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EVALUATION OF DIHYDROARTEMISININ PIPERAQUINE USE IN THE PATIENTS WITH VIVAX MALARIA IN WULANDONI SUB-DISTRICT, LEMBATA REGENCY

Michael Bhadi Bia[1], Norma T Kambuno[2], M. Sultan Aulya[3]

[1,2)]*Poltekkes Kemenkes Kupang*, Department of Medical Laboratory Technic
[3)]Politeknik Bina Husada Kendari, Department of Medical Laboratory Technic

Background: The highest case of malaria in East Nusa Tenggara Province is in Lembata Regency. The use of Artemisinin-based Combination Therapy (ACT) combined with Primaquine (PQ) in the treatment of vivax malaria aims to prevent treatment failure. The development of drug resistance and recurrence has been reported to have Plasmodium falciparum in several areas. For Plasmodium vivax, no resistance has been reported to the given regimen. Evaluation of the efficacy of Dihydroartemisinin piperaquine (DHP) combined with Primaquine (PQ) has never been done. **Objective:** To evaluate the efficacy and side effects of DHP + PQ in the treatment of Vivax malaria in the Wulandoni Sub-district, Lembata Regency. **Methods:** The subjects were vivax malaria patients who met the inclusion criteria as stated in the WHO anti-malarial drug resistance test. Clinical manifestations and side effects are monitored during the evaluation. Results: There were 52 respondents who followed the study to completion. The age of the patients involved ranged from 2 to 76 years consisting of toddlers, children, productive and elderly (≥ 46 years). From the Mann-Whitney test results, it was obtained p value <0.05 for groups of toddlers with productive age, toddlers with elderly, children with productive age and productive age with elderly. It was concluded that there were differences in parasite density among groups. **Conclusion:** There was a treatment failure as evidenced by blood tests with parasites still found in H3 because the patient did not take the medication completely. Clinical symptoms of vivax malaria patients were fever, chills and sweating accompanied by additional symptoms such as nausea, vomiting, diarrhea, headache, anorexia, aches and coughs. Side effects of DHP + PQ drugs were still in the mild category. Parasitological and clinical conditions and age had no relationship at all.

Keywords: vivax malaria, Dihydroartemisinin Piperaquine, side effects

1. Introduction

Malaria is still a public health problem in more than 100 countries. The number of malaria sufferers in the world is estimated at around 300-500 million clinical cases each year[1,2]. Malaria is a disease caused by Plasmodium which is transmitted through Anopheles sp[3]. There are 4 types of Plasmodium that infect humans namely Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium falciparum[4,-6]. Plasmodium falciparum is the most dangerous species and causes high morbidity and mortality (1 million per year)[7,8].

Early diagnosis and proper treatment are the main components of the global strategy and malaria eradication. The proper use of anti-malarial drugs not only shortens the duration of malaria but also decreases the incidence of complications and death[9]. In addition, the ideal requirements for anti-malarial drugs are: 1) the drug has an effect on all types and stages of parasite, 2) ease of use, 3) affordable prices and availability, 4) mild side effects and low toxicity[10,11].

Prevention of malaria has faced obstacles because of the discovery of plasmodium strains that are resistant to malaria treatment. Naturally plasmodium has a defense mechanism to prevent extinction[12,13]. On the other side of sub-therapeutic doses, patient adherence to taking drugs can result

in the occurrence of plasmodium immunity against existing anti-malarial drugs[14]. In the presence of resistant plasmodium, treatment failure occurs. Resistance can have an impact on treatment failure which is characterized by the persistent or reappearance of asexual parasites in the peripheral blood (recrudescence) which can be accompanied by clinical symptoms of malaria. Treatment failure or delayed initial treatment will increase gametocyte carriage which is the source (reservoir) of transmission and has the potential to cause malaria epidemics / extraordinary events[15,16].

To overcome treatment failure, there is a new type of anti-malarial drug that is very effective in eradicating plasmodium in areas that have been resistant to old anti-malarial drugs. The anti-malaria drug is Artemisinin Combination Therapy (ACT)[17,18]. Currently, the more frequently used ACT regimen is Dihydroartemisinin Piperaquine (DHP) in combination with Primaquine (PQ)[14]. The use of DHP and PQ is often complained by patients because of the side effects that arise. Side effects include shortness of breath, nausea and vomiting. This event is at risk of a drop out of treatment which results in treatment failure[19]. Treatment failure is one of the biggest challenges in efforts to eradicate malaria in Indonesia due to the efficacy of the use of some anti-malarial drugs, even there is resistance to chloroquine drugs. The implication of this resistance is the spread of malaria to new areas or the reemergence of malaria in areas that are already malaria-free. Resistance can have an impact on treatment failure which is characterized by the persistent or reappearance of asexual parasites in the peripheral blood (recrudescence) which can be accompanied by clinical symptoms of malaria[20,21].

Clinical symptoms / manifestations of malaria vary widely. Many factors can influence the severity of these clinical manifestations. These factors are the agent, host and the environment. Plasmodium parasite species, parasite density in patients is one of the agent and host factors that influence the severity of the disease[22,23]. Malaria parasites can cause clinical symptoms including fever accompanied by chills and sweating. These typical clinical symptoms can be accompanied by headaches, nausea, vomiting, diarrhea and muscle aches or weariness. However, in endemic areas people with parasitemia can be found but not cause symptoms (asymptomatic)[24].

Lembata is a regency in East Nusa Tenggara (NTT) Province with the highest malaria cases where the Annual Paracites Incidense (API) is 102.74 (2014). The number of Falciparum malaria cases in 2014 reached 831 people and 11,694 people with vivax malaria. From this data, it can be seen that the highest number of malaria cases in Lembata is vivax malaria and is the only region with the highest number of vivax malaria cases.[6]

Wulandoni sub-district is one of the sub-districts in Lembata which has quite large cases of malaria with 509 out of 8376 residents (UNICEF). Malaria cases in Wulandoni sub-district are always found every day. Malaria prevention follows an existing program that is passive patient discovery and patient treatment. Evaluation of the use of DHP has never been done. However, according to health workers at the Puskesmas Wulandoni, it is often found that patients who come are recurrent patients. There are also patients who do not take anti-malarial drugs into completion.

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Research on evaluating the use of Dihydroartemisinin Piperaquine in the treatment of vivax malaria has never been done in Lembata regency. Evaluation was carried out to determine treatment failure both parasitologically and clinically. Parasitological conditions of patients were determined by measuring the amount of parasites (species and stages) before and after treatment and side effects of drugs. Therefore, the problem can be formulated in the research question below "How is the evaluation of the use of Dihydroartemisinin Piperaquine combined with Primaquine related to parasitological and clinical conditions, side effects, medication adherence in patients with vivax malaria in Wulandoni sub-district?"

The purpose of this study was to evaluate the use of Dihydroartemisinin Piperaquine combined with Primaquine in patients with vivax malaria in Wulandoni sub-district. Specific purposes; finding out the clinical symptoms of vivax malaria sufferers in Wulandoni sub-district, finding out the parasitological condition of vivax malaria sufferers before and after treatment by measuring the parasite density through monitoring for 3 days, finding out the side effects of using Dihydroartemisisnin Piperaquine in the treatment of vivax malaria in Wualndoni, to find out the relationship of parasite density with monitoring for 3 days, finding out the side effects of using Dihydroartemisisnin Piperaquine in the treatment of vivax malaria in Wulandoni, to determine the relationship of parasite density with age and clinical symptoms of vivax malaria sufferers in Wulandoni sub-district and to find out the proportion of medication adherence in Wulandoni sub-district.

1. Material and Method

The type of research is descriptive with cross sectional design in the study of evaluating the use of DHP + PQ in patients with vivax malaria in Wulandoni sub-district, Lembata regency by comparing the results of examinations before, during and after treatment. The population in this study was all patients with vivax malaria who had been diagnosed microscopically in the laboratory of Wulandoni Puskesmas in Wulandoni sub-district in October 2016. The samples in this study were patients with vivax malaria in Wulandoni sub-district based on the criteria: patients with a single Plasmodium vivax infection which is proven through microscopic examination, able to take OAM orally, willing to be visited during re-examination visits according to agreement, willing to be involved in research by signing informed consent of patients or parents of young patients or children, no serious conditions such as coma, respiratory syndrome , severe anemia or even patients who need hospitalization, do not suffer from malnutrition and do not suffer from other diseases that have the same clinical symptoms as fever[25]. The sampling technique in this study was purposive sampling. The confidence level of the sample is 95%. According to WHO (2009)[26], the minimum sample needed to evaluate the use of Dihidroartemisinin Piperaquine is 50 people as representatives.

2. Results and Discussion

In this study 52 research subjects were recruited who followed the last day of follow-up. Fifty-two people have been using anti-malaria drugs for the treatment of vivax malaria. All of these patients complied with a repeat visit on day 3 after treatment and malaria blood sampling. The patients involved until the end of the study came from 9 villages out of 15 in Wulandoni sub-district. Characteristics of research subjects can be seen in Table 1.

Table 1. Distribution of vivax malaria cases by sex, group of age and place of residence in Wulandoni.

Sex, Age and Place of Residence of research subject	Total of research subject
Sex	
Male	28(53,8%)
Female	24(46,2%)
Age	
Toddler (0 – 5 years)	16 (30,8%)
Children (6 – 15 years)	14(27%)
Productive Age (16 – 45 years)	16(30,8%)
Elderly (≥46 years)	6(11,5%)
Total	**52(100%)**

In this study, there were 70 patients found but only 52 people managed to follow the study to completion. The age of the patients involved ranged from 2 to 76 years consisting of toddlers, children, productive age and elderly (≥ 46 years). The age group of toddlers, children and productive age groups are the largest group of patients in the taken sample.

The data of clinical and parasitological examination results of patients before being treated can be seen in Table 2.

Table 2. Results of parasitological examination of vivax malaria patients in Wulandoni before giving DHP + PQ

Stage and density of *Plasmodium*	The number of patient
Stage of *Plasmodium*	
Trophozoites	40(76,9%)
Trophozoites + Gametocytes	12(19,2%)
Schizonts	0(0%)
Gametocytes	0(0%)
Total	**52(100%)**

Density of *Plasmodium*	
≤ 2560	18 (34,6 %)
>2560	34 (65,4%)
Total	**52 (100%)**

Table.3. Average distribution of parasite density based on age of patients with vivax malaria in Wulandoni sub-district

Age	Average parasite density
Toddler (0 – 5 years)	2519,8±2407 (16 people)
Children (6 – 15 years)	3025±2918(14 people)
Productive Age (16 – 4 years)	5981±2649(16 people)
Elderly (≥46 years)	742±56,7(6 people)

To test whether there are differences in parasite density between age groups, a Kruskal Wallis test was performed. The results of the test obtained a value of p = 0.005 (p <0.05), so it was concluded that there were differences in parasite density between the two groups of age. To be able to find out the differences between the two groups of age, Post Hoc analysis was performed, the Post Hoc analysis for the Kruskal-Wallis test was the Mann-Whitney test. The results of the Post Hoc-Mann-Whitney analysis can be seen in the table below.

From the Mann-Whitney test results obtained p value of <0.05 which is a group of toddlers with productive age, a group of toddlers with elderly, children with productive age and productive age with elderly. If the p value <0.05, it can be concluded that there were differences in parasite density between the groups. Meanwhile, in the group of toddlers with children and the group of children with elderly obtained p value of > 0.05, which can be concluded that there was no difference in parasite density.

Clinical Symptoms of Malaria

Of the 52 study subjects, typical clinical symptoms of malaria were found in the form of fever, sweating and chills in 50 patients. Other clinical symptoms that accompany typical clinical symptoms are cough, runny nose, diarrhea, lack of appetite, dizziness, aches, nausea, vomiting and headaches.

To determine the relationship of clinical symptoms in each age group, the Mann-Whitney test was performed. The results of the Mann-Whitney test obtained p value of <0.05 in clinical symptoms of lack of appetite which indicates a difference in the groups age of toddlers and children; toddler and productive age. The clinical symptoms of diarrhea also differ among toddler - children groups;

toddlers - productive age groups; toddler - elderly groups. The clinical symptoms of aching also differ among the toddler-productive age groups and the productive age - elderly groups. Headaches also differ between the age groups of toddler - elderly. The clinical symptoms of dizziness also differ among the age groups of toddler - elderly, children - productive age and children - elderly.

The average number of asexual parasites in vivax malaria patients in Wulandoni sub-district with clinical symptoms of fever can be seen in Table 4 below.

Table.4. Bivariate test relationship of parasite density with age and clinical symptoms of vivax malaria patients in Wulandoni sub-district.

Variable	Parasite density		*p*- value
	≤2560	**>2560**	
Age	14(26,9%)	12(23,1%)	0,193
≤ 10 years	12 (23,1%)	14 (26,9%)	
>10 years			
The number of clinical symptoms	12 (23,1%)	22(42,3%)	0,751
≤ 5	6 (11,5%)	12 (23,1%)	
>5			

The result of Spearman Correlation test to determine the relationship of age or clinical symptoms with parasite density found p-value = 0, 193 (p> 0.05). This suggested that the two variables do not affect the parasite density in patients with vivax malaria in Wulandoni sub-district.

Treatment Response

Parasitological response

The parasitological response of 52 patients on the 3rd day of the repeat visit after administration of DHP + PQ can be seen in Table 6.

Table 5. Parasitological responses in vivax malaria patients in Wulandoni sub-district after the administration of DHP + PQ during October 2016

Day of *Follow-up*	Average number of asexual parasites / µl blood			
	≤ 2560	*P*	< 2560	*p*
D0	850±492 (26)	0,000	6143± 1896(26)	0,068
D3	244±87 (12)		329±180(4)	

To find out whether there are differences in parasite density before and after treatment, a Wilcoxon alternative test was conducted. Wilcoxon test analysis obtained the first output showing a comparison of parasite density before and after treatment. In the parasite density group of ≤ 2560, 14 people were found to have no parasites on Day 3, 11 people on Day 3 have less parasite density than ones on Day 0 and 1 patient have parasite density on Day 3 is higher than on Day 0. In the parasite density group of > 2560 there were 22 patients no longer have parasites on Day 3 and 4 people in Day 3 have lower parasite density than on Day 0.

Wilcoxon test results also obtained a significance value of 0,000 ($p < 0.05$) in both groups of parasite density. Thus, it was concluded that there were significant differences / decrease in the number of parasites between before and after treatment.

Side Effects of DHP+PQ

The side effects of DHP + PQ found during observation for 3 days of treatment can be seen in Table 6.

Table 6. Distribution of side effects proportion of DHP + PQ use

Side effects	Regimen Therapy
	DHP+PQ (n= 52)
Nausea	26(50%)
Shortness of breath	10(19,23%)
Nausea and Vomiting	7(13,46%)
Shortness of breath and vomiting	9(17,31,%)

Of the 52 patients who were given DHP + PQ treatment, it was found that 16 patients dropped out of treatment while the other 36 patients continued the treatment

Table 10. Distribution of DHP + PQ medication adherence in patients with vivax malaria in Wulandoni sub-district

Age of Patients	Medication adherence	
	Dropped out of treatment	Complete treatment
Toddler (0 – 5 years)	10(19,23%)	6(11,5%)
Children (6 – 15 years)	4(7,7%)	14(26,9%)
Productive age (16 – 45 years)	2(3,8%)	14(26,9%)
Elderly (≥46 years)	0	6(11,5%)

Characteristics of patient subjects

From 52 patients, Plasmodium vivax at gametocyte stage was found in 12 of them. This indicated that the patient had been infected for a long time when associated with the life cycle of Plasmodium Vivax less than one month had been infected[27]. The appearance of gametocyte in the patient's blood can be a source of malaria transmission around the patient because gametocyte stage is the Plasmodium stage which can be a source of malaria transmission.

The average parasitie density of each age group is not too different among the age groups. After performing the Kruskal Wallis test, it was found that groups of toddlers or children towards the elderly group differ in parasite density. This is different from the research of Hasugian et al (2007) where it was found that parasites will decrease at an older age[28]. This depends on the immune system at a productive age which prone to be more adaptive to plasmodium vivax. This condition occurs only in residents aged ≥ 45 years who have a low parasite density.

Clinical symptoms of vivax malaria patients in Wulandoni sub-district are quite diverse. All patients have a typical malaria fever and are followed by additional clinical symptoms such as diarrhea, nausea and vomiting, headaches, dizziness, aches, anorexia. Additional clinical symptoms such as diarrhea generally occur in children and toddlers. Clinical symptoms can generally be influenced by age and parasite density. However, it is not possible in high endemic areas, because people have enough immunity so that the clinical symptoms are not severe and some do not even have clinical symptoms. After statistical test was conducted, the results showed no relationship between parasite density with age and the number of clinical symptoms.

Clinical symptoms that arise are also caused by variations in the antigenic strain of Plasmodium so that the body's immune system takes a long time to recognize specific antigens[2930].Variations in clinical symptoms are also influenced by variations in antigens from parasites. According to Syafruddin (2011)[9], each Anopheles malaria vector mosquito consists of at least 3 sporozoite strains[31].

4. Conclusions

There was a treatment failure as evidenced by blood tests and parasites still found on Day 3 due to the incompleteness of medication. Clinical symptoms of vivax malaria patients in Wulandoni sub-district are generally fever, chills and sweating accompanied by additional symptoms such as nausea, vomiting, diarrhea, headache, anorexia, aches and coughing. Side effects of DHP + PQ drugs are still in the mild category. Parasitological and clinical conditions and age had no relationship at all.

REFERENCE

1. World Health Organization. *Assessment and Monitoring of Antimalarial Drug Efficacy for the Treatment of Uncomplicated Falciparum*.; 2003.
2. Natadisastra, D., Agoes R. *Parasitologi Kedokteran Ditinjau Dari Organ Tubuh*.; 2009.
3. Setiawati, A., Zunilda, S.B., Suyatna FD. *Pengantar Farmakologi. In: Farmakologi Dan Terapi*.; 1995.
4. Resi EM. Effect of antimalaria herbal sambiloto (Andrographis paniculata Nees) on morphology changes of development and parasite Plasmodium Falciparum. *J Info Kesehat*. 2014;12:661-666.
5. Selasa P. Implementation of malaria elimination policy at Kupang City Public Health Center. *J Info Kesehat*. 2017;15(1):97-109.
6. Kristina, R. H., & Peni JA. Compliance Of Malaria Drug Intake And The Using Of Bed Nets Of Malaria Patients In Public Health Center Of Waipukang, Lembata District, East Nusa Tenggara In 2018. In: *In Proceeding 1st. International Conference Health Polytechnic of Kupang*. ; 2018:153-168.
7. Tjitra E. Pengobatan Malaria dengan Kombinasi Artemisinin. *Bul Penelit Kesehat*. 2005;33(2):53-61.
8. Noviyanti R. *Patogenesis Molekuler Plasmodium Falciparum. Dalam Malaria Dari Molekuler Ke Klinis. Eds. P.N. Harijanto*.; 2010.
9. Sutanto, I., Pribadi W. Parasitologi Kedokteran 4th rev. *FKUI Press Jakarta*. 2008.
10. Suparman E, Suryawan A. Malaria pada Kehamilan. *Jkm*. 2004;4(1):21-39.
11. Kinansi RR. Pengobatan Malaria Kombinasi Artemisinin (ACT) Di Provinsi Papua Barat Tahun 2013 Artemisinin-based Combination of Antimalaria Therapy (ACT) in West Papua at 2013. *Balaba*. 2017;13(1):43-54.
12. Simamora D, Fitri LE. Antimalarial Drug Resistance : Mechanism and the Role of Drug. *Kedokt Brawijaya*. 2007;23(2):82-92.
13. Tjitra E, Oemiyati S, Pribadi W, et al. Pengobatan Penderita Malaria Falsiparum Tanpa Komplikasi Dengan Meflokuin Di Daerah Resisten Klorokuin. *Bul Penelit Kesehat*. 1992;20(1).
14. Kristina RH. Screening Test penderita Malaria Dengan Gold Standar Uji Laboratorium Untuk Validasi Kasus Malaria Positif Di Wilayah Puskesmas Lewoleba Dan Puskesmas Waipukang Kabupaten Lembata, Propinsi Nusa Tenggara Timur Tahun 2016. *J Info Kesehat*. 2016;16(1):164-177.
15. Kody MM, I Gede Ariyawan. Pengetahuan dan Peran Orang Tua dalam Pencegahan Malaria Pada Anak di Ruang Anggrek Rumah Sakit Umum Waingapu. *J Kesehat Prim*. 2016;2:153-161.
16. Tuti, Dewi RM, Kristi N, Gunawan A. Pemantauan Efikasi Klorokuin Untuk Pengobatan Malaria Falciparum Ringan Di Daerah High Case Incidence (Hci) Banjarnegara, Jawa Tengah Sekar. *Bul Penelit Kesehat*. 2007;35(3):97-107.
17. Ora AT, Barat S. Perilaku Ibu Rumah Tangga dalam Menggunakan Kelambu di Wilayah kerja Puskesmas Kabukarudi di Kab Sumba Barat. *J Kesehat Prim*. 2016;1(1):38-46.
18. Syamsudin. *Efek Samping Obat*.; 2011.
19. Atameha JB, Malo M. JFactors Related to Malaria in Pregnant Women in the Work Area of Kambaniru Health Center East Sumba District. *J Kesehat Prim*. 2018;3(1):30-45.
20. Surira Kombonglangi R. Manajemen Terapi Malaria Falciparum Yang Resisten Terhadap Klorokuin. *J Major*. 2015;4(6):27-30.

ISSN 2515-8260 Volume 10, Issue 07, 2023

21. Chin J. Control of Communicable Disease Manual 17th edition. *Am J Epidemiol*. 2000;154(8):783-784.
22. Sekunda M, Doondori AK, Studi P, Ende K. Risk Factors of Physical Condition of House Against Malaria Occurrence in Ende East Nusa Tenggara Indonesia Faktor Risiko Kondisi Fisik Rumah Terhadap Kejadian Malaria Di Ende Nusa Tenggara Timur Indonesia. *J Kesehat Prim*. 2017;2(2):230-237.
23. Arwati. Pemberantasan Malaria di Indonesia. *Cermin Dunia Kedokt Indones*. 1981;21:41-43.
24. Azlin E. Obat Anti Malaria. *Sari Pediatr*. 2016;5(4):150. doi:10.14238/sp5.4.2004.150-4
25. WHO WHO. Malaria Case Management- Operations Manual. *WHO Press Geneva Switzerland*. 2009.
26. WHO WHO. Guidlines for The Treatment of Malaria. *WHO Press Geneva Switzerland*. 2009;21(1):31-39.
27. Garcia, L.S., Bruckner DA. *Diagnostik Parasitologi Kedokteran Eds L. Padmasutra*. Vol 1.; 1996.
28. Hasugian, A.R., Purba, H.L.E., Kenangalem, E., Wuwung, R.M., Ebsworth, E.P., Maristela, L., Panttinen, P.M.P., Laihad, F., Anstey, N.M., Tjitra, E., and Price RN. Dihydroartemisinin-Piperaquine versus Artesunate-Amodiaquine: Superior Efficacy and Posttreatment Prophylaxis against Multidrug-Resistant Plasmodium falciparum and Plasmodium vivax Malaria. *Clin Infect Dis*. 2007;44(8):1067-1074.
29. Harijanto PN. *Malaria. Dalam Ilmu Penyakit Dalam 4th.Eds. A.W. Sudoyo*. Hindawi; 2007.
30. Kristina, R. H., Subekti, S., Dachlan, Y. P., Martini, S., & Nugroho HSW. Mapping the Model of Ecological Vegetation as Potential Malaria Habitats in a Malaria-Endemic Region in Oesao Village, Kupang Regency, Indonesia. *Indian J Public Heal Res Dev*. 2018;9(12).
31. Kristina, R. H., Subekti, S., Dachlan, Y. P., & Martini S. The Effectiveness of The Malaria Cadres on Drug Intake Supervision, The Use of Mosquito Net and Environmental Modification on Malaria Sufferers at Malaria Endemic Area of Public Health Center of Waipukang, Lembata District, Nusa Tenggara Timur Province, I. *Heal Notionsvicenna J Med*. 2017;1(3):373-382.