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Relapse of Plasmodium Vivax Malaria and Use of Primaquine in Pediatric Population at Tertiary Care Hospital

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Author`s Contribution

[1,3]Substantial contributions to the conception or design of the work; or the acquisition, [2]Final approval of the study to be published,[4,5] Active participation in active methodology, [2,3]analysis, or interpretation of data for the work, [5,6]Drafting the work or revising it critically for important intellectual content

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ABSTRACT

Objective: To determine the relapse rate of Plasmodium vivax malaria in pediatric patients treated with primaquine.

Methodology: A prospective comparative interventional study was conducted in the Department of Pediatrics at Combined Military Hospital Malir, Karachi, from August 2024 to April 2025. Patients aged 1–12 years who presented with either a first episode or relapse of P. vivax malaria, were clinically stable, and of either gender were included. Children were categorized into a treatment group receiving standard antimalarial therapy with primaquine and a control group receiving standard therapy alone. Relapse was defined as the reappearance of Plasmodium vivax parasites on peripheral blood smear following initially documented successful treatment. Data were analyzed using SPSS version 26.

Results: A total of 132 pediatric patients were included, with a mean age of 7.73 ± 3.58 years and an almost equal gender ratio. At one month post-treatment, relapse occurred in 9.1% of patients in the control group compared with 2.3% in the study group ($p = 0.076$). At the second month, relapse was significantly higher in the control group (29.5%) than in the study group (5.7%). At the third-month follow-up, the difference was even more pronounced (38.6% vs. 6.8%) ($p = 0.0001$). Additionally, the 14-day primaquine regimen showed the lowest relapse rates at both 2 months (4.5%) and 3 months (4.5%) compared with the 7-day regimen (6.8% and 9.1%, respectively) and the control group, indicating that prolonged primaquine therapy is most effective in preventing relapse. Furthermore, relapse rates did not differ significantly according to age within the pediatric population ($p > 0.05$).

Conclusion: The use of primaquine significantly reduced the relapse rate of Plasmodium vivax malaria in pediatric patients compared with standard treatment alone, with the most sustained protection observed with the 14-day regimen.

Keywords: Pediatric malaria; Plasmodium vivax; primaquine; chloroquine; relapse rate

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Introduction

Malaria remains one of the most serious global public health issues, primarily affecting tropical and subtropical regions. Malaria is a parasitic infection caused by five species of *Plasmodium* and is transmitted to humans through the bite of infected female *Anopheles* mosquitoes.[1,2] The disease is a major contributor to morbidity and mortality worldwide, imposing a substantial health and economic burden.[1] Based on data from 85 malaria-endemic countries, the global malaria burden increased from 227 million cases in 2019 to 241 million cases in 2020, with most of this increase occurring in countries within the African Region.[3,4]

Plasmodium vivax is the most common malaria-causing organism, generating significant morbidity. Unlike Plasmodium falciparum, P. vivax has the potential to generate dormant liver stages called hypnozoites, which can reactivate weeks to months after the original infection, resulting in relapses.[5,6] These relapses greatly increase the total disease burden and hinder malaria control efforts. Recurrent infection of P. vivax malaria due to hypnozoites is a serious challenge, especially in children who are more vulnerable to severe illness and associated consequences. The occurrence and onset of symptomatic relapses fluctuate across the areas and are further influenced by age of the patient as well as the local level of malarial transmissions.[7,8]

Malaria outbreaks have a significant impact on children's health and development, as well as on healthcare systems. Subsequently, the improvement for new antimalarial therapies that effectively prevent the relapse of *Plasmodium vivax* and are safe and well-tolerated among populations in most effected regions is very important for advancing control of malaria and ultimately achieving its eradication.[9] Primaquine is the only extensively used antimalarial medication that inhibits the hypnozoite stage of P. vivax. When used with blood-stage antimalarials, primaquine can significantly lower the chance of relapse.

Despite primaquine's proven efficacy in avoiding P. vivax relapses, there is inadequate data on its use and results in juvenile populations in tertiary care settings. According to the initial clinical trials, it was perceived that chloroquine potentiated the radical curative effectiveness of primaquine.[7] However the exact mechanism behind this association and its implications for clinical practice have not yet to be fully understood. The radical therapy effectiveness is equivalent when primaquine is administered with either artemisinin-based combination therapy (ACT) or the chloroquine, with rates of healing exceeding around 95% achievable under supervised treatment situations.[10] According to a study in P. vivax, patients prescribed primaquine had a lower risk of relapse around 7.1%.[11] Understanding the recurrence rates and effectiveness of primaquine in children is critical for refining treatment protocols and improving patient outcomes. This study intends to bridge this knowledge gap by prospectively assessing the relapse rates of P. vivax malaria and the safety and effectiveness of primaquine in a Paediatric population at a tertiary care hospital.

Methodology

This prospective comparative interventional study was conducted in the Department of Pediatrics at Combined Military Hospital (CMH) Malir, Karachi, from August 2024 to April 2025. A sample size of 132 patients was calculated using Raosoft® software for sample size estimation, based on a reported recurrence risk of 32.4%.[12] The calculation was performed with a 95% confidence level and 80% study power.

All pediatric patients aged ≤12 years with a confirmed diagnosis of *Plasmodium vivax* malaria, presenting with either a first episode or relapse, who were clinically stable, able to receive oral antimalarial therapy, and willing to comply with the assigned treatment regimen were included, regardless of gender. Patients diagnosed with mixed malaria infections (e.g., *Plasmodium falciparum*), glucose-6-phosphate dehydrogenase (G6PD) deficiency, known hypersensitivity to primaquine or chloroquine, significant comorbidities such as anemia, inability to complete the prescribed treatment regimen, or loss to follow-up during the study period were excluded.

Baseline data were collected at the time of diagnosis and included demographic information and clinical parameters such as presenting symptoms, disease severity, and laboratory findings. Ethical approval was obtained from the Ethics Review Committee of CMH Malir (Ref. No. 136/2024/Trg/ERC). Written informed consent was obtained from the parents or guardians of all participants prior to enrollment.

The enrolled pediatric patients were equally divided into three groups (n = 44 per group). The control group received standard antimalarial therapy according to World Health Organization (WHO) guidelines, which typically involve chloroquine. The two intervention groups received standard therapy plus primaquine, administered either as a 7-day or a 14-day regimen at a dose of 0.25–0.5 mg/kg body weight per day.

All patients were followed prospectively for three months after completion of therapy. Follow-up visits were scheduled at 1, 2, and 3 months post-treatment. At each visit, patients were clinically assessed for recurrence of fever or other malaria-related symptoms. Relapse was defined as the reappearance of *Plasmodium vivax* parasites on peripheral blood smear following previously documented clinical and parasitological cure. Children who developed symptoms between scheduled visits were advised to report immediately for evaluation.

All personal identifiers were anonymized prior to data analysis to ensure participant confidentiality. Access to

identifiable data was restricted to authorized study personnel only. Data were entered and analysed using SPSS version 26. Quantitative variables were expressed as mean ± standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Post-stratification was performed for effect modifiers using the chi-square test, with a p-value < 0.05 considered statistically significant.

Results

This study enrolled the 132 pediatric patients, 44 were in the control group and 88 in the study group. Overall mean age of patients 7.73±3.58 years, with approximately one-third of patients in each age group (p = 0.786). According to gender distribution the ratio was almost similar, with males comprising 50.8% and females 49.2% (p = 0.538).

Whereas, a significant difference was noted in place of residence, as a higher proportion of patients in the study group belonged to urban areas compared to the control group (p = 0.009). Socioeconomic status was evenly distributed across groups, with most patients belonging to the middle and poor categories, and statistically insignificant across the groups (p = 0.844), as presented in Table I.

Table I: Demographic variable analysis of the patients. (n=132)

Variables		Overall study groups		Total	p-value
		Control (44)	Study group (88)		
Age groups	<4 years	17	29	46	0.786
		38.6%	33.0%	34.8%	
	5-8 years	15	31	46	
		34.1%	35.2%	34.8%	
	9-12 years	12	28	40	
		27.3%	31.8%	30.3%	
Gender	Male	24	43	67	0.538
		54.5%	48.9%	50.8%	
	Female	20	45	65	
		45.5%	51.1%	49.2%	
Residence	Urban	19	59	78	0.009
		43.2%	67.0%	59.1%	
	Rural	25	29	54	
		56.8%	33.0%	40.9%	
Socioeconomic status	Upper	13	22	35	0.844
		29.5%	25.0%	26.5%	
	Middle	17	35	52	
		38.6%	39.8%	39.4%	
	Poor	14	31	45	
		31.8%	35.2%	34.1%	

Study showed the, relapse rates consistently higher in the control group at all follow-up time periods. At 1-month post treatment, relapse occurred in 9.1% of control patients compared to 2.3% in the study group (p = 0.076), on the 2nd moth follow-up the relapse was significantly more common in the control group (29.5%) in contrast to the study group (5.7%) (p = 0.001). Such difference became even more pronounced at 3rd month post treatment, with the significantly higher relapse rates of 38.6% in the control group against 6.8% in the study group, (p = 0.0001) as shown in Table II.

Table II: Overall comparison of relapse rate between control and study group. (n=132)

Variables		Overall study groups		Total	p-value
		Control (44)	Study group (88)		
Relapse rate after 1 month of treatment	Yes	4	2	6	0.076
		9.1%	2.3%	4.5%	
	No	40	86	126	
		90.9%	97.7%	95.5%	
Relapse rate after 2 months of treatment	Yes	13	5	18	0.001
		29.5%	5.7%	13.6%	
	No	31	83	114	
		70.5%	94.3%	86.4%	
Relapse rate after 3 months of treatment	Yes	17	6	23	0.0001
		38.6%	6.8%	17.4%	
	No	27	82	109	
		61.4%	93.2%	82.6%	

Furthermore, on the patients equally distributed into three groups, relapse rates were highest in the control group and progressively lower in patients receiving primaquine, particularly with the 14-day regimen. At the 1-month post treatment, relapse was uncommon across all groups (control 9.1%, 7-day 2.3%, 14-day 2.3%), without significant difference (p = 0.508). Though, at 2nd month follow-up, relapse rates significantly raised in the control group (29.5%) compared to the primaquine 7-day (6.8%) and 14-day groups (4.5 (p = 0.001). On the third month post treatment follow-up, relapse was occurred in more than one-third of control patients (38.6%), whereas significantly lower in the 7-day (9.1%) and specifically in 14-day primaquine group (4.5%), p = 0.0001 indicating that the primaquine significantly reduces relapse of *Plasmodium vivax*, with the 14-day regimen providing the greatest and most sustained protection against relapse**.** (Table III)

Discussion

Pakistan, as a resource-limited country, faces numerous challenges in malaria control, including limited diagnostic facilities, unreliable follow-up systems, and restricted access to newer antimalarial drugs. *Plasmodium vivax*

Table III: Comparison of relapse rate between control and study group based on primaquine dosage duration. (n=132)

Variables		Overall study groups			Total	p-value
		Control (n=44)	Primaquine 7 Days (n=44)	Primaquine14 Days (n=44)		
Relapse rate after 1 month of treatment	Yes	4	1	1	6	0.508
		9.1%	2.3%	2.3%	4.5%	
	No	40	43	43	126	
		90.9%	97.7%	97.7%	95.5%	
Relapse rate after 2 months of treatment	Yes	13	3	2	18	0.001
		29.5%	6.8%	4.5%	13.6%	
	No	31	41	42	114	
		70.5%	93.2%	95.5%	86.4%	
Relapse rate after 3 months of treatment	Yes	17	4	2	23	0.0001
		38.6%	9.1%	4.5%	17.4%	
	No	27	40	42	109	
		61.4%	90.9%	95.5%	82.6%	

remains highly prevalent, and its tendency to cause relapse further complicates effective disease control and elimination efforts. In this context, effective, feasible, and affordable treatment strategies—such as optimized use of primaquine—are crucial for reducing relapse rates and supporting malaria control in endemic regions. This study evaluated the relapse rate of *Plasmodium vivax* malaria among pediatric patients treated with primaquine and compared the outcomes with a control group receiving standard antimalarial therapy.

Overall mean age of patients was 7.73±3.58 years, with approximately one-third of patients in each age group (p = 0.786). Additionally, gender distribution ratio was almost similar, with males comprising 50.8% and females 49.2%. The comparable pediatric age and gender distributions were reported in the study conducted by Commons et al[13], where *P. vivax* predominates among school-aged children, and in the studies of Gonzalez-Ceron et al[14], and Ladeia-Andrade et al[15] where no significant differences in gender distribution were observed.

In present study, a significantly higher proportion of patients in the study group belonged to urban areas (67.0%) compared to the control group (43.2%); p = 0.009. Moreover, socioeconomic status was evenly distributed across groups, with most patients belonging to the middle (39.4%) and poor (34.1%) categories, and statistically insignificant across the groups (p = 0.844). In line with our findings, in the study of Chamma-Siqueira et al[16], urban predominance was noted, which can be explained by better access to tertiary care facilities and adherence to follow-up schedules.

In this study, the relapse rates were consistently higher in the control group at all follow-up time periods, as at 1-month post treatment, relapse occurred in 9.1% of control patients compared to 2.3% in the study group (p = 0.076), on the 2-moth follow-up the relapse was significantly more common in the control group (29.5%) in contrast to the study group (5.7%) (p = 0.001). Such difference became even more pronounced at 3rd month post treatment, with the significantly higher relapse rates of 38.6% in the control group against 6.8% in the study group, (p = 0.0001). our findings were also in line with the study conducted by Wångdahl et al[17], who documented lower relapse rate for P. vivax in patients receiving primaquine (7.1%) compared to those without Primaquine (33.3%), with 80% reduction in the likelihood of relapse. Similarly, in another study conducted by Galappaththy et al[18] demonstrated that primaquine effectively reduced P. vivax relapse rates from 18.0% to 9.0% during the course of 14-days. Consistently, a recent study conducted by Commons et al[19] reported that primaquine treatment can effectively reduce relapse rates up 50% for P. vivax.

Additionally, in this study relapse rates were progressively lower in patients receiving primaquine, particularly with the 14-day regimen. At 2nd month follow-up, relapse rates significantly raised in the control group (29.5%) compared to the primaquine 7-day (6.8%) and 14-day groups (4.5%) p = 0.001. On the third month post treatment follow-up, relapse was occurred in more than one-third of control patients (38.6%), whereas significantly lower in the 7-day (9.1%) and specifically in 14-day primaquine group (4.5%), p = 0.0001, indicating that the primaquine significantly reduces relapse of *Plasmodium vivax*, with the 14-day regimen providing the greatest and most sustained protection against relapse**.** The consistent with these findings, in the study of Galappaththy et al,[18] relapse rates for *P.* vivax were lower over the follow up of 6-months in 14-day regimen compared to five-day regimen in patients treated with Primaquine. In agreement with our findings, in the study of Alvarez et al,[20] relapse rates with

7-day primaquine (42%) were higher with 14-day primaquine (19%) over the follow-up of two months.

Overall, the findings of this study revealed that the use of primaquine significantly reduces the relapse of *Plasmodium vivax* malaria among the pediatric population, with the 14-day regimen providing the greatest and most sustained protection compared with shorter regimens and standard treatment alone. However, this study has several limitations, including its single-center design, relatively small sample size, and limited follow-up period of three months, which may not have captured late relapses. Therefore, further multicenter studies involving larger populations, longer follow-up periods, and molecular confirmation of relapse are recommended to validate these findings. In addition, future research should assess treatment adherence, cost-effectiveness, and the safety of longer primaquine regimens, particularly in resource-limited settings such as Pakistan.

Conclusion

The study revealed that the use of primaquine significantly reduces the relapse rate of *Plasmodium vivax* malaria in pediatric patients compared with standard treatment alone. Primaquine regimens were particularly effective in decreasing relapse rates, with the 14-day regimen demonstrating the lowest relapse rates and providing the most sustained protection, followed by the 7-day regimen. Overall, these findings emphasize the critical role of primaquine in preventing relapse of *P. vivax* malaria and suggest that a 14-day primaquine regimen remains the most effective strategy for long-term relapse prevention in pediatric populations, especially in resource-limited settings.

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