

## Research Article



## Therapeutic Effects of Dihydroartemisinin Piperavaquine Versus Chloroquine for Uncomplicated Vivax Malaria in Kupang, East Nusa Tenggara, Indonesia.

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### ABSTRACT

Indonesian Ministry of Health has recommended Artemisinin based combination therapies (ACTs) including dihydroartemisinin piperavaquine (DHP), as an antimalarial in Indonesia. However, chloroquine is still used as an antimalarial in some health services. The objective of the study was to compare the therapeutic effect of chloroquine (CQ) with DHP. This study was a quasi experimental study. Total subject was 51 people. Twenty five subjects received DHP and 26 subjects received CQ. Clinical and parasitological responses were observed for 42 days in both treatment groups. Success cumulative incidence of the DHP group was 0.76 with 95% CI 0.542-0.884 and the CQ group was 0.577 with 95% CI 0.368-0.739. Failure cumulative incidence of DHP group was 0.24 with 95% CI 0.116-0.458 and the CQ group was 0.423 with 95% CI 0.261-0.632. There was not any significant difference between CQ therapy response and DHP therapy response,  $p = 0.166$  with RR 2.69 (95% CI 0.69-7.73). It is concluded that, the therapeutic effect of DHP is better than CQ although statistically not significant. It has been found therapeutic failure rate of over 10% and a cure rate of less than 90 % in the DHP and CQ group.

**Keywords:** dihydroartemisinin piperavaquine, chloroquine, clinical response, parasitological response

### INTRODUCTION

Malaria represented one of the parasite infectious diseases that became world health problem; especially in tropical countries including Indonesia.<sup>1</sup> It was still found in all of the provinces of Indonesia. In 2008-2009, East Nusa Tenggara (ENT) belonged to the 3 provinces with the API (Annual Parasite Incidence) that was above national API of 2.47 per 1000 population in addition to Papua and West Papua provinces.<sup>2</sup> Kupang district was one of the districts with quite high malaria case in ENT. In 2010 the API of Kupang district was 7 cases per 1000 population.<sup>3</sup>

According to WHO in its Global Report on Anti Malarial Drug Efficacy and Drug Resistance 2000-2010, chloroquine was still the drug of choice in *P. vivax* therapy in the areas in which the chloroquine was still effectively used. Confirming studies of the resistance to chloroquine were still highly required.<sup>4</sup> In WHO's treatment guideline 2010, anti malaria recommended for uncomplicated malaria *vivax* was chloroquine or Artemisinin-based Combination Therapies (ACTs) in the areas in which the resistance to the drug has been established with additional primaquine for 14 days.<sup>5</sup> In 2004 the Ministry of Health of Republic Indonesia did not recommend the drug for any longer for first line therapy of malaria and replaced it with the ACTs.<sup>6,7</sup> There were still problems in the distribution of this drug especially for private health centres.<sup>8</sup>

Studies of the resistance of *P. vivax* to chloroquine especially in Kupang district have not been conducted and up to the present the chloroquine has been being used at some health care service centers in this district because

of it is relatively cheap, safe, well-tolerated and may be used as malaria therapy for babies and pregnant mothers.<sup>9,10</sup>

This study aims to determine the difference between the therapeutic effects of chloroquine (CQ) which has long been used and considered to be resistant, compared with the effect of dihydroartemisinin piperavaquine (DHP) which is one of the recommended ACTs as an antimalarial in ENT, especially in Kupang district, East Nusa Tenggara Province, Indonesia.

### MATERIALS AND METHODS

The study was of quasi-experimental one with non-equivalent control group design. It was conducted in February 1<sup>st</sup>, 2013 to October 30<sup>th</sup>, 2013 in the covering area of Takari and Oesao community health center, Kupang district, ENT province, Indonesia.

The subjects of the study were the patients with fever who came to the health centres positively infected by *P. vivax* with microscopic confirmation and met the existing inclusion and exclusion criteria. The inclusion criteria were among others those of  $\geq 18$  years to 65 years of age, males and females, infected by *P. vivax* (mono-infection) with the parasite density of  $> 250$  per  $\mu\text{l}$ , axillaries temperature  $\geq 37.5$  °C or with fever history in the last 48 hours and prepared to involve in the study (informed consent). The patients excluded from this study were those who took anti malaria drugs in the last month, pregnant or breast feeding, the presence of another species of plasmodium, non-malaria fever, the presence of acute malaria symptoms and other symptoms related to the malaria caused by the *P. vivax* that required



hospitalized treatment, consuming drugs that must be taken regularly, and having history of allergy to DHP or CQ. Protocol of the study has been approved by the ethics committee of the Faculty of Medicine of Gadjah Mada University.

The patients who met the inclusion and exclusion criteria were assigned to 2 therapy groups, which were DHP and CQ. The CQ group was given CQ for 3 days at the dose of 10 mg base/kg on the first and second days, continued by giving 5 mg base/kg on the third day. The DHP was given following the guideline of the implementation of malaria treatment issued by Darplex was given 3 tablets daily for 3 days.<sup>6</sup> It was available in the form of fixed dose combination (FDC). Each tablet contained 40 mg dihydroartemisinin and 320 mg piperazine. It was given orally for 3 days at the single daily dose of dihydroartemisinin 2-4 mg/kg, and piperazine 16-32 mg/kg.<sup>5,7,11,12</sup> Each of the groups was also given the primaquine for 14 days at the dose of 0.25 mg/kg.

Clinical and parasitological responses were observed in the two groups for 42 days (Day0, Day1, Day2, Day3, Day7, Day14, Day21, Day28, Day35 and Day42).

The clinical response was evaluated by observing clinical condition, fever clearance time (FCT), the symptoms after taking drugs and the emergence of acute malaria during the observation. The parasitological response was evaluated by observing parasite density and parasite clearance time (PCT).

## RESULTS AND DISCUSSION

**Table 1:** Patient characteristics at baseline in a study of dihydroartemisinin-piperazine versus chloroquine group.

Characteristics	DHP (n=25)	CQ (n=26)
Sex, n (%)		
Male	12 (48)	13 (50)
Female	13 (52)	13 (50)
Age, n (%)		
18-35 years	13 (52)	16 (61,5)
36-55 years	11 (44)	8 (30,8)
≥ 56 years	1 (4)	2 (7,7)
Weight		
Mean ± SD, kg	40,32 ± 7,576	40,96 ± 7,518
Haemoglobin concentration		
Mean ± SD, g/dl	10,288 ± 0,938	10,3 (8,8-11,4)
Median (range), g/dl		
Temperature (Day 0)		
Mean ± SD, °C		39,023 ± 0,801
Median (range), °C	39 (38-40)	
Parasite Density (Day 0)		
Mean ± SD, / µl	5588,8±5719,02	4055,38±3374,9

¶ DHP = Dihydroartemisinin piperazine, CQ = Chloroquine

There were 1.122 patients with suspected malaria fever coming to health centres for treatment. Their blood smears showed that there were only 89 patients who *vivax* malaria positive. The *vivax* malaria patients were selected using the predetermined inclusion and exclusion criteria and it resulted in 51 *vivax* malaria patients without complication who might be included in the study. They were assigned to 2 therapy groups, which were 26 subjects with chloroquine therapy and 25 subjects with DHP therapy (Table 1). All of the samples were successfully followed-up and there was not any drop-out patient till the end of the study.

## Clinical Response

**Table 2:** The comparison of the clinical response of the DHP and CQ groups.

Clinical responses	DHP	CQ	p
Fever*, n/N (%)			0,894 <sup>a)</sup>
Day 1	22/25 (88)	22/26 (84,6)	0,728
Day 2	16/25 (64)	16/26 (61,5)	0,857
Day 3	5/25 (20)	4/26 (15,4)	0,669
Day 7	2/25 (8)	0/26 (0)	
Day 14	1/25 (4)	0/26 (0)	
Day 21, 28, 35 and 42	0/25 (0)	0/26 (0)	
Fever clearance time			
Median (range), day	3 (1-21)	3 (1-7)	0,267 <sup>b)</sup>
Symptom after taking drugs, n/N (%)			0,008 <sup>c)</sup>
Nausea	2/25 (8)	8/26 (30,8)	
Vomiting	8/25 (32)	18/26 (69,2)	
Vertigo	0/25 (0)	7/26 (26,9)	
Headache	5/25 (20)	2/26 (7,7)	
Allergic reaction	0/25 (0)	0/26 (0)	
No symptom	17/25 (68)	8/26 (30,8)	
Severe Malaria	0	0	

¶ DHP = Dihydroartemisinin piperazine, CQ = Chloroquine \* Fever was axillaries temperature ≥ 37.5 °C.

a) Shapiro-Wilk normality test,  $p = 0.000$ , Mann-Whitney statistic test,  $p = 0.894$

b) Shapiro-Wilk normality test,  $p = 0.000$ , Mann-Whitney statistic test,  $p = 0.267$

c) Shapiro-Wilk normality test,  $p = 0.000$ , Mann-Whitney statistic test,  $p = 0.008$

Before treatment (D0), the axillary temperature of all the subjects in the DHP and CQ groups was ≥37.5 °C and it decreased since the first treatment day (D1). There was not any significant difference in the velocity resolution of the fever at the beginning of the therapy (D1, D2, and D3) between the two groups. On the first day (D1) and on the second day (D2) after taking the drug, the majority of the subjects in the two groups still got fever. On the third day (D3) after taking the drug, 5 patients (20%) of the DHP group still got fever although the results of blood smear one of them showed that there was not any plasmodium found. There were 2 patients who still got fever on the

day 7 (D7) and one patient still got fever on D14 though from D7 to D42 there was not any plasmodium in the blood smears of all of the subjects in this group. There were 4 patients in the CQ group who still got fever with parasitemia on D3. All of the subjects in this group from D7 to D42 did not get any fever for any longer though there was plasmodium still found in the blood smears. It was clearly observed in Table 2 and Table 3.

The median of the fever clearance time, in the DHP group was 3 days with the range of 1-21 days, while that in the CQ group was 3 days with the range of 1-7 days. It was also not any significant difference ( $p = 0.267$ ). Table 2.

### Parasitological Response

**Table 3:** The comparison of the parasitological response of the DHP and CQ groups.

Parasitological Response	DHP	CQ
Parasite Density Mean $\pm$ SD, / $\mu$ l		
Day 0	5588,8 $\pm$ 5719,0	4055,4 $\pm$ 3374,9
Day 1	2038,4 $\pm$ 3142,2	2150,8 $\pm$ 2101,2
Day 2	648,3 $\pm$ 744,9	910,7 $\pm$ 897,5
Day 3	244,8 $\pm$ 409,7	486,2 $\pm$ 1031,6
Day 7	0	55,4 $\pm$ 151,8
Day 14	0	43,1 $\pm$ 152,1
Day 21, 28, 35 & 42	0	0
Parasitemia, n/N (%)		
Day 0	25/25 (100)	26/26 (100)
Day 1	25/25 (100)	26/26 (100)
Day 2	22/25 (88)	22/26 (84,6)
Day 3	11/25 (44)	14/26 (53,8)
Day 7	0/25 (0)	4/26 (15,4)
Day 14	0/25 (0)	2/26 (7,7)
Day 21, 28, 35 & 42	0/25 (0)	0/26 (0)
Parasite clearance time Median (range), day	2 (2-7)*	7 (2-21)*

¶ DHP = Dihydroartemisin piperazine, CQ = Chloroquine. \* Shapiro-Wilk normality test,  $p = 0.000$ ; Mann-Whitney statistic test,  $p = 0.056$ ; there was not any significant difference.

On the day before treatment (D0), the mean parasite density in the DHP group was 5588.8 (SD 5719)/ $\mu$ l blood, decreased on D1 by 2038.4 (SD 3142.2)/  $\mu$ l blood though there was still parasite found in the blood smears of all of the subjects. On D2, the parasite density of the groups decreased with the mean of 648.3 (SD 744.9) / $\mu$ l and there was not any parasite found in the blood smears of the 3 subjects. From D7 to D42 there was not any parasite in the blood smears of all of the subjects. When compared with CQ group, the mean parasite density of the CQ group on D1 was 2150.7 (SD 2101.2) parasite/ $\mu$ l blood. It was lower than D0, which was 4055.4 (SD 3374.9) parasite/ $\mu$ l blood. Most of the subjects in group CQ still having parasitemia on D2 (84.6%) and D3 (53.8%).

Until D14, plasmodium still found in the blood smear of some subjects (7.7%). Plasmodium was not found in the blood smear of all the subjects in this group since D21 to D42.

The median PCT of the DHP group was 2 days with the range of 2-7 days, while that of the CQ group was 7 days with the range of 2-21 days. There was not any significant difference between the PCT of the DHP group and the CQ group ( $p = 0.056$ ). Table 3.

There was significant difference in the parasite density of DHP group and CQ group before and after the treatment at  $p = 0.000$ . The parasite density of the DHP group before the treatment was not significantly different from that of CQ group at  $p = 0.970$ . Similarly, the parasite density after therapy in DHP group was not significantly different than in CQ group,  $p = 0.389$ .

Both clinical and parasitological response were evaluated using WHO protocol 2009 whether the patients were classified as cured (ACPR) or as treatment failure, which included ETF, LCF and LPF.<sup>4,13</sup> There was 76% (19 patients) in the DHP group classified into ACPR, while the remaining 24% (6 patients) experienced failure at the beginning of the treatment both clinically and parasitological so that they were classified into ETF. In the ETF classification the subjects still got fever till D3 and there was still plasmodium found in the blood smears. There was not any treatment failure found in the DHP group both clinically and parasitological since D4 to the end of the observation.

There was 57.7% (15 patients) in the CQ group on D42 cured and classified into ACPR classification, while 34.6% (9 patients) were classified into ETF. There was not any clinical treatment failure (LCF) found in the CQ group since D4, while there was parasitological treatment failure found in 2 patients (7.7%). There was plasmodium found in the blood smear of the subject no. 5 till D14, while there was still malaria plasmodium found in the subject no. 21 till D7 so that they were classified into LPF.

The results of Kaplan Meier analysis showed that the success cumulative incidence of the DHP group was 0.76 with 95% CI 0.542-0.884 and the CQ group was 0.577 with 95% CI 0.368-0.739. Failure cumulative incidence of DHP group was 0.24 with 95% CI 0.116-0.458 and the CQ group was 0.423 with 95% CI 0.261-0.632. There was not any significant difference between CQ therapy response and DHP therapy response,  $p = 0.166$  with RR 2.69 (95% CI 0.69-7.73).

The follow-up duration recommended by WHO 2009 was minimal 28 days for anti malaria with the half life of less than 7 days such as chloroquine and artemisinin derivative. Longer follow-up was required for the anti malaria with longer half life time such as piperazine and mefloquine. The follow-up of 42 days was considered to be optimal to regularly monitor the majority of drugs. The chloroquine has the half life of 3-5 days, while that of the piperazine was long enough, which was 28 days.<sup>14-18</sup> It



indicated that actually the efficacy test of the chloroquine could be conducted using the follow-up of 28 days, while the efficacy test of the DHP required longer time, which was 42 days.

Fever occurred on D7 and after D7 in the DHP group that might be caused by other infection and it did not relate to the treatment failure because there was not any parasite found in all of the blood smear preparations of the subjects in the group since D7 to D42. On the contrary, there was still plasmodium found in the blood smears of some subjects of the CQ group since D7 to D42, though 100% of the subjects did not get fever for any longer. It related to the immune status of the subjects so that they become as asymptomatic carriers.

The use of DHP and CQ would decrease the number of parasites; reduce the release of chemical mediators such as TNF- $\alpha$  and IL-6 that decrease/eliminate the interaction of malaria antigen and immune system so that the fever disappeared. The fever is a classic clinical symptom of malaria.<sup>19</sup> It occurred because of broken blood skin that produced various antigens. The antigens stimulated macrophage cells, while monocyte or lymphocyte produced various cytokines such as TNF (Tumor Necrosis Factor) and IL-6 (Interleukin-6). It caused the induction of prostaglandin by the malaria antigen so that hypothalamus changed body normal temperature threshold and fever occurred.<sup>19,20</sup> The symptoms after taking the drugs (D0, D1 and D2) occurs as a result of taken antimalaria or due to individual response to the malaria infection itself. The individual response to the malaria infection could result in various clinical symptoms. It was because of the release of chemical mediators that triggered the clinical symptoms. The use of the CQ and the DHP reduced the release of the chemical mediators because of the decrease in or the disappearance of parasitemia.<sup>20</sup> There was significant difference between the proportion of the subjects with the symptoms after taking the drugs in the DHP group and those in the CQ group at  $p = 0.008$ . Thus, it might be concluded that the symptoms were due to effects associated with the drug, but further study was required to find out precisely the causal factors of the symptoms.

Similar study by Awab compared the therapy response of the DHP and the CQ as the therapy of uncomplicated vivax malaria in Afghanistan.<sup>21</sup> Awab found that on the first and second days after therapy the subjects of the two groups had good clinical response to the therapy. The proportion of the subjects who still got fever on the first and second days was not more than 50%. The DHP group had velocity resolution of the fever better than the chloroquine group at  $p = 0.049$ .<sup>21</sup> As compared to the efficacy test of the CQ and the DHP conducted in Indonesia both separately and the comparison with other anti malaria, there were studies with different results, while there were those with similar results. Some studies found the median FCT of the chloroquine ranged from 1 to 2 days, even in Maumere FCT CQ was less than 24

hours, although in these areas CQ was not recommended.

Similarly, the side effects were minor such as headache, anorexia, fatigue, dizziness, nausea and vomiting.<sup>10,22,23-25</sup> In this study the median FCT of the DHP was 3 days, which was different from the study in Timika, Papua that was 2 days and the side effects after the treatment included diarrhea and headache.<sup>9,26</sup>

Meanwhile, the study in Kalimantan and Sulawesi found that the mean FCT of the DHP on the day 7 (D7) and the adverse events after the DHP treatment included diarrhea, anorexia and sweating.<sup>27</sup> World Health Organization 2010 established the minimum therapy failure of 10% or the cure rate of less than 90% in the implementation of the treatment policy in an area.<sup>5</sup>

The DHP therapy response in this study was better than the CQ therapy response though there was not any significant difference between the two therapy groups at  $p = 0.166$ . Probably, it was caused by the decrease in the DHP efficacy as the therapy for the vivax malaria in Kupang district. The decrease in the DHP efficacy might be caused by the resistance to the DHP in Kupang district. Similar to other studies that found the CQ treatment failure as the therapy of the vivax malaria in some areas in Indonesia,<sup>10,23-25,28</sup> this study also found that the CQ treatment failure rate was high enough (42.3%, 95% CI 26.1-63.2). The treatment failure might relate to the chloroquine resistance to the plasmodium vivax considering that the chloroquine has been being used for about 50 years as anti malaria agent in Indonesia, including in Kupang district, ENT.

## CONCLUSION

The DHP therapy response was better than the CQ therapy response though statistically there was not any significant difference between the two therapy groups. The therapy failure rate was more than 10% and cure rate was less than 90% in the DHP group and the CQ groups, which was not in accordance with the recommendation of WHO 2010 of the use of the anti malaria in an area and hence it was necessary to consider other alternative therapy of DHP.

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