Artesdiaquine and Primaquine combined treatment is more effective for Malaria vivax

Santoso

Vector Borne Disease Control Research and Development Council, Baturaja, South Sumatra

Abstrak

Latar belakang: *Pengobatan malaria di Kabupaten OKU sejak tahun 2009 telah menggunakan artesdiakuin untuk malaria vivak dan malaria falsiparum. Penelitian bertujuan untuk mengetahui perbedaan gejala klinis awal penderita malaria vivak dan malaria falsiparum, efektivitas dan efek samping pemberian artesdiakuin.*

Metode: *Penelitian merupakan kuasi eksperimen menggunakan metode pre-post test. Sampling dilakukan secara consecutive terhadap pasien Puskesmas Pengaringan, OKU selama bulan Februari sampai Juni 2010. Diagnosis malaria didasarkan adanya plasmodium pada darah pasien secara mikroskopis. Seluruh pasien yang didiagnosis malaria diterapi artesdiakuin pada H0 sampai H2 sedangkan pemberian primakuin hanya dilakukan pada H0. Pengamatan dilakukan i selama 28 hari yaitu pada H0 sampai H3, H7, H14, H21 dan H28. Pengamatan efek samping dilakukan pada H0 sampai H3 sedangkan penilaian efikasi obat dilakukan setelah H28.*

Hasil: *Diperoleh jumlah penderita malaria falsiparum sebanyak 23 orang dan malaria vivak sebanyak 12 orang. Gejala klinis awal sebelum terapi ditemukan pada 91,3% pada subjek dengan malaria falciparum berupa menggigil, anoreksia, sakit kepala, pusing dan nyeri otot. Gejala tersebut terjadi pada 50% subjek dengan malari vivak. Obat anti-malaria artesdiakuin memiliki efikasi yang baik (100%) terhadap penderita malaria vivax namun pada penderita malaria falsiparum hanya diperoleh 87%. Efek samping artesdiakuin ditemukan berupa gatal, pusing, mual, muntah dan nyeri lambung. Efek samping obat lebih berat pada penderita malaria falsiparum dibandingkan malaria vivak.*

Kesimpulan: *Penderita malaria vivax lebih banyak yang tidak mengalami gejala klinis awal. Artesdiakuin lebih efektif pada penderita malaria vivak dibandingkan penderita malaria falsiparum. Efek samping yang ditemukan berupa menggigil, anoreksia, sakit kepala, pusing dan nyeri otot. (**Health Science Indones 2010; 1: 26 -32)***

Kata kunci: *malaria, artesdiakuin, efektivitas, efek samping*

Abstract

Background: Malaria treatment in Souh Sumatra has been using artesdiaquine since 2009 for falciparum and vivax malaria. This study is aimed to examine the comparison of the effectiveness of anti-malaria drugs artesdiaquine and its side effects between falciparum malaria and vivax malaria treatment.

Methods: This consecutive sampling quasi experimental research was conducted during February to June 2010 in a district of South Sumatra (Indonesia).

Diagnosis based on peripheral blood smear plasmodium finding. All patients positive for Plasmodium were observed for 28 days: 0-3 (D0) to 3th (D3), 7th (D7), 14th (D14), 21th (D21) and 28th day (D28). Therapy of artesdiaquine on D0 to D2, while primaquine was only gives on D0. The observations of side effects were done on D0 to D3. The assessments of drug efficacy were immediately after D28.

Results: Twenty three falciparum malaria patients and and twelve vivax malaria patients were included as study subjects Initial clinical symptoms of chills, headache, dizziness, anorexia, and muscle aches were found in falciparum malaria subjects and vivax malaria subjects were 91.3% and 50% respectively. The results showed anti-malaria drugs artesdiaquine had 100% efficacy of vivax malaria patients however for falciparum malaria acquired was only 87%. Artesdiaquine side effects consisted of itching, dizziness, nausea, vomiting, and stomach pain, were more prevalent in patients with falciparum malaria than vivax malaria.

Conclusion: The number of malaria vivax patients less clinical symptoms occurred than falciparum malaria. The effectiveness of artesdiaquine anti malaria drugs combination for vivax malaria was better than falciparum malaria. ***(Health Science Indones 2010; 1: 26 - 32)***

Key words: malaria, artesdiaquine, effectiveness, side effects

Corresponding author: Santoso
E-mail: santosbta@yahoo.co.id; santoso@litbang.depkes.go.id

Malaria is still a public health problem in Indonesia and endemic area in keeps increasing. Further problem is the resistance of the widely used antimalarial drug chloroquine to *Plasmodium falciparum*. The increase of the number of cases was also accompanied by the increase of the resistance of chloroquine and sulphadoxine-pyrimethamine in almost all provinces in Indonesia, including South Sumatra Province.[1]

The malaria treatment especially falciparum malaria in Indonesia has implemented The Ministry of Health policy since 2004 which is artemisinin base combination therapy (ACT) involved artesunate and amodiaquine (artes-diaquine), in accordance the WHO recom-mendation.[2] The implementation of ACT as treatment for antimalarial has been conducted also in one malaria endemic districts in South Sumatra Province that is Ogan Komering Ulu (OKU) regency since 2007.

OKU Regency in South Sumatra is. The Annual Malaria Incidence (AMI) in OKU Regency in 2008 were 21.79 per mile with the highest of AMI at the health center of Pengaringan were 80.00 per mile. The number of positive malaria cases in 2008 was 311 people, in which 190 were *P. falciparum* with Annual Parasite Incidence (API) 1.01 per mile.[3]

The purpose of this study was to identify the symptoms of malaria, and the effectiveness and the side effects of artesdiaquine therapeutic use on malaria patients in OKU Regency.

METHODS

A quasi experiment study with pre-post test was carried out on falciparum and vivax malaria in OKU regency from February to June 2010 to compare the efficacy of artesdiaquine and primaquine on falciparum and vivax malaria patients. Consecutive sampling from falciparum or Plasmodium vivax of peripheral blood. As many as 35 patients with positive malaria, 23 are P.falciparum and 12 are P.Vivax fulfilled inclusion criteria. Patients with falciparum and vivax were observed for 28 days, on the 0 day (D0) to 3th day (D3), 7th day (D7), 14th day (D14), 21th day (D21) and 28th day (D28). Malarial patients in Penggaringan Health Centre were used in this stud. . Diagnosis is based on the finding of either Plasmodium Artesdiaquine was given on D0 to D2, while primaquine was given on D0 to all patients. The observation of side effects was performed on D0 to D3, while the assessment of drug efficacy was performed after D28. The peripheral blood tests to see malaria parasite were carried out on D0 to D3, D7, D14, D21 and D28. Observations were conducted to assess clinical symptoms, effectiveness of artesdiaquine as anti-malarial drugs, and side effects.

Clinical examination was performed by center public health nurse, while peripheral blood collection was performed by laboratory analyst and examination of malaria parasites done by researchers with cross check to the parasitology laboratory of Universitas Gadjah Mada.

Evaluation of the treatment effectiveness based on WHO criteria, which are Early Treatment Failure (ETF), Late Clinical Failure (LCF), Late Parasitological Failure (LPF) and Adequate Clinical and Parasitological Response (ACPR).[4]

Chi-square test was used to describe the comparative clinical symptoms between falciparum and vivax malaria. Paired t-test was used to comparative mean of parasitemia in patients between D0 and D1. Independent t-test used to comparative mean of parasitemia between falciparum and vivax malaria.

RESULTS

Table 1 shows twenty three *P.falciparum* and 12 of *P.Vivax* subjects were fulfilled inclusion criteria. Most of the subjects were falciparum malaria patients (65.7%).

Table 1. Characteristics of study subjects

	Malaria	
	Falciparum	Vivax
Gender		
Male	9 (25.7%)	7 (20.0%)
Female	14 (40.0%)	5 (14.3%)

Table 2 shown the initial clinical symptoms found in this study are chills, headache, dizziness, anorexia and muscle aches. The clinical symptoms that are often found in patients with symptoms of malaria, which incurred before the main symptoms is fever. The early clinical symptoms of malaria patients

in D0 were more common in falciparum malaria patients compared to vivax malaria. The most clinical symptoms were found in falciparum malaria were chills, headache, anorexia (40.4%), while in vivax malaria were chills and headache (25%). Falciparum malaria patients who did not experience the early clinical symptoms were only 2 people (8.7%) of all falciparum malaria patients, while vivax malaria patients were found in 6 people (50%) that had no early clinical symptoms. There were significant differences (p=0.000) between falciparum and vivax malaria patients to the emergence of the early clinical symptoms.

Table 2. Distribution of clinical symptoms in malarial patients

Early symptoms D0	Malaria		Sub total
	Falciparum	Vivax	
Chills	0 (0.0%)	1 (8.3%)	1 (2.9%)
Chills, anorexia	3 (13.0%)	0 (0.0%)	3 (8.6%)
Chills, dizziness	4 (17.4%)	1 (8.3%)	5 (14.3%)
Chills, headache	5 (21.7%)	3 (25%)	8 (22.9%)
Chills, headache, dizziness, anoreksia	1 (4.3%)	0 (0.0%)	1 (2.9%)
Chills, headache, anorexia	7 (30.4%)	0 (0.0%)	7 (20.0%)
Chill, headache, anorexia, muscle aches	1 (4.3%)	0 (0.0%)	1 (2.9%)
Headache	0 (0.0%)	1 (8.3%)	1 (2.9%)
No symptoms	2 (8.7%)	6 (50.0%)	8 (22.9%)

Artesdiaquine effectiveness

After observation for 28 days, all vivax malaria patients cured (100%), while as many as 3 people (13%) falciparum malaria patients experienced ETF. Axillary temperature on D3 was ≥37.5°C and the existence of gametes was still found.

The mean of temperature malaria patients in D0 was higher in falciparum malarial than that of vivax malarial. From the observation, during 28 days the average of temperature in malaria patients in both groups decreased. Table 3 shown that the mean parasitemia of falciparum malaria patients before therapy (D0) were 4542±3174/µl blood and after therapy (D1) of 814±2003/µl blood shown in Table 3. Statistical test using paired t-test obtained the average value of D0 and D1 parasitemia differences was 3728±2248/µl blood with p=0.000. It can be concluded that there was a significant difference between parasitemia before and after therapy. The mean temperature of falciparum malaria patients before therapy was 37.4°C±0.8°C and the mean of temperature after therapy was 37.3oC±0.8oC.

Statistical test using paired t-test obtained average value of the temperature difference of D0 and D1 which were 0.11oC±0.50oC, p=0.288. It can be concluded that there was no significant difference the average temperature between before and after therapy.

The mean of parasitemia vivax malarial patients before treatment was 5383±2823/µl blood and after treatment was 0. Statistical test using paired t-test obtained the average value of D0 and D1 parasitemia differences for blood 5383±2823/µl with p=0.000. It can be concluded that there was a significant difference between parasitemia before and after therapy.

The temperature mean of vivax malaria patients before therapy was 37.04oC±0.75oC and the mean after therapy was 36.98oC±0.48oC. Statistical test using paired t-test obtained an average value of D0 and D1 temperature difference of 0.1oC±0.4oC, p=0.567. It can be concluded that there was no difference between the average temperature before and after therapy.

Corresponding author: Santoso
E-mail: santosbta@yahoo.co.id; santoso@litbang.depkes.go.id

Table 3. The mean of malaria parasitemia and temperature before treatment (D0) and after treatment (D1)

Days observation	Parasitemia/µl blood		Temperature (°C)		n
	Mean	P	Mean	P	
Falciparum malaria:					
D0	4542±3174	0,000	37.44±0.82	0.288	23
D1	814±2003		37.33±0.75		
Vivax malaria:					
D0	5383±2823	0,000	37.04±0.75	0.567	12
D1	0		36.98±0.48		

The most common side effects of therapy in patients with falciparum malaria artesdiakuin are nausea which was found in six patients (26.1%). While in patients with vivax malaria, the side effects were dizziness, nausea which was found in three persons (25%). Dizziness, nausea and vomiting were found in three people (25%). In falciparum malarial patients who did not experience medication, the side effects were found in five people (21.7%) and as much as two people (16.7%) in patients with vivax (Table 4).

Table 4. Distribution of the proportion of side effects in treatment of malaria patients

Side effects	Malaria patients		Sub total
	Falciparum	Vivax	
Itching, nausea	1 (4.3%)	0 (0.0%)	1 (2.9%)
Nausea	6 (26.1%)	1 (8.3%)	7 (20.0%)
Nausea, vomiting	1 (4.3%)	2 (16.7%)	3 (8.6%)
Nausea, vomiting, stomach pain	0 (0.0%)	1 (8.3%)	1 (2.9%)
Dizziness, nausea	3 (13.0%)	3 (25.0%)	6 (17.1%)
Dizziness, nausea, vomiting	5 (21.7%)	3 (25.0%)	8 (22.9%)
Dizziness, nausea, vomiting, stomach pain	2 (8.7%)	0 (0.0%)	2 (5.7%)
No side effects	5 (21.7%)	2 (16.7%)	7 (20.0%)

DISCUSSION

The mean density of parasites in malaria patients was associated with early clinical symptoms such as fever. The parasite density mean before treatment in patients with a fever is greater than the mean of parasites density in patients with no fever. Statistical analysis showed no significant difference between the mean of parasite density in patients with malaria fever incidence before getting treatment. Clinical symptom such as fever before treatment in falciparum malaria is more common than the incidence of fever in patients with vivax malaria. Test results also showed a statistically significant difference between falciparum malaria and vivax malaria in term of the incidence of fever.

Clinical symptoms in patients with vivax malaria were not always obvious. In Vivax malaria patients who experience only 50% of clinical symptoms, it were happen because of the increase of immune in malaria patients, especially in areas with high endemicity. Results of a research in Brazil and Papua New

Guinea found a humoral immune response against naturally acquired vivax MSP1 protein. Immune responses played by IgG in each of the different regions. Plasmodium vivax MSP1 in Brazil was recognized by IgG3, while in Papua New Guinea was recognized by IgG1.[5]

White (2009) states that in high malaria endemic areas, high parasitemia >10.000/µl blood often do not cause symptoms.[6] According to White, there are three possible

cause of malaria patients without clinical symptoms including the ability of the immune response to control parasite densities below the limit pyretogenesis (causes a fever), low parasite density and low ability mitosis, and the speed of movement of the parasite.

From the study of 35 malaria patients who were given therapy with artesdiakuin it was found that as many as three people (13%) patients with falciparum malaria had Early Treatment Failure (ETF). Axillary temperature patients in D3 were ≥ 37.5^{o}C and the existence of parasite gametes that meet the criteria for staging the ETF was still found. Combination therapy is given to the granting of artesunat-amodiakuin for three days and primaquine is given on the first day for patients with falciparum malaria. Primaquine is a strong gametosidal against four species of malaria and plasmodium usually used for eradication of *P.falciparum* gametes. After treatment with primaquine orally, it was well absorbed and reaches peak plasma within 1-2 hours. Primaquine plasma half-life is 3-6 hours and only a small part that remain after 24 hours.[7] Dose of primaquine is given only on the first day of primaquine, while part-time only 3-6 hours allowing the re-emergence of gametes to the erythrocyte-stage parasites. Amodiaquine has similar properties to chloroquine, so the possibility of cross-resistance can occur. Artesunate is a derivative of artemisinin that has an effect on all stages of *P.falciparum.* However, the mechanism of artesunate has not been known.[8] Emergence of *P.falciparum* gametes stage in the patient's blood indicates that malaria patients have been infected for a long time when it connected with the life cycle of *P.falciparum,* which has a long incubation period of 9 days and 48 hours (2 days) erythrocyte asexual cycle. The emergence of gametes in the patient's blood can be a source of transmitting malaria in some patients because the stadium is a phase of Plasmodium gametocytes that can be a source of malaria transmission. Research conducted by Bousema et al. (2004) found that 18.6% of malaria patients who did not receive treatment developed into gametocytes.[9]

Based on the interview, it was found that the three people who have a history of early treatment failure had moved to other regions with high malaria endemicity. These three patients also had a history of fever both before treatment and at the time of treatment. Both groups of patients with malaria, late treatment failure criteria were not found. All stages of the parasite were not found any longer in the D7-D28, and no patients who developed severe malaria or axillary temperature of ≥ 37.5^{o}C.

The results showed that the ACPR in patients with falciparum malaria was only 85%, whereas in patients with vivax malaria was 100%. However, after observation for 28 days, parasitemia was not found in all patients and there were no patients whose developed severe malaria and has a temperature ≥37.5^{o}C. The results of this study were not much different from the results conducted by Oyakhirome.[10] WHO obtain treatment cure rate for falciparum malaria with artesdiakuin 86% in the group observed and 63% in the unsupervised group. According to WHO[8], when the results of research on drug efficacy rate was obtained <75%, then the drug should be immediately replaced with another drug. Meanwhile, when the results of efficacy scores <90%, the WHO recommends for use of other drugs. Research on the efficacy artesdiaquine conducted in sub-Saharan Africa by conducting 26 clinical trials also obtained a various cure rate. In comparison, a random test obtained artesdiakuin efficacy of 75.9% and after the examination that was performed by PCR and the efficacy rate was 93.9 %. While in the territory of Uganda, risk of developing gametocytes in artesdiakuin therapy was higher than therapeutic use of artemether + lumefantrin and dihydropiperaquine. In patients who were given therapy with artesdiakuin the existence of gametocytes to D28 was still found.

This research obtains a result that there were differences between D0 and D1 parasitemia in falciparum malaria patients. Parasitemia in D1 was found in 10 patients (43.5%), while on a study by Zwang[11] obtained higher parasitemia number (66.4%). Parasitemia in D2 was found in six patients (26.1%) and in D3 was found in three patients (13.0%). Parasitemia in the D2 and D3 in this study were higher than that obtained parasitemia Zwang research on D2 at 1.85% and 0.6% in D3.

Research conducted by Ndiaye[12] comparing artesdiakuin with once-daily administration and two meals a day found gametes in

Corresponding author: Santoso
E-mail: santosbta@yahoo.co.id; santoso@litbang.depkes.go.id

treatment with artesdiaquine. In the once-daily administration it was still found artesdiakuin gametes until day 14 while on providing two meals a day were still found until day 21. Assessment results indicate ACPR criteria in the group receiving once-daily treatment of 95.2%, while in the group who received treatment two times a day was 94.9%.

According to IDA Foundation[13], the use of artesdiaquine often give side effects such as stomach pain, diarrhea, vomiting, and headaches, While the use of a single dose artesunate often give side effects such as stomach upset, diarrhea and nausea. The side effects treatment of malaria often occurs in patients who were given anti-malarial therapy. The results of this study showed that patients who experience side effects (25 people) experienced nausea (100%). Whereas among patients experiencing the side effects of treatment, 14 (40%) of them experienced vomiting. Research was conducted by Susiawan[14] in Banjarnegara also get a side effect of treatment with artesdiaquine. The most common were nausea (25%).

Research conducted on children in sub-Saharan Africa16 found that 44.8% (52/116) of malaria patients who received treatment with artesdiakuin experience symptoms of nausea and vomiting. While complain of fatigue and a lot of sleep was found in 4.3% patients with malaria. Complains experienced by patients between the first to the third day in the form of nausea or vomiting was found in 27.5% (32/116) malarial patients.

Faye[16] found that in patients with uncomplicated malaria who were given treatment with artesdiaquine experience side effects from treatment. Side effects include headaches found (27.5%), stomach pain (25.6%), nausea and vomiting (31.2%), dizziness (11.2%) and asthenia (7.5%).

Side effects such as anorexia, nausea and vomiting are often seen in anti-malarial drug therapy as a response from the absorption of anti-malarial drugs.[8] Drug reactions that give the effect of causing vomiting drug absorption can not be perfect, especially if side effects occur shortly after drinking anti malaria.

Medication side effects were found such as vomiting is probably one of the factors that cause malaria treatment failure. Patients who experienced early treatment failure as much as three persons, two of them experienced side effects of dizziness, nausea and vomiting during D1, D2 and D3, whereas patients with only one person experienced dizziness and nausea.

In conclusion, the number of malaria vivax patients less clinical symptoms occurred than falciparum malaria. The effectiveness of artesdiaquine anti malaria drugs combination for vivax malaria was better than falciparum malaria.

Acknowledgements

The author wishes to thank all subjects who willingly participated in this study. Thank to: Prof. Supargiyono (main supervisor); Dr. Mahardika Agus Wijayanti, (counselor); Prof. Mustofa, Yulian Taviv, Suharmasto, Havisah, Yose and Edwin for their technical assistance.

REFERENCES

1. Harijanto PN. Perubahan Radikal dalam Pengobatan Malaria di Indonesia. Cermin Dunia Kedokteran. 2006; (152): 30-6. Indonesian.
2. Departemen Kesehatan Republik Indonesia. Pedoman Penatalaksanaan Kasus Malaria di Indonesia. Jakarta: Depkes RI; 2009. Indonesian.
3. Dinas Kesehatan Kabupaten OKU. Laporan Penemuan dan Pengobatan Penderita Malaria. Baturaja: Dinkes Kab. OKU; 2009. Indonesian.
4. World Health Organization. Assessment and monitoring of antimalarial drug efficacy for the Treatment of uncomplicated Falciparum Malaria. Geneva: The Organization; 2003.
5. Becerra CF, Sanz S, Brucet M, Stanisic DI, Alves FP, Camargo EP, et al. Naturally-acquired humoral immune responses against the N- and C-termini of the Plasmodium vivax MSP1 protein in endemic regions of Brazil and Papua New Guinea using a multiplex assay. Malaria Journal. [Internet] 2010 Sep [cited 2010 May 5]; 29(9). Available from: http://www.malariajournal.com/content/9/1/29.
6. White NJ, Pongtavornpinyo W, Maude RJ, Saralamba S, Aguas R, Stepniewska K, et al. Hyperparasitaemia and low dosing are an important source of anti-malarial drug resistance. Malaria Journal. [Internet] 2009 Aug [cited 2010 Jun 19]; 253(8). Available from: http://www.malariajournal.com/content/8/1/253

7. Goldsmith RS. Obat-obat Antiprotozoa. Dalam: Farmakologi Dasar dan Klinik, Edisi VI. Ed. Bertram G. Katzung. Jakarta: EGC; 1994, 813-34. Indonesian.
8. World Health Organization. Guidelines for the Treatment of Malaria. 2nd edition. Geneva: The Organization; 2010.
9. Bousema JT, Gouagna LC, Drakeley CJ, Meutstege AM, Okech BA, Akim INJ, et al. Plasmodium falciparum gametocyte carriage in asymptomatic children in western Kenya. Malaria Journal. [Internet] 2004 Mar [cited 2009 Dec 3]; 18(3). Available from: http://www.malariajournal.com/content/3/1/18.
10. Oyakhirome S, Pötschke M, Schwarz NG, Dörnemann J, Laengin M, Salazar CO, et al. Artesunate – amodiaquine combination therapy for falciparum malaria in young Gabonese children. Malaria Journal. [Internet] 2007 Jun [cited 2010 Feb 18]; 29(6). Available from: http://www.malariajournal.com/content/6/1/29.
11. Zwang J, Olliaro P, Barennes H, Bonnet M, Brasseur P, Bukirwa H, et al. Efficacy of artesunate-amodiaquine for treating uncomplicated falciparum malaria in sub-Saharan Africa: a multi-centre analysis. Malaria Journal. [Internet] 2009 Aug [cited 2010 May 21]; 203(8). Available from: http://www.malariajournal.com/content/8/1/203
12. Ndiaye JL, Randrianarivelojosia M, Sagara I, Brasseur P, Ibrahima NI, Faye B, et al. Randomized, multicentre assessment of the efficacy and safety of ASAQ-a fixed-dose artesunate-amodiaquine combination therapy in the treatment of uncomplicated Plasmodium falciparum malaria. Malaria Journal. [Internet] 2009 Aug [cited 2010 May 4]; 25(8). Available from: http://www.malariajournal.com/content/8/1/125
13. IDA Foundation. ACT: Artemisinin–based Combination Therapy. [Internet] [cited 2010 Jul 6]. Available from: www.idafoundation.org.
14. Susiawan LD. Efikasi Artesdiaquine Pada Pengobatan Malaria Falciparum Tanpa Komplikasi Di Kabupaten Banjarnegara. [tesis]. Jogjakarta: Gadjah Mada University; 2006. Indonesian.
15. Adjei GO, Kurtzhals JAL, Rodrigues OP, Alifrangis M, Hoegberg LCG, Kitcher ED, et al. Amodiaquine-artesunate *vs* artemether-lumefantrine for uncomplicated malaria in Ghanaian children: a randomized efficacy and safety trial with one year follow-up. Malaria Journal. Internet] 2008 Jul [cited 2010 Jul 6]; 127(7). Available from: http://creativecommons.org/licenses/by/2.0.
16. Faye B, Offianan AT, Ndiaye JL, Tine RC, Toure W, Djoman K, et al. Efficacy and tolerability of artesunate-amodiaquine (Camoquin plus@) versus artemether-lumefantrine (Coartem@) against uncomplicated Plasmodium falciparum malaria: multisite trial in Senegal and Ivory Coast. Tropical Medicine and International Health. 2010; 15:608–13.

Corresponding author: Santoso
E-mail: santosbta@yahoo.co.id; santoso@litbang.depkes.go.id