid confirmatory diagnosis of malaria even at the peripheral levels of the health care system and can be performed by health workers with minimal training. This method can detect vivax and falciparum malaria. As it detects plasmodium lactate dehydrogenase (pLDH) of viable parasites, decline of viable parasites can be reflected in sequential samples from the patients during treatment. Thus, this method can also be used for monitoring of chloroquine therapy. (Palmer et al., 1998, WHO, 2000).

Antimalarial drugs are used empirically and prescribing chloroquine to any case of fever is a common practice (Khan, 1993). This causes unnecessary expense to the patient and risks avoidable adverse effects as well as selection of resistant strains. In addition to that, their is a widespread use of chloroquine as self-medication and inadequate dose or dosage schedule are prescribed at the health centres (Pfeiffer et al., 2008, McCombie, 2002). The cost of an RDT in developing countries is more than microscopic peripheral smear examination. However, prompt and accurate diagnosis will not only improve malaria treatment, but possibly reduce morbidity due to other febrile illnesses. The cost effectiveness of RDTs may depend upon many factors e.g. prevalence of malaria, cost of RDT, cost of anti-malarial treatment, and the cost of treatment of other febrile illnesses when malaria has been ruled out. RDTs may become more cost effective as the price of anti-malarials increase (Chansuda et al., 2007; WHO, 2006).

As per recommendation by National treatment guidelines on malaria (2010), all fever cases suspected to be malaria should be investigated by microscopy or RDT and presumptive treatment with chloroquine should not be given.

Hence, We conclude that early diagnosis, treatment and reduction in overprescribing based on presumptive symptoms alone may delay the progress of drug resistance and reduce in overall morbidity and mortality due to malaria. Rapid diagnostic tests can be useful in monitoring and management of malaria. This may reduce the unnecessary use of antimalarial drugs and also reduce risk of complications of P. falciparum malaria particularly in endemic areas.

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REFERENCES


Garg, MR, Gogtay NJ, Kshirsagar NA. Resurgence of malaria in mumbai is escalating chloroquine resistance a cause. J Assoc Physicians India.1999 ; 47; 377-379


