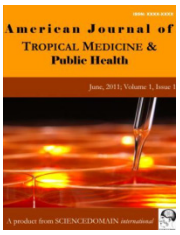

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Possible Antiplasmodic Effects of Antituberculosis Drugs on Tuberculosis Patients with Malaria in Owerri Imo State, Nigeria

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Research Article

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ABSTRACT

Malaria and Tuberculosis are diseases of poverty with oftentimes fatal outcome especially amongst the very poor. The possible chemotherapeutic effect of some Anti-tuberculosis drugs (Isoniazid, Rifampicine, Pyrazinamide and Enthambutol) on the malaria parasitemia of Tuberculosis (TB) patients undergoing treatment was assessed between April 2008 and September 2009. A total of 832 TB positive patients made up of 446 TB patients who had not commenced treatment (control) and 386 TB patients undergoing Chemotherapy at different regimented stages were involved in this study. These were periodically screened for malaria parasitemia and other blood parameters. The intensity of malaria parasitemia in positive blood smears were grouped into low (+), medium (++) and high (+++) based on average numbers of parasites per microscopic field (WHO, 1991). The '+' indicates the relative parasite count. From the control group; 229 (51.3%) had malaria parasitemia of +, 69 (15.5%) and 57 (12.8%) had ++ and +++, respectively while 91 (20.4%) had no malaria. Of the 386 TB patients already undergoing therapy; 251 (65.0%) of the group at the initial phase of the study had no malaria parasite, while 135 (34.9%) had I+ parasitemia only. A total of 84 patients at the initial phase of treatment had no malaria parasite. As the study

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progressed, from a total of 151 TB patients at the continuation stage of 2 – 6 months, 79 (52.3%) had no malaria parasite, 67 (44.4%), 5 (3.31%) had + and ++, respectively. The 151 TB patients at the final stage of 7-8 months of treatment, had 37 patients (24.5%) with no malaria parasite, 48 (31.7%), 34 (22.5%) and 32 (21.2%) had +, ++ and +++ of malaria parasitemia, respectively. Age related prevalence of malaria parasite load showed that TB patients between the ages of 10 – 20 yrs. (3 no. (1.18%) had lower parasitaemia than TB patients in between the ages of 70 – 80yrs. (78 no. (30.7%). The sex related prevalence shows the male TB patients (53.9%) had more malaria parasitaemia than their female counterparts (46.1%). This study shows that TB drugs could have some antiplasmodic effect.

Keywords: Antiplasmodic; malaria; Tuberculosis; anti-tuberculosis; parasitaemia;

1. INTRODUCTION

Tuberculosis and malaria co-infection is one of the major public health challenges undermining development in the poorest countries of the world (RBM, 2001). Both malaria and tuberculosis are important tropical infectious diseases and large proportion of people live in malaria endemic areas, so co-infection with these two organisms is likely to be common (Scott et al., 2004).

The endemicity of malaria and tuberculosis co-infection has been reported in many regions of the world (Viroji, 2000). Audu et al., (2005) working on the possible impact of co-infection of tuberculosis and malaria on the CD4+ cell counts of HIV patients in Nigeria confirmed a progressive depletion of CD4+ cell of HIV infected subjects. The levels of CD4+ cells count of subjects with either single infections of TB, malaria or multiple infections with TB/malaria were within the normal range reported for adult Nigerian population (Audu et al., 2005). This implies that neither TB nor malaria infections have direct impact on the CD4+ cells (Audu et al., 2005).

This present study was initiated to test the possible chemotherapeutic effect of common anti-TB drugs on the malaria parasite load of Patients on TB treatment in DOTS center in Aboh-Mbaise Imo State Nigeria. This will help to possibly lessen the burden of malaria / TB co-infection in malaria endemic communities as well as guide the rationale use of anti-malaria in the treatment of already immune - compromised TB patients in Nigeria and elsewhere in the world.

2. MATERIALS AND METHODS

2.1 The study area

This study was conducted between April 2008 and September 2009 in two Tuberculosis DOTS centers in Aboh - Mbaise. The centers were (1) Tuberculosis control department of the Aboh Mbaise Local Government and (2) the Acid Fast Bacilli (AFB) microscopic centre of the General Hospital at Aboh Mbaise, Imo State, Nigeria. The study population thus was patients attending the Directly Observed Therapy Shortcourse Units (DOTS) at these sites within the study period.

2.2 Ethical Considerations

All the patients involved in this study were counseled and made to sign a consent form after the study objectives were clearly explained to them.

2.3 Study Subjects

Two groups of the study subjects were used for the study; Group A was made of 446 persons whose sputum samples were found to be positive for Tuberculosis but have not commenced treatment and Group B consisted of 386 TB patients who had started treatment at different regimented levels. The subjects consisted of both males and females within the age range of 10yrs to 80years.

2.4 Sample Collection and Analysis

About 2mls venous blood was taken from each patient involved in this study. Malaria parasites were detected through thin blood films stained with Field's stain A and B. Patients were categorized into two groups (A: 446 control group and B: treated group) based on duration and period of treatment to enable one ascertain the effect of TB therapy on their Malaria parasite Load.

The intensity of malaria parasitemia in positive blood smears were grouped into low (+), medium (++) and high (+++) based on average numbers of parasites per microscopic field (WHO, 1991). The '+' indicates the relative parasite count as follows:

+ = 1 -10 parasites per 100 thick-film fields
++ = 11 – 100 parasites per 100 thick-films fields
+++ = 1 – 10 parasites per thick-film field
++++ = more than 10 parasites per thick-film field (WHO 1991)

The patients were also screened for their blood groups and genotype and its effects on their malaria parasite load.

The drugs used in this study are in two categories which include:

Category 1 – Rifampicine, Pryzinamide, Isoniazid, Ethambutol (for 2 months)
Category 2 – Streptomycin, Rifampicine, Isoniazid, Pryzinamide, Ethambutol (for 8 months)

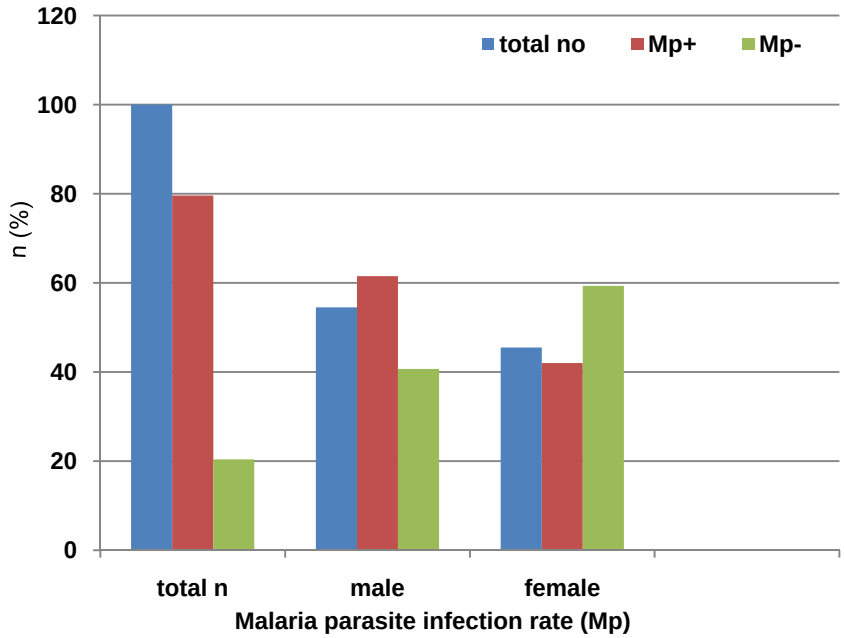
3. RESULTS

Total of 832 detected tuberculosis patients were involved in this study (Table 1). The study subjects were divided into two groups. Group A study subjects served as control and were made up of 446 persons (243 males and 203 females) aged between 10 to 80 years diagnosed with Tuberculosis. The rate of malaria infection within this control group in relation to age is shown on table 1. Group B study subjects were TB patients at varying stages of chemotherapy.

Table 1. The rate of Malaria infection amongst just detected TB patients (Control) who have not commenced TB treatment (N = 446)

Age groups (yrs.)	No. examined	Malaria Parasite positive (%)	% within Age group	Negative (%)
10 – 20	65	43 (12.1)	66.2	22 (24.2)
21 – 30	145	125 (35.2)	86.2	20 (22.0)
31 – 40	109	85 (23.9)	78.0	24 (26.4)
41 – 50	24	15 (4.2)	62.5	9 (9.9)
51 – 60	9	6 (1.7)	66.7	3 (3.3)
61 – 70	16	10 (2.8)	62.5	6 (6.6)
>71	78	71 (20.0)	91.0	7 (7.7)
TOTAL	**446**	**355 (79.6)**	**79.6**	**91 (20.4)**

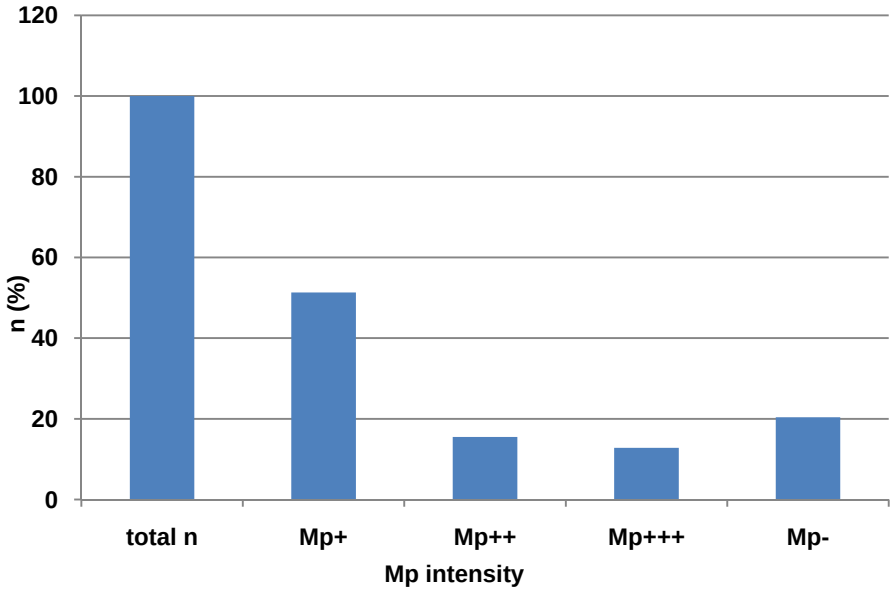
The Group A study subjects had a 79.6% prevalence of malaria, with the age group 21 – 30 years showing the highest overall occurrence level of 35.2%. Within the age groups however the age group >71 had the highest prevalence of 91.0%. The occurrence of malaria in this study group was assessed based on sex (Fig. 1).



Key: Y axis: n (%) indicates number of patients (%); X axis: Malaria parasite (Mp) infection rate; Mp^+ - malaria parasites positive; Mp^- - malaria parasites negative

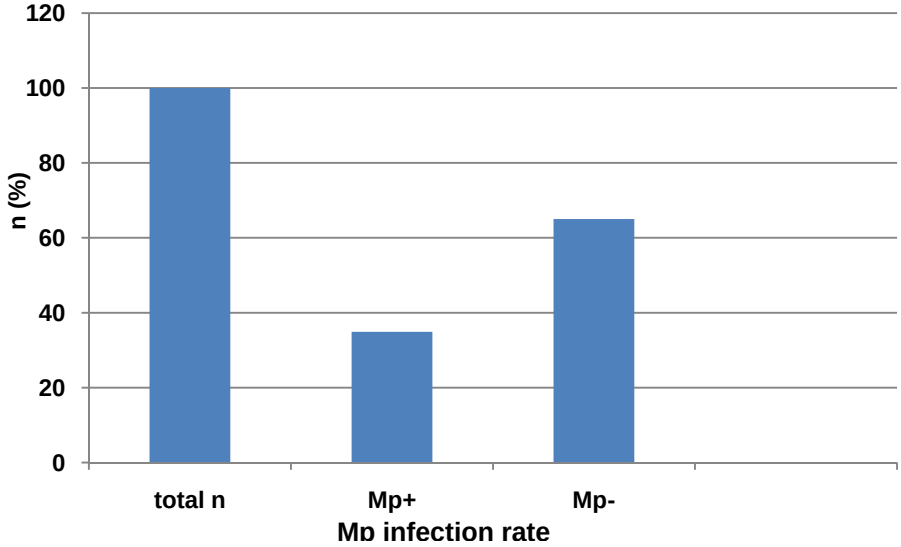
Fig. 1. The sex relationship between malaria infection rates in the just detected TB patients yet to commence treatment (control)

The study group A had more males than females and malaria parasites were seen more in the males than in the females. The intensity of malaria parasitemia expressed as '+' sign in this study group is shown in Fig. 2.



Key: Y-axis: n (%) – no. of patients (%); X- axis: Malaria parasite (Mp) intensity

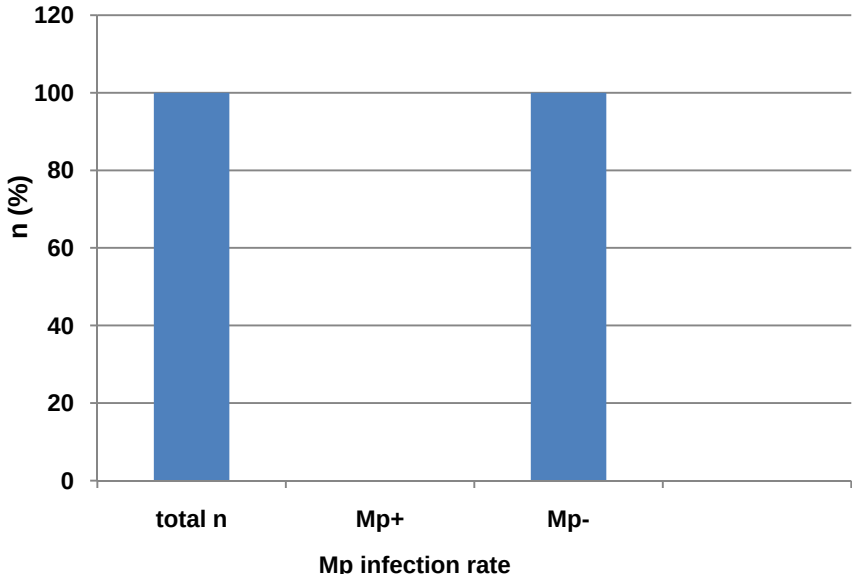
Fig. 2. Malaria parasite load of the TB control group



Key: Y axis – n (%) - number of patients (%); X axis - malaria parasites (Mp) infection rate

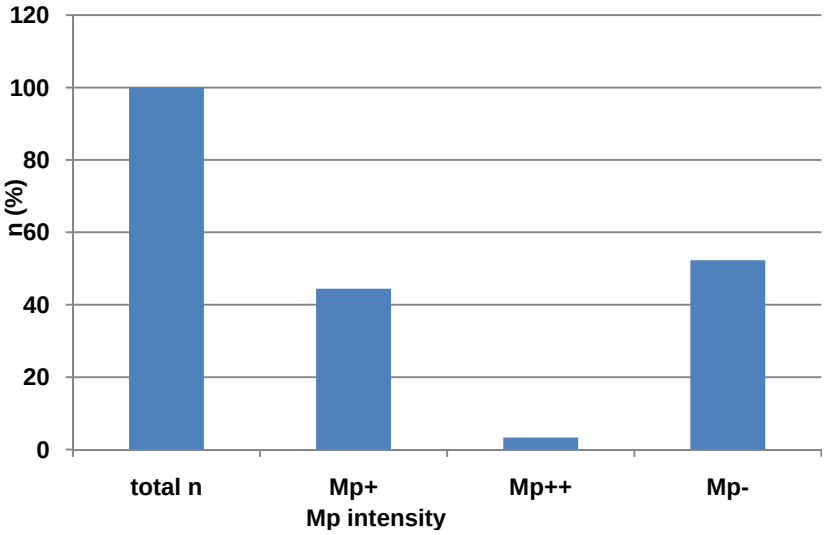
Fig. 3. Malaria parasite infection rate in the TB patients in Group B already in TB chemotherapy N = 386

In Nigeria, Mp^+ which implies low malaria parasitemia is often seen as indicative of resistant *P. falciparum* infection. This however, in the above result is of the highest occurrence in the study subjects while high malaria intensity occurred least in this study population.



Key: Y axis – n (%) - number of patients (%; X axis – Malaria parasites (Mp) infection rate

Fig. 4. Malaria parasite load of the TB patients at the initial phase of chemotherapy (n= 84)



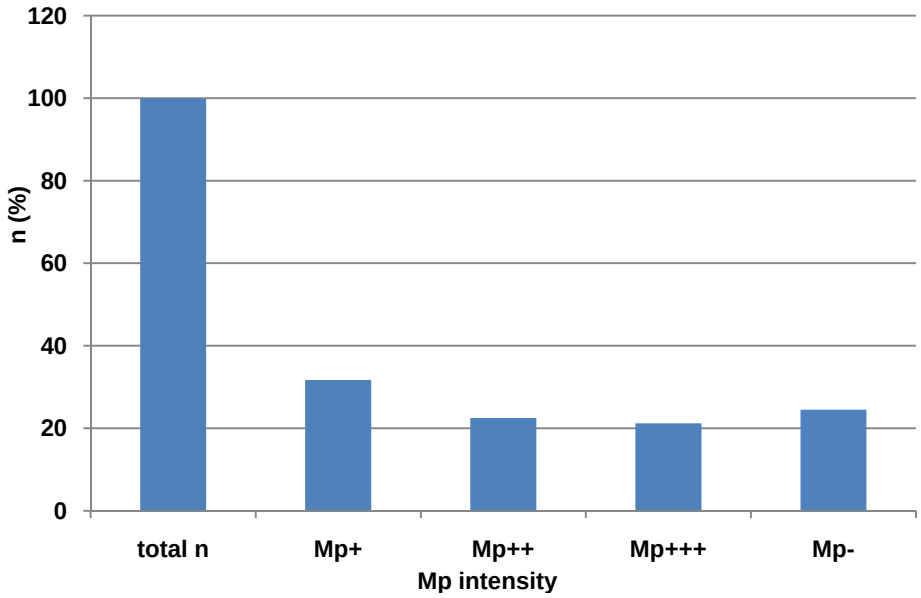
Key: Y axis – n (%) - number of patients; X axis - malaria parasites (Mp) intensity

Fig. 5. Malaria parasite load of TB patients in the 2 -6 months treatment regimen (n = 151)

The study group B is made up of study subjects at different stages of TB therapy. The Malaria parasite infection rate in this group was observed to be less in this study group. The patients without malaria parasites (Mp^-) were more than those with malaria parasites (Mp^+) in their blood. This group B was further segregated into specific stages of TB therapy. The malaria parasitemia of the subjects at the initial phase of therapy is shown in Fig. 4.

None of the study subjects at this initial phase of chemotherapy with anti-TB drugs had malaria parasites in their blood.

At the second phase of anti-TB therapy, the malaria parasites re-appeared in the blood of the study subjects. The intensity of malaria parasitemia was low but this low intensity (Mp^+) is also indicative of resistant *P. falciparum* infection.



Key: Y axis – n (%) - no of patients (%); X axis - malaria parasites intensity (Mp)

Fig. 6. Malaria parasite load of TB patients in the 7 – 8 months treatment regimen (n = 151)

Towards the end of TB therapy, most of the study subjects had malaria parasites in their blood. The low malaria intensity indicative of resistant falciparum infection was still highest in occurrence but many of the subjects also had high malaria parasitemia.

4. DISCUSSION

Findings from this study indicate that the intensity of malaria parasite load in TB Patients undergoing treatments with anti-tuberculosis drugs at the different regimens were far less than those not an anti-tuberculosis drugs. Pukrittayakamee et al. (1994) working in South East Asia made similar observations.

Within the intensive phase of treatment, malaria parasites were not seen in 65% of the study population in Group B and monitoring of 84 volunteers some weeks after; these had no malaria parasite. This indicates that anti-tuberculosis drugs are potential alternative choice antibiotics for combination with common anti-malarial drugs in the treatment of malaria. Such combinations will help to improve cure rates and also prevent or delay the emergence of anti-malaria drugs resistance (Pukrittayakamee et al., 1994; Freerksen et al., 1995; 1996). Rifampicine and Isoniazid are anti-tuberculosis drugs which have been identified to have anti-plasmodic activity (Freerksen et al., 1995; 1996). The anti-tuberculosis drug Cotrifazid is a fixed combination of Cotrimoxazole, Rifampicine, Isoniazid which has been proven safe and efficacious in the treatment of uncomplicated, complicated or drug resistant falciparium malaria in malaria patients including under - 6 months of age children from malaria endemic areas (Freerksen et al., 1995,1996; Genton et al., 2006).

Hutchinson and Farquhar (1982), Bloland et al. (1991) in their respective studies showed that Cotrimoxazole has some activity against malaria in humans. Studies have shown that Rifampicine (an anti-tuberculosis drug) has some activity against *Plasmodium berghie* in rodents (Alger et al., 1970). In humans, Rifampicine has shown partial efficacy against *Plasmodium vivax* when associated with Primaquine (Pukrittayamee et al., 1994). Isoniazid (another active anti-tuberculosis drug) has been shown to inhibit malaria transmission in the mosquito gut by inhibiting exflagellation, ookinete formation as well as oocyst development. The drug however, could not inhibit parasite development in the blood of the vertebrate host but delayed malaria mortality in mice as well as reduced the overall parasite load especially when given in combination with Rifampicine and Cotrimoxazole (Alger et al., 1970; Scott et al., 2004). In this study Cotrimoxazole was not in the combination cocktail of the anti-tuberculosis drugs used.

At the final treatment stage of 7-8months, more TB patients had malaria parasite load and there was also an increase in the malaria parasite intensity. The reason could be treatment failures on the part of some TB patients, who usually at this stage are tiring of taking their drugs more regularly thereby creating room for possible drug resistance.

Another reason may also be due to other Pharmacokinetic factors. For example, it is known that there is a Pharmacokinetic synergism between Cotrimoxazole and Rifampicine with increased half- life and efficacy when administered simultaneously. Similarly, Isoniazid reduces overall parasite load when given in combination with Rifampicine and Cotrimoxazole (Bhatia et al., 1991; Genton et al., 2006). Thus, one may suggest that the drugs given in combination with Isoniazid and Rifampicine at the final stage of therapy may not synergically complement the antimalaria activity of these drugs.

5. CONCLUSION

This study has successfully highlighted the fact that some commonly used anti-tuberculosis drugs have anti-malaria activity. Therefore the use of these drugs (Rifampicine, Isionazid) particularly in combination with some anti-malarial drugs will improve cure rates and equally delay the emergence of anti-malarial drug resistance.

The cost effectiveness of these drugs as well as the fact that they are already in-use may increase their acceptance of use in combination with anti-malarials. However, further research is also recommended to elucidate the pharmacokinetic synergy of these chemotherapeutic agents.

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