ORIGINAL RESEARCH

Present Status of Drug Resistance in Malaria in Elderly

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ABSTRACT

Introduction: Malaria is one of the major public health problem in South East Asian & African countries especially in India. This is a protozoan disease transmitted by a vector i.e. female anopheles mosquito. The prevalent species of malarial parasite are plasmodium vivax and falciparum. The present study has been undertaken to evaluate the efficacy of various drugs chloroquine, quinine, doxycycline and artimisinin (artesunate) combined therapy (ACT) in uncomplicated vivax and falciparum malarial infection. **Material and Methods:** A total of 120 hospitalized patients (smear positive cases 60 each of P. vivax (group A) and P. falciparum or mixed malaria (Group B)) of medical wards (including elderly age group also) in Dr. D.Y. Patil Medical College and Hospital, Navi Mumbai, were included. Complicated cases were excluded which had target organ damage. Complete blood count and parasitic index were done on day I, 4 and 7 in addition to liver, kidney, pulmonary and cardiac functions. **Results:** The observations revealed that patients of group A responded early to treatment as compared to group B regarding fever and parasitic index disappearance. The group A did respond partially and statistically significant to chloroquine than to other drugs combinations whereas group B did not respond satisfactorily to chloroquine but had reasonable statistically significant effect to other drugs **Conclusions**: The best medications were artesunate and quinine in combination with doxycycline in both the groups A and B whereas chloroquinewith doxycycline did not fare well in either group. Thus the artesunate combination therapy (ACT) is emerging as the first line treatment in drug resistant malaria under present circumstances.

Keywords: World Health Organization, Artimisinin (artesunate) combined therapy.

INTRODUCTION

Malaria ranks among top 10 killer diseases on this earth and has been a global[1] health hazard for centuries. Nearly 100 countries in the world account for this deadly disease especially in sub – Saharan Africa where one half (i.e. 3.3 billion) of the malarial patients are living in fear of transmission. South East Asian countries (e.g. Thailand, Indonesia)[2] and Western Pacific regions (e.g. 1.2 billion) are the other half to harbour this ailmentand thus account for 1.1 to 2.7 million deaths annually in the world according to WHO. The maximum casualty is in children.The Indian scenario accounts for 77% of total malaria in South East Asia,[3-5] being a part of tropical countries with mortality of 20,000 deaths/year though 13 times less under reported. South East Regional Office[6-8] (WHO SEARO) estimates 15 million cases. 1.5 million cases are reported annually by National Vector Borne diseases Control Programme (NVBDCP) and 40-50% are due to P. falciparum. North Eastern states report 50% cases as being of falciparum malaria. The Sub-Saharan Africa[5] continent also accounts for 50% falciparum malaria; the construction work where stagnant water accumulates for breeding mosquitoes is the main cause- Vivax malaria accounts for the remaining 50% of this disease in the Asian continent.

The emergence of uncontrolled severe malaria[6] disease is attributed to multiple factors (collapse of vector control, misuseand ineffective cheap, duplicate and waning efficacy of antimalarial drugs and particularly use of artesunate alone).

In 1970s the incidence of falciparum malaria increased by 50% as per NVBDCP data.[7] In 2007 there were reported 14,76,562 malaria cases, half being due to falciparum species.In India, Orissa[8] tops the list accounting for 25% of total cases in India with majority being Falciparum malaria. 18.2%of deaths in the country occurred here in 2007 (Fig. 1).[9,10] The

number of deaths[4-6] due to malaria in elderly individuals (>40 years of age) is 20,000 per year.

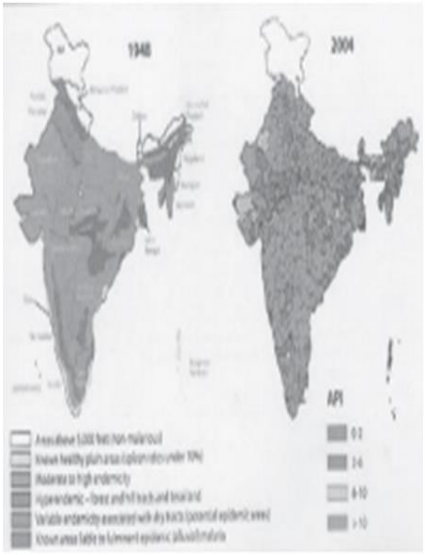

Fig.1:MalariaendemicityinIndia

Fig.2: Distribution of plasmodium falciparum resistance to antimalarial drugs in South-East Asia

Antimalarial drug resistance has emerged as the one of the greatest challenges for malaria control due to collapse of vector control and waning efficacy of existing drugs. Chloroquine andquinine were effective drugs till 2001 but lately the effect of chloroquinine is fading. The other drugs like sulfadoxine pyrimethamine did well for next five years but also started showing resistance lately due to genetics and to mutations in same enzymes in its metabolism. Mefloquine came next in use in resistant malaria but use lasted for a short time because of emergent resistance. Finally the artemisinin derivatives (artemether, arteether and artesunate) appeared on the scene and are being used increasingly in Asia, Africa and Europe. These drugs have potency, efficacy in reducing parasitemia in multidrug resistant malaria[11-14] with lack of side effects, thus being better option for chloroquine resistant cases.[15-20] 3 grades of resistance exists according to WHO. Low grade R1 – Recrudescence of infection[21] between 7 and 28 days of completing the treatment with initial resolution of symptoms and parasite clearance. High grade R2 – Reduction of parasitemia by >75% at 48 hours but failure to clear the parasites within 7 days. High grade R3 – Parasitemia does not fall by >75% within48 hours (Fig. 2).

Considering the above criterion of suspicion of drug resistance and burden of increasing falciparum malaria prevailingin our country, this study was assigned with use of newer artimisinin drugs i.e. artesunate, chloroquinine and quinine with doxycycline (tetracycline) with their comparison in combined therapy, after review in various randomized trials done earlier in various parts of the country showing good results with ACT.

MATERIAL AND METHODS

A total of 120 adult patients (60 cases of P. vivax and 60 cases of P. falciparum or mixed malaria) were undertaken for the study. A pre-informed consent was obtained in every case.The age and sex distribution of the cases is shown in Table I.

Table 1: Age range

Age range	No. of patients (N=60)	
>40 years	Male=45	Female=15
<40 years	Male=52	Female=8

The inclusion criterion was smear positive cases only. The exclusion criteria were smear negative cases, target organ damage in complicated malaria, pediatric age group <12 years, pregnant women, evidence of infection in either systems e.g. respiratory, urinary, HIV etc., patients with smear positive reports who had received antimalarial drugs and past history of allergy to doxycycline. They were subjected to complete blood count, peripheral blood film (PBF) for malarial parasites, parasitic indexon day 1, 4 for all patients and on day 7 for refractory ones; renal, liver function, x-ray chest, urine examination. The countswere repeated in case of ruling out of blood dyscrasias[22] due to drugs or severe disease.

The patients were divided in two groups (Table 2):

The Aims and objectives of the study were to find out the uncomplicated vivax and falciparum +/- vivax mixed malaria patients in our medical ward hospital

admission and to find out the resistance to various antimalarial drugs in these patients.

Table 2: Group A P. vivax infestation Group B P. falciparum & mixed infestation					
Subgroup (a)	**Subgroup (b)**	**Subgroup (c)**	**Subgroup (a)**	**Subgroup (b)**	**Subgroup (c)**
Chloroquine + Doxycycline	Quinine + Doxycycline	Artemisinin (Artesunate) + Doxycycline	Chloroquine + Doxycycline	Quinine + Doxycycline	Artemisinin (Artesunate) + Doxycycline

RESULTS

A total of 120 cases of positive malaria (P. vivax; P. falciparum and mixed varieties) were studied. The series included 97 maleand 23 female patients.

CLINICAL FEATURES

The 120 patients were divided into 2 groups depending on the malarial parasite manifestations and drug combinations. Fever, chills & rigors, headache, vomiting, abdominal pain, abnormal behaviour, oliguria, breathlessness were more pronounced in group B patients. Similarly, physical signs like hypotension, hyperpyrexia, icterus, pallor, petichiae, abdominal tenderness and hepatosplenomegaly were also predominant findings in group B as compared to group A patients.

SPECIFIC INVESTIGATIONS

Peripheral smear (PS) both thick and thin for malarial parasite(MP) with parasite index (number of MP/1000 RBCs) were evaluated as shown in Table 3.

Table 3					
Stages	**Parasitic index (No. of MP/1000 RBCs)**				
	Ring	**Gametocyte**	**Ring and Gametocyte**	**<1%**	**>1%**
Group A No. of patients	24	20	16	30	30
Group B No. of patients	8	29	23	28	32

The 120 subjects in group A and B were also allotted at random into three subgroups to the combination of antimalarial drugs as in group A. It is as follows:
Subgroups a – Choroquine and Doxycycline; b – Quinine and Doxycycline; c – Artesunate and Doxycycline. After the medication the disappearance of fever was observed from day 1 to day 28 along with parasitic index and absence of malarial parasites in peripheral smears. If the response to the group of drugs was not satisfactory, the patient was switched on to the next alternative group respectively as shown in Table 4.

Table 4					
GROUPA (60 PATIENTS)					
No. of patients (subgroup a) 20	**Disappearance of fever**		**Parasitic index clearance**		**Switch on to alternative combination**
	</= Day 4	**> Day 4**	**< / = Day 4**	**> Day 4**	
Chloroquine plus doxycycline – 20 patients	13/20 (65%)	7/20 (35%)	5/20 (25%)	15/20 (75%)	7/20 To artesunate plus doxy
No. of patients (20) Sub group b Quinine and Doxycycline combination	8/20	12/20	7/20	13/20	Nil
No. of patients (20) Sub group c Artesunate and Doxycycline combination)	18/20	2/20	8/20	2/20	2/20 To quinine + doxy
GROUP B (60 PATIENTS					
No. of patients (20) Sub group a Chloroquine + Doxycycline combination	4	16	4	16	8/8 To artesunate + doxy Quinine + doxy
No. of patients (20) Sub group b Quinine and Doxycycline combination	18	2	18	2	2/20 To artesunate + doxy
No. of patients (20) Sub group c (Artesunate and Doxycycline combination)	19	1	19	1	1/20 To Quinine + doxy

ROUTINE INVESTIGATIONS

All the 120 patients underwent following investigations. Table V reveals the range of haemoglobin (Hb); white blood cells (WBC) and platelets.

Table 5: Investigations

	Group A (60 patients)	Group B (60 patients)
Hemoglobin (Hb) <10.0 gm%	26	34
Hemoglobin (Hb) >10.0 gm%	34	26
White blood cells (WBCs)		
<4000/cmm (UL)	10	9
>4000-11000/cmm (UL)	50	51
Platelet count		
<30,000 to 50,000 (UL)	20	11
>51,000 to 1,50,000 (UL)	40	49

An observation was kept to see the effect of drugs on leucocytes whether there occurred leucopenia or pancytopenia[23] in falciparum malaria.

There was an early disappearance of fever and parasitic index in patients of P. vivax (Group A) as compared to those of P. vivax and falciparum mixed infections (Group B).

DISCUSSION

One hundred and twenty cases of smear positive (60 cases of uncomplicated P. vivax Group A and 60 cases of uncomplicated P. falciparum or mixed malaria Group B) were taken into study. Patients of group A were subdivided in subgroup a, b and c and of group B were subdivided in subgroups a, b and c. Subgroup a, b, c of both groups were given. Chloroquine + Doxy; Subgroup b – Quinine + Doxy; Subgroupc – Artesunate + doxy respectively.

Group A

Subgroup a (chloroquine + doxycycline – 20 patients). It was detected that this group had 65% success rate, rest 35% were drug resistant as in the study conducted by Assam state[24,25] and were shifted to other drugs artesunate / quinine with doxycycline. In subgroup b no patients were shifted and this group had 100 percent success rate. In Subgroup c 18 out of 20 recovered fully and within 3 days (90 percent success rate). Two patients had to be switched on to quinine and doxycyclinecombination for recovery.

Group B

Subgroup a (chloroquine + Doxycycline – 20 patients) - there was 80 percent failure rate; 4 patients responded to this combination and 16 had to be switched over to other combinations i.e. artesunate and quinine with doxycycline. Thisstudy is similar to one conducted in Arunachal Pradesh with 83% failure rate.

Subgroup b - 18 out of 20 patients recovered fully with disappearance of fever within next 3 days and only 2 patients had to be switched on to artesunate and doxycycline combination for complete recovery. This subgroup had 90% success rate. Subgroup c - 19 out of 20 patients recovered fully with disappearance of fever within 3 days. Only 1 patient had to be switched over to quinine and doxycycline and he responded within 7 days. This subgroup had 95% success rate. In the elderly population the mortality has been around 20,000/ year according to WHO data. The collapse of vector control, waning efficacy of existing cheap duplicate ineffective drugs and misuse of drugs are the causes of drug resistance.

This study reveals that the best combination of drugs in P. vivax group infections and P. falciparum mixed malarial infection are artesunate followed by quinine along with doxycycline combination as compared to chloroquine with doxycycline. However, in P. vivax (subgroup a of group A) the patients did show a response (65%) to chloroquine and doxycycline drugs combination. They all were given primaquine 15 mg daily x 14 days for prevention of relapse. Artesunate or quinine with doxycycline combination proved tobe the ideal choice in mixed infection of P. falciparum and P. vivax cases and in drug resistance cases with chloroquine.

CONCLUSIONS

- In group A (P. vivax) in (subgroup a) with chloroquine and doxycycline combination therapy, 65% of patients responded well and 35% had to be switched to other groups.
- In group A (sub group b) and (sub groups c), quinine and doxycycline combination and artesunate and doxycycline combination had 100% and 90% success rate respectively. Artesunate should have limited use in uncomplicated P. vivax so that resistance does not occur.
- In group B, (sub group a) on chloroquine and doxycycline combination, patients with falciparum malaria had 80% failure rate and had to be switched to other drugs like artesunate or quinine to which they responded. Falciparum malaria responds poorly to chloroquine due to resistance tothis drug.
- In group B sub group b and c on quinine and artesunate with doxycycline combinations had 90

and 95% success rate respectively. Artesunate followed by quinine are most effective drugs in uncomplicated falciparum and mixed (vivax and falciparum) malaria.

- Artesunate and Quinine have earlier onset of action and does very well with other combination of drugs i.e. doxycycline having longer duration of action in killing and eradicating the malarial parasites. Total duration of treatment being 3-7 days.

CARRY HOME MESSAGE

- Thus ACT acts as first line of drug in drug resistant cases. One of the drug acts on the mutant resistant parasite and the other antimalarial drug acts on the sensitive parasites. Thus mutual protection prevents the emergence of resistance. The partner drugs are independently effective.
- Monotherapy is out these days and two drugs of different mode of actions are the mainstay in the management of resistant malaria.
- Thus short course of therapy (3 day regimen) is physician friendly and patient friendly and will act for a decade or so.
- ACT causes less risk of hypoglycaemia or cardiac toxicity.
- P. vivax is no more benign and should be treated like other P.species with ACT.
- Follow up programme is a must.
- Prevention (By larvicidal measures, mosquito repellents andin future malarial vaccine) is better than cure.

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