

Evaluation of the Effect of Supervised Antimalarial Treatment on *P. Vivax* Malaria Recurrences

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Research

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Abstract

Background

Relapses in vivax malaria have posed great challenges to malaria control, accounting for a great proportion of reported cases. Knowing the real effectiveness of 7 day primaquine (PQ) scheme is crucial to understand not only the cost-effectiveness of implementing new anti-hypnozoite drugs but how health education strategies can guarantee better compliance and be reinforced. This study aimed the evaluation of the daily supervised treatment effect with chloroquine and PQ (in consented patients) versus prescription without supervision (non-consented patients), and the outcome was the passive detection of new positive thick blood smears until 180 days, based on the official data records from the National Malaria Control Program. The recurrences seen in the real life were therefore used as a surrogate for true relapses. Patients under supervised treatment had a lower risk of recurrence until day 180 when compared to the unsupervised treatment (17.9% vs 36.1%; $p=0.027$). The lack of consent in the non-supervised group (which followed standard of care in the real life) enabled proper comparison, as consent itself could lead to better compliance in this group. Future studies should scale such analysis to different settings in the Brazilian Amazon.

Introduction

Plasmodium vivax is the most prevalent malaria etiological agent in Brazil (~ 90%) (1). The development of latent hepatic forms called hypnozoites, responsible for relapses months or years after an episode of vivax malaria, contribute to the maintenance of the transmission cycle (2).

In 2009, the frequency of recurrences in the Amazon was 20.8% and in the municipality of Porto Velho it was 23% in the same period (3). Others studies demonstrated that 30.9% (4) and 29.4% (5) of the individuals who were tested presented with recurrence malaria. The scheme recommended for *P. vivax* in Brazil consists of the association between chloroquine (CQ) for 3 days and primaquine (PQ) (0.5 mg/kg/day) for 7 days. One of the limiting aspects of treatment success is the variation in the response of parasites to the therapeutic regimens used and poor adherence to treatment (6).

The interruption of medication on their own and difficulty in accessing basic health units are some of the factors that are related to non-adherence and consequently to recurrences (7, 8, 9). Some studies indicate that after the first doses of antimalarials, patients infected with *P. vivax* become asymptomatic and tend to interrupt treatment with PQ, which is the essential drug for radical cure (10). To determine the effectiveness of PQ in endemic areas, it is necessary to assess recurrences until 180 days, which is enough to detect most recurrences in Brazil (11). In a rural settlement area in the Western Brazilian Amazon, *P. vivax* relapsing episodes were observed in 29.4% of the individuals in 90 days of follow-up (12). The debate around the distinction between recrudescence, relapse and reinfection usually needs biomolecular markers to distinguish, but even with these tools, the clear distinction has limitations (13). Evaluating the impact of recurrences is one valuable tool towards vivax malaria elimination, where public

health policies may impact especially at primary care. Thus, this study aimed to evaluate the impact of supervised treatment in recurrences of vivax malaria in a municipality in the Brazilian Amazon.

Methods

Patients over 16 years old, with a positive thick blood smear for vivax malaria, were recruited in Rio Preto da Eva, Amazonas, Brazil, located 75 km from the capital (Manaus). According to the Brazilian malaria treatment guideline, patients should receive CQ (25 mg/kg given during the first 3 days) and a short-course PQ (0.5 mg/kg/day, for 7 days) (1). All patients with confirmed vivax malaria are prescribed with both drugs, without previous G6PD screening, except children under 6 months of age and pregnant women. In Brazil, antimalarial drugs are free for patients and there is no supervision by health professionals of their daily administration.

Patients were randomized to consent using Zelen's design (1), where only one group was randomized to sign an informed consent form (ICF), and was daily visited at home for drug supervision by one health agent. A randomization list was prepared by an independent statistician using the R program in order to consent patients to the supervision group. Others patients diagnosed with vivax malaria were treated without supervision, without any intervention. Both supervised and unsupervised treatment groups followed the instructions of performing a new thick blood smear in case they presented with new symptoms (passive surveillance). All exams and positive malaria cases are reported in the national surveillance system (SIVEP-Malaria). Recurrent episodes were assessed within 180 days of the beginning of antimalarial treatment. No active surveillance was performed and therefore, no additional thick blood smear was collected for the study, in the absence of symptoms. Quality control of the microscopic diagnosis followed the standard routine of the Amazonas State Surveillance Central Laboratory, in which a percentage of negative smears and all the positive smears are revised by an experienced microscopist.

Extracted data from SIVEP-Malaria were merged into electronic forms (REDCap). Descriptive statistics were used for demographic variables. Student's t test was used to compare means while Fisher's exact or Chi-squared (χ^2) test were used to compare proportions, as appropriate. Kaplan-Meier survival estimates were used to compare recurrences in 180 days between groups. All analyzes were performed using the Stata v15 (Stata Corp, USA). This study was approved by the Ethics Review Board (ERB) at *Fundação de Medicina Tropical Dr Heitor Vieira Dourado* (CAEE: 18314019.5.0000.0005). Consented patients signed an ICF and the ERB waived the ICF for those patients not consented, which followed the standard of care, without supervision.

Results

From November 20th, 2019 to November 3rd, 2020, 117 participants were included and finished the 180-day follow-up period, being 56 (47.8%) randomized for the supervised treatment group and 61 (52.2%) in the unsupervised routine treatment group. There was no significant differences between groups characteristics at baseline (Table 1).

Table 1
Clinical and demographic characteristics of 117 participants at inclusion.

	Total	Supervised	Unsupervised	<i>p</i>
Variable	n = 117	n = 56 (47.8%)	n = 61 (52.2%)	
Age (± SD)	38.3 (14.4)	36.6 (14.3)	39.9 (14.6)	0.21
Gender (F)	41/117 (35.0%)	21/56 (37.5%)	20/61 (32.8%)	0.59
School education				0.06
Incomplete primary school	36/117 (30.8%)	14/56 (25.0%)	22/61 (36.1%)	
Completed primary school	14/117 (12.0%)	4/56 (7.1%)	10/61 (16.4%)	
Incomplete high school	29/117 (24.8%)	14/56 (25.0%)	15/61 (24.6%)	
Completed high school	27/117 (23.1%)	15/56 (26.8%)	12/61 (19.7%)	
Bachelor's degree	11/117 (9.4%)	9/56 (16.1%)	2/61 (3.3%)	
Residency area				0.34
Rural	98/117 (83.8%)	45/56 (80.4%)	53/61 (86.9%)	
Urban	19/117 (16.2%)	11/56 (19.6%)	8/61 (13.1%)	
Parasitemia				0.60
< +/2	20/117 (17.1%)	11/56 (19.6%)	9/61 (14.8%)	
+ /2	15/117 (12.8%)	9/56 (16.1%)	6/61 (9.8%)	
+	26/117 (22.2%)	11/56 (19.6%)	15/61 (24.6%)	
++	56/117 (47.9%)	25/56 (44.6%)	31/61 (50.8%)	
SD, standard deviation. F, female; Parasitemia described by the Brazilian Ministry of Health: < +/2 = Number of less than 40 parasites in the 100 fields examined, +/2 = 40 to 60 parasites in 100 microscopic fields, + = 1 parasite per field, ++ = 2 to 20 parasites per field, parasites/μL				

When comparing recurrences between groups, 32 (27.4%) participants had at least 1 vivax malaria recurrence, with significant statistical difference between supervised and unsupervised treatment (17.9% vs 36.1%; $p = 0.027$) (Table 2). There was also a significant difference in time to first recurrence ($p = 0.04$). Survival analysis showed a higher risk of recurrence in the unsupervised treatment group [Hazard Ratio 2.44, $p = 0.019$ (95%CI 1.15–5.15)] compared to supervised treatment (Fig. 1).

Table 2

Recurrences between supervised and unsupervised treatment groups with 180-day follow-up period.

	Total	Supervised	Unsupervised	<i>P</i>
	n = 117	n = 56 (47.8%)	n = 61 (52.2%)	
Recurrence in 180 days (n/N)	32/117 (27.4%)	10/56 (17.9%)	22/61 (36.1%)	0.027
Number of recurrences (n/N)				0.07
1	18/32 (56.2%)	8/10 (80.0%)	10/22 (45.5%)	
≥ 2	14/32 (43.8%)	2/10 (20.0%)	12/22 (54.5%)	
Time to first recurrence (d) (n/N)				0.04
≤ 60	6/32 (18.8%)	1/10 (10.0%)	5/22 (22.7%)	
61–90	14/32 (43.8%)	2/10 (20.0%)	12/22 (54.5%)	
91–180	12/32 (37.5%)	7/10 (70.0%)	5/22 (22.7%)	

Discussion

Results show that the PQ short treatment unsupervised presented an increased risk of recurrence compared to the supervised group. The shorter PQ regimen (7 days of 0.5 mg/kg/day) is used in Brazil to improve adherence since the middle 1990s, and the 14-day (0.25 mg/kg/day) course actually does not seem to be superior in preventing relapses (14). However, data on compliance to the 7-day regimen is still scarce and has to deal with the methodological issues of randomizing a non-supervision group to serve as a comparator, in which the mere commitment to the study may increase drug intake, not reflecting therefore, the real life situation. In order not to cause any distortion of reality, possibly influencing adherence, an unsupervised treatment group was used in our study, taking advantage of the Zelen's design, where some patients were not randomized to consent and have their treatment supervised, and therefore, no intervention or contact with the participant happened throughout the study duration. ERB allowed for a waiver of consent in this group, understanding that any consent process would bias the results. All participants randomized to the supervised group had home visits from D1 to D7, for drug administration.

In Thailand and Papua New Guinea, a recurrence rate for *P. vivax* after treatment with CQ and PQ can reach up to 65% over 30 to 180 days of follow-up (15). In the current study, we demonstrated that relapses occurred between 42 to 180 days, possibly the group of unsupervised participants who had the highest number of relapses was due to non-adherence. Many studies have shown that there are problems in the treatment of *P. vivax* malaria, one of which is the precariousness of the dispensing system and inadequate storage conditions. Several other factors can contribute to the increase in recurrence rates in the Amazon region, including genetic factors, e.g., abnormal CYP2D6 activity (16).

The number of patients who experienced recurrence due to *P. vivax* in this study raises the hypothesis that recurrence in vivax cases was higher due to improper treatment of these cases (17), considering that participants in each group were randomized. In the Amazon region, treatment is not supervised and there are few studies that discuss the importance of adherence and the often-precarious conditions of dispensing and storing medications can contribute negatively (18). In Pará, Brazil, the relative risk of parasitic resurgence was 3.04 times higher in non-adherent patients (19). Other study reported that adherence frequency was 86.4% (81.7%-90.1%) (20).

Non-adherence to treatment affects the health of patients and is one of the main factors of therapeutic failure that directly impacts the control of the disease and places a socioeconomic burden on health systems. Information on non-adherence to the current antimalarial treatment is essential for interventions aimed at reducing therapeutic failure and further recurrences. However, with the possibility of introducing tafenoquine, the 8-aminoquinoline given as a single dose, with similar efficacy to 14-day PQ regimen (21), there is a concern that the high levels of efficacy observed in clinical trials may not be repeated in the real life (22).

The major limitations of the study are: the small sample size, which should be increased as to include other endemic areas in Brazil, and increase national representativeness; no compliance could be estimated in those under 18 years of age; there is also an underestimation of asymptomatic relapses, as no active microscopic surveillance was performed.

These preliminary data, from a municipality in the Brazilian Amazon, might be used as a first reliable reference, based on real life data, of to which extent the lack of compliance to the 7-day PQ regimen in the treatment of vivax malaria affects recurrences until day 180. Non-supervision more than doubles such risk, which might be a bottleneck if any program pursues malaria elimination.

Conclusions

In conclusion, treatment supervision provides an additional valuable tool for the elimination of vivax malaria in this scenario. Future studies should be realized through multicenter studies, in order to assess different environments and patient profiles. Additionally, the perception of failure or adherence to treatment can later be assessed by qualitative studies, in order to understand the local factors associated with recurrences.

Declarations

Ethics approval and consent to participate

The FMT-HVD Ethics Review Board (ERB), Manaus, Brazil, approved this study.

Availability of data and materials

Datasets from the current study are available upon reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study conceptualization and design: MVGL, AMS, WMM, GCM. Supervision: KMOD, SV-S, GCM, CP, SR. Data collection: SV-S. Statistical analysis: JDB-S, VSS. Writing of the first draft: KMOD, SV-S, JDB-S. Critical revision: All authors read and approved the final manuscript version.

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Figures

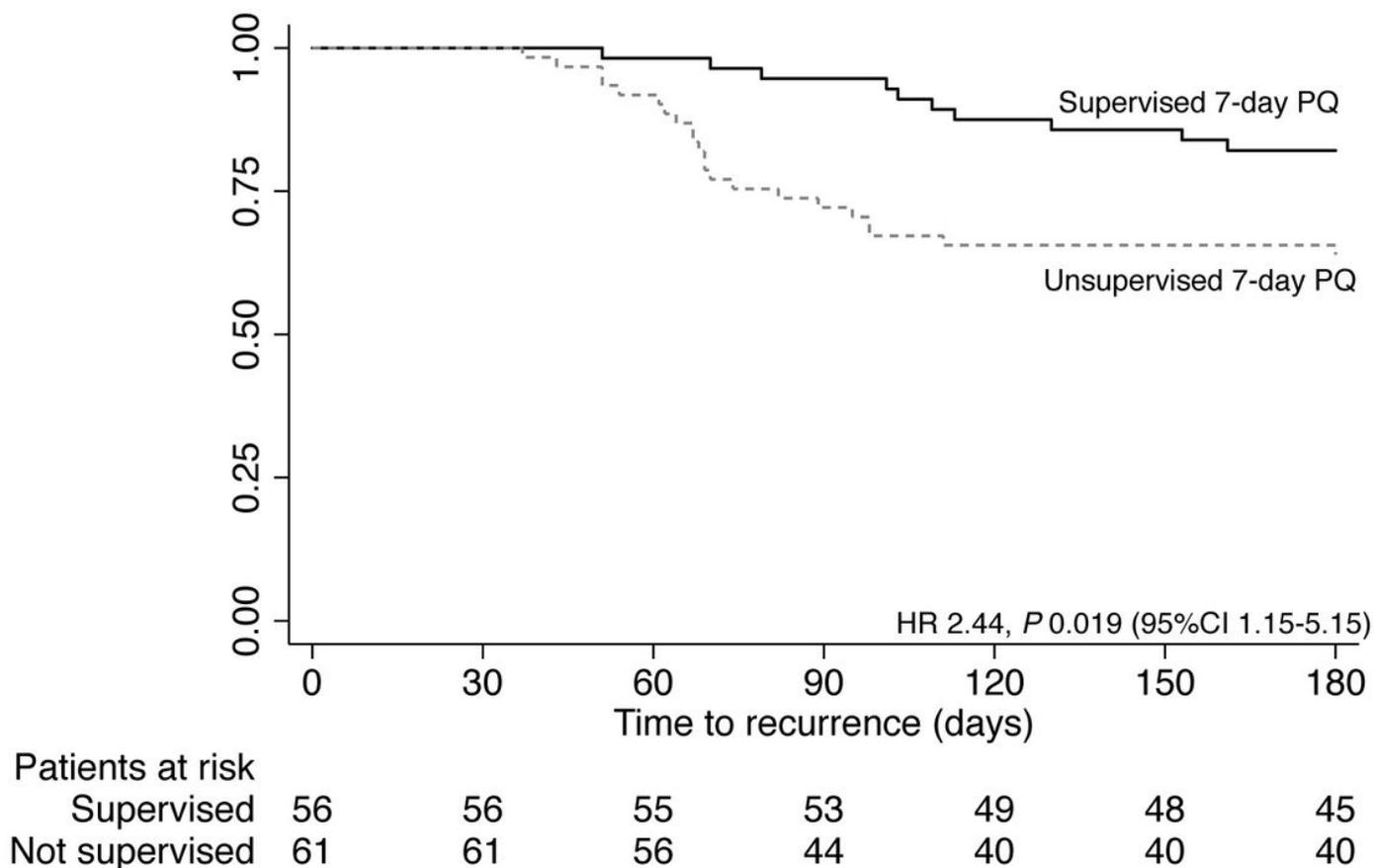


Figure 1

Time to recurrence between supervised and unsupervised 7-day primaquine treatment in 180 days of follow-up. PQ, primaquine; HR, hazard ratio; CI, confidence interval.