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Original Article

Effectiveness of dihydroartemisinin-piperaquine after 10 years as treatment for vivax malaria in Indonesia

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Abstract

Introduction: Dihydroartemisin-piperaquine (DHP) is a type of artemisinin-based combination therapy (ACT) that is extensively used in Indonesia as first-line malaria treatment over the past 10 years. Therefore, DHP has been known to have high efficacy, but re-evaluation of the efficacy was needed since the treatment was being used for a long time.

Methodology: A cohort prospective study on pediatric and adult patients diagnosed with vivax malaria in Kualuh Leidong health centre was conducted from November 2019 – April 2020 to evaluate the efficacy of DHP for the treatment of malaria vivax. The efficacy of DHP was monitored by evaluating the clinical symptoms and serial peripheral blood smear at day 1,2,3,7,14,21 and 28.

Results: A total of 60 children and adults diagnosed with malaria vivax were enrolled for this study. Major symptoms such as fever, sweating and dizziness were found in all of subjects. The mean number of parasites on day 0 of observation in the child and adult groups was 313.33/µL and 328/µL respectively (p = 0.839). Meanwhile, the mean number of gametocytes on day 0 was 74109.33/µL in the child group and 61661.33/µL in the adult group. There was a reduction in the number of gametocytes on the 1st day of observation in the child and adult groups to 669.33/µL and 489.33/µL respectively (p = 0.512). No recrudescence occurred in either group within 28 days of observation.

Conclusions: DHP is still efficacious and safe as a first-line treatment for vivax malaria in Indonesia, with 100% cure rate at 28 days of observation.

Key words: malaria; *Plasmodium vivax*; dihydroartemisinin-piperaquine.

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Introduction

Malaria is a disease caused by *Plasmodium*, and the transmission to humans happens through the bites of the female *Anopheles* mosquitoes. The World Health Organization (WHO) in the World Malaria Report 2021 estimated 241 million malaria cases in 85 malaria endemic countries. The highest prevalence of malaria cases was caused by *Plasmodium falciparum* followed by *Plasmodium vivax*. The number of cases due to *Plasmodium vivax* was about 4.5 million. The Southeast Asia region was the second largest contributor and estimated to have 2 % of the burden of malaria cases globally and 39% of them were caused by *Plasmodium vivax* [1].

The WHO launched the Global Technical Strategy for Malaria 2016–2030 program that includes 4 targets: decreasing malaria mortality, reducing incidence of malaria, eliminating malaria, and preventing the re-establishment of malaria in all countries that had been declared as malaria free [2]. This is aligned with the global commitments in Sustainable Development Goals (SDGs), where malaria eradication efforts are contained in the third goal with a specific objective to end the malaria epidemic by year 2030 [3]. One of the biggest challenges, especially in Indonesia, to reach that goal is the decrease in the efficacy of several antimalarial drugs. Drug resistance cases against chloroquine and fansidar have also been reported. One of the causes of antimalarial drug resistance is irrational use of medicines [4,5].

Antimalarial drugs that are used worldwide are artemisin-based combination therapies (ACTs). There are 5 types of ACTs spread across the world; among them are artemisinin derivatives that are known as the most potent and fast-acting antimalarial drugs [6]. An example of artemisinin derivative is dihydroartemisinin-piperaquine (DHP), which is used in Indonesia. DHP is a very effective artermisinin derivative that clears the asexual form of malaria and reduces gametocythemia. However, it does not affect adult gametocytes. Nonetheless, DHP is known to inhibit the development of young gametocytes into adult gametocytes. Adult gametocytes are found in the peripheral circulation for a few weeks which allows the

ingestion process by mosquito vectors. Therefore, DHP is administered together with primaquine, which is the only drug that can eliminate adult gametocytes [7].

Denis *et al*. conducted a study based in Cambodia where they reported 28 days cure rate of DHP therapy resulting in 98.6% and 92.3% cure for children and adults respectively. There were incidences of minor side effects in 18.4% children and 26.6% adults [8]. DHP alone was introduced as first-line therapy in 2008 to eradicate *Plasmodium falciparum* and *P vivax* infections in Papua, Indonesia [9].

Plasmodium parasites are known to develop resistance against antimalarial drugs through their ability to adapt. The incidences of antimalarial drug-resistance started in West Cambodia due to reasons that are not yet understood. Moreover, resistance to the most common forms of chloroquine, pyrimethamine, and sulfadoxine also originated from the same region [10-12]. Clinical resistance to artemisinin and its derivatives has been reported in West Cambodia and appeared to have extended to the surrounding areas [10,13]. Akunuri *et al*. reported artemisinin resistance in areas in Thailand, Cambodia and the Thailand-Myanmar border [14]. One of the main causes of such resistance was the presence of a number of mutations in *PfKelch13* (K13) propeller domain, which was associated with delayed parasite clearance [15,16]. The WHO, in the Global Malaria Programme 2018, reported a decrease in efficacy of artemisinin derivatives as first-line *Plasmodium falciparum* malaria therapy without complications due to drug resistance in several countries, in the Greater Mekong region, which includes Cambodia, China, Laos, Myanmar, Thailand, and Vietnam [15,17].

Drug resistance is highly probable when repeat malaria episodes occur within 14 days of the primary episode [18]. Drug resistance appears to be caused by a change in the structure, function or quantity of a protein mediated by genetic changes. Drug resistances emerge due to several reasons including parasite mutation rate, parasite load, drug dose used, and malaria treatment compliance. Poor pharmacokinetic properties and fake drugs also lead to inadequate drug exposure [19-21].

The extensive use of DHP as first-line therapy has decreased. Therefore, reassessment to re-evaluate the effectivity of the drug is required. Nonetheless, the study by Poespoprodjo *et al.* in Papua reported that DHP still had high efficacy after 9 years of administration in the region [9]. This is aligned with the clinical study in North Sumatra by Pasaribu *et al.* (2013) who reported better tolerance level and post-therapeutic prophylactic effect of DHP compared to artesunate-amodiaquine [22].

There has not been any research to assess and re-evaluate DHP among children and adults in the west side of Indonesia. This study was conducted to observe the efficacy of DHP in malaria vivax pediatric and adult patients after 10 years of first-line malaria therapy use in West Indonesia, especially in North Sumatra.

Methodology

This research was a prospective study to observe the efficacy of DHP as vivax malaria treatment for children and adult patients in Kualuh Leidong, Labuhan Batu Utara regency, North Sumatra. Labuhan Batu Utara regency was chosen as the research location because it was one of the regencies with high annual parasite incidence (API) in North Sumatra [23]. The research was conducted for 6 months, from October 2019 to January 2020, upon approval from the ethical committee.

Research Subjects

Research subjects were pediatric (aged 2-18 years) and adult patients in Kualuh Leidong public health centre (Puskesmas) who met the inclusion and exclusion criteria. Inclusion criteria were patients with fever (axillary temperature ≥ 37.5 °C) or history of fever in the last 48 hours, diagnosed with single or mixed *Plasmodium vivax* malaria with no complications – confirmation by blood smear examination, not in a condition requiring hospitalization, and without history of allergy to antimalarial drugs. Exclusion criteria were patients with severe malaria clinical symptoms, severe malnutrition, recurrent vomiting, and additional infectious diseases, and patients whose follow-up was not possible during the study period.

Research ethics

Consent for involvement in the research was obtained from all research subjects who met the inclusion and exclusion criteria. Consent from pediatric patients was obtained from the parents/guardians. The consent form was signed after they received explanation about the research, patients' clinical conditions, and the examinations to be done on the patients. This research has received approval from the Research Ethics Committee of Medical Faculty, Universitas Sumatera Utara/Haji Adam Malik General Hospital No: 127/TGL/KEPK FK USU-RSUP HAM/2020.

Research process

Basic characteristic data of the patients was obtained from questionnaires and interviewing the parents/guardians. Next, anamnesis, physical examination, and additional tests such as rapid diagnostic test and thin and thick blood smear tests were done. After the diagnosis of *Plasmodium vivax* malaria was confirmed, DHP and primaquine therapy was started with dosage based on the patients' body weights, following the provision from the Ministry of Health of the Republic of Indonesia. Each tablet contained 40 mg dihydroartemisinin and 320 mg piperaquine phosphate. During the therapy, clinical symptoms and side effects of each patient were observed. DHP and primaquine with the same dose would be re-administered if the patients vomited within 30 minutes of drug administration. However, if recurrent vomiting occurred, the patients would be excluded from the study.

All research subjects were asked to return to the health centre as outpatients, on day 1, 2, 3, 7, 14, 21, and 28 for follow-up assessments which involved anamnesis, physical examination, and repeated thin and thick blood smear tests. All research subjects were closely monitored for 28 days. Side effect evaluations, such as nausea, vomiting, and or diarrhea, was done during each visit. If the patients encountered any symptoms or health complaints, they were allowed to visit and seek treatment outside the scheduled visit days.

Data analysis

Characteristic data such as numerical data was presented in the form of mean and standard deviation (SD). Categorical data was presented as frequency distribution. The data was analyzed in a general linear model to assess the efficacy on day 28. All analysis was done using statistical software SPSS version 23 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

Results

Characteristics of research subjects

Research data was collected by the consecutive sampling method from November 2019 until April 2020 for 6 months. During this period, there were 60 patients (30 pediatric and 30 adults) from Kualuh Leidong health center (Puskesmas), Labuhan Batu Utara regency, North Sumatra, who met the inclusion and exclusion criteria.

The research subjects were grouped into child and adult group based on age. Malaria vivax symptoms, i.e., fever, sweating, dizziness, nausea, vomiting, chills, and fatigue were found in all subjects. DHP dose was administered based on body weight, with average dosage of 2.35 and 3.05 tablets for child and adult respectively

The average body weights in the child and adult groups were 40.00 kg and 57.53 kg respectively. The mean body temperature in the child group was 39.43 °C, while in the adult group it was 39.65 °C. All the research subjects in both groups had clinical symptoms, such as fever, sweating, and dizziness. Clinical symptoms such as nausea, vomiting, chills, and fatigue were found in 27 children (90%), 19 children (63.3%), 8 children (26.7%), and 1 child (3.3%) respectively. Meanwhile, in the adult group, the same clinical symptoms were found in 23 adults (76.7%), 19 adults (63.3%), 3 adults (10%), and 1 adult (3.3%) respectively (Table 1).

Efficacy of DHP treatment in children and adults

The efficacy of DHP treatment was measured based on the numbers of parasites and gametocytes, and the

Table 1. Research subject characteristics based on age.

Subject Characteristic	Child (n = 30)	Adult (n = 30)
Body weight, mean (SD)*, kg	40.00 (12.98)	57.53 (8.42)
Body temperature, average (SD). °C	39.43 (0.67)	39.65 (0.78)
Symptoms		
Fever, n (%)	30 (100)	30 (100)
Sweating, n (%)	30 (100)	30 (100)
Dizziness, n (%)	30 (100)	30 (100)
Nausea, n (%)	27 (90)	23 (76.7)
Vomiting, n (%)	19 (63.3)	19 (63.3)
Chills, n (%)	8 (26.7)	3 (10)
Fatigue, n (%)	1 (3.3)	1 (3.3)
DHP dose		
Day I-III, mean (SD), tab	2.35 (0.68)	3.05 (0.30)

*SD: Standard deviation. Research subjects were grouped into child and adult group based on age. There were 30 subjects in each group. Malaria vivax symptoms, i.e., fever, sweating, dizziness, nausea, vomiting, chills, and fatigue were found in all subjects. dihydroartemisinin-piperaquine DHP dose was administered based on body weight, with average dosage of 2.35 and 3.05 tablets for child and adult respectively.

time when fever was gone from 0th to 28th day. The mean number of parasites on the 0th day observation in the child group was 313.33/µL, while in adult group it was 328/µL. Based on the general linear model test, there was no significant difference in the number of parasites between the child and adult groups (p = 0.839). Parasites were no longer found in both groups from day-1 until day-28.

The mean number of gametocytes on 0th day observation in the child group was 74109.33/µL, whereas in the adult group was 61661.33/µL. On the 1st day, the number of gametocytes in both child and adult groups decreased to 669.33/µL and 489.33/µL respectively. Based on the general linear model test, there was no significant difference in the number of gametocytes in the child and adult groups (p = 0.152). Gametocytes were no longer found in both the child and adult groups from the 2nd to the 28th day.

Fever was observed in 100% of the members of the child and adult groups on 0th and 1st day of observation. However, on the 2nd day, fever decreased to 63% and 73% in the child and adult groups respectively. Based on the general linear model, there was no significant difference in the average time of fever loss between the child and adult groups (p = 0.414). Fever was no longer observed from the 3rd until 28th day of observation in both groups. No recrudescence occurred in any member of the child or adult group during the 28 days of observation.

There were no significant differences observed in the total number of parasites and gametocytes, as well as fever occurrence between the child and adult groups. Parasites were no longer observed from day-2 to day-28 of observation. Meanwhile, fever was no longer observed from day-3 onwards (Table 2).

Table 2. Total parasite clearance, gametocytes and fever-loss time.

Treatment efficacy	Child (n = 30)	Adult (n = 30)	*p*
Total asexual parasites, mean (SD), /µL			
Day 0	313.33 (242.53)	328.00 (310.26)	0.839
Day 1	0	0	
Day 2	0	0	
Day 3	0	0	
Day 7	0	0	
Day 14	0	0	
Day 21	0	0	
Day 28	0	0	
Total sexual parasites (gametocytes), mean (SD), /µL			
Day 0	74109.33 (25340.19)	61661.33 (29122.04)	0.152
Day 1	669.33 (450.21)	489.33 (379.42)	
Day 2	0	0	
Day 3	0	0	
Day 7	0	0	
Day 14	0	0	
Day 21	0	0	
Day 28	0	0	
Fever, mean (SD), %			
Day 0	1 (0)	1 (0)	0.414
Day 1	1 (0)	1 (0)	
Day 2	0.63 (0.49)	0.73 (0.44)	
Day 3	0	0	
Day 7	0	0	
Day 14	0	0	
Day 21	0	0	
Day 28	0	0	

*SD: Standard deviation. There were no significant differences observed in total number of parasites and gametocytes, as well as fever between the child and adult groups. Parasites were no longer observed from day 2 to day 28 of observation. Meanwhile, fever was no longer observed from day 3 onwards.

Table 3. Side effects evaluation of dihydroartemisinin-piperaquine (DHP) therapy.

Side Effects n (%)	Child		Adult	
	Day 0	Day 1	Day 0	Day 1
Dizziness	26 (86.7)	4 (13.3)	13 (43.3)	6 (20.0)
Stomach pain	14 (46.7)	5 (16.7)	7 (23.3)	1 (3.3)
Nausea	15 (50.0)	0	7 (23.3)	0
Vomiting	0	0	0	0
Rash	0	0	0	0

Side effects on DHP therapy were only observed on day 0 and 1 of DHP administration.

DHP side effect evaluation in children and adults

The side effects in this study were measured based on the symptoms experienced after the administration of DHP on 0th to 28th day. No side effects, such as dizziness, stomach pain, nausea, vomiting, and rashes were observed from day-2 to day-28, in the child and adult group Table 3).

Discussion

Indonesia is one of the countries which adopted ACTs as the first-line management policy of malaria with no complications from other species types of malaria. Moreover, Indonesia is the first country to have used DHP as ACTs since March 2006 [9]. After 10 years as the first-line therapy, DHP required re-evaluation to assess the efficacy as there was a risk of resistance as reported in several areas in Greater Mekong, including Cambodia, Thailand, and Myanmar [15]. Clinical symptoms of vivax malaria can be caused by direct or indirect effects of the parasites in the blood. Mild symptoms include headache, dizziness, weakness, muscle ache, abdominal pain, chills, sweating, nausea, and vomiting [24]. The study by Lover and Coker (2014) stated that the incubation period, from infection to the onset of clinical symptoms, was related to the strains of parasites and the species vectors causing the infection [25].

In this study, research subjects from both groups had symptoms such as fever, sweating, and dizziness.

The mean body temperature in the child group was 39.43 °C, while in the adult group was 39.65 °C. Fever was accompanied by chills in 8 children (26.7%) and 3 adults (10%). High fever and chills symptoms in vivax malaria were known to coincide with schizoid rupture. Classic paroxysmal symptoms of fever in vivax malaria lasted for 4–8 hours and occurred over a period of 48–56 hours [26]. Song *et al*. (2003) in their study on clinical features of *Plasmodium* vivax also reported fever and chill symptoms in all research subjects in their study [27]. Fever in malaria is known to be related to the release of toxins and antigen substances triggered by the release of cytokines and leukocytes. The study by Kotepui *et al*. explained a directly proportional relationship between the duration of fever and severity of prognosis in vivax malaria patients [28].

Another most common symptom found was related to gastrointestinal functions such as nausea and vomiting. The child group had 27 patients (90%) and 19 patients (63.3%) with such symptoms respectively; similarly, the adult group had 23 patients (76.7%) and 19 patients (63.3%) with such symptoms respectively. The number of patients with gastrointestinal symptoms was higher in this study than in the study by Song *et al*. who reported 34.1% cases [27]. Meanwhile, fatigue was only found in 1 patient in each group.

In this study, the mean body weight in the child group was 40 kg (SD 12.98), while that in the adult group was 57.53 kg (SD 8.42) with the mean DHP dosage of 2.35 tablets and 3.05 tablets in the child and adult groups respectively. All research subjects consumed DHP with appropriate dose and administration duration. The physiological process of DHP is not linearly proportional to body weight. Consequently, the children required higher dose relative to their body weights than the adults in order to achieve equivalent concentration of drugs [29]. Hoglund *et al.* reported about the pharmacokinetics of piperaquine under the recommended dose from the manufacturer. They stated that body weight significantly affected the volume and parasite clearance parameters, in which under recommended doses, lower piperaquine exposure was observed in children (< 25 kg) than in adolescents and adults (≥ 25 kg) [30].

The percentage of fever on 0^{th} and 1^{st} day observation in both the child and adult groups was 100%. However, there were decreases in fever as symptoms on day-2 to 63% and 73% in the child and adult group respectively. Fever was no longer found in either group from day-3 to day-28. Pasaribu *et al*. (2013) reported that all patients receiving DHP and primaquine therapy experienced reduction in clinical symptoms, such as fever, starting on the 1^{st} day of therapy [22].

There were no significant differences in the numbers of sexual and asexual parasites in the child and adult groups between day-0 and day-1. This was similar to the observation by Pukrittayakamee *et al*. who reported that the initial parasite clearance time underwent significant acceleration upon the administration of DHP [31]. *Plasmodium vivax* transmission blocking was the most important step for prevention of relapse, especially in patients with high density of asexual parasites. This is considered related to the increase in recrudescence, as well as a reflection of low immunity resulting in an increased risk of recurrent incidence [32]. The high risk of parasitological failure in children below 5 years of age with DHP therapy was assumed to be related with their low immunity, as well as low piperaquine concentration in the blood [33].

Resistance towards ACTs should be suspected when no clinical nor parasitological responses were observed after 72 hours of therapy administration. However, the clearance time of parasites is dependent on several factors, such as the initial density of parasites, carrier factors with or without renal dysfunction, history of a splenectomy, and comorbidities such as sickle cell disease [14].

Poespoprodjo *et al*. studied the efficacy of DHP against *Plasmodium falciparum* and *vivax* in Papua in 2016 and reported fast parasite clearance time after therapy, where 74.6% vivax malaria patients experienced parasitemia during the first 24 hours of therapy, and it increased to 96.9% after 48 hours of observation [9]. Similarly, Pasaribu *et al*. found 85% vivax malaria patients underwent gametocyte clearance on day-1 and this increased to 100% on day-2 of therapy [22].

The relapse event began with the primary infection process, where a number of *Plasmodium vivax* became dormant in the liver, and subsequently caused repeated relapses. The timing of recurrence may vary – based on the region, in which it could occur every 3 weeks in the equatorial regions, and often at a greater interval of 6 months in regions with subtropical climate. These recurrences had ensured that the transmission of parasites may occur, even in unsupported environmental conditions for mosquito vector development [24].

There was no significant difference in the mean number of parasites between the child and adult groups. No more parasites were found from day-1 until day-28 in both groups. Moreover, there were no gametocytes

found on day-2 to day-28 of observation. Poespoprodjo *et al*. showed 100% efficacy of DHP to fight *Plasmodium vivax* until the 28th day of observation [9]. In the study by Tavul *et al*., the administration of DHP as the first-line vivax malaria therapy in Papua New Guinea also showed high efficacy [34]. Popovici *et al*. also explained that the combination of DHP and primaquine therapy had high effectivity to prevent the recurrence of vivax malaria by up to 56 days [35]. However, the damages to active cytochrome metabolite P450 2D6 (CYP2D6) played an important role in the failure of therapy leading to the recurrence of incidence [36]. Meanwhile, the study done by Commons *et al*. stated that vivax malaria patients with DHP therapy had cumulative risk of recurrence at the rate of 1.2% on day 28 and 9.3% on day 42 [37]. Nonetheless, this study showed that DHP had 100% efficacy as first-line vivax malaria therapy, and no recrudescence occurred in both the child and adult groups.

This was the first study in North Sumatera, Indonesia to evaluate the efficacy of DHP. However, the sample size in this study was considered small, which may affect the reliability of the results presented. Moreover, the subjects in this study were observed for only 28 days. Long term observational study is recommended since there is possibility of recurrence after more than 28 days of follow up to provide a more in-depth explanation.

Conclusions

The administration of DHP as the first-line vivax malaria therapy continued to have high efficacy in pediatric and adult patients after 10 years of use. The cure rate at 28 days of observation in Kualuh Leidong area was 100%. This report could give some perspective about the application of DHP as antimalarial drug, especially in Indonesia although research to identify novel antimalarial drugs are still needed.

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