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Artesunate Therapy for Severe Malaria: Mechanisms, Efficacy, and Cost - Effectiveness

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Abstract: ***This article comprehensively explores the mechanisms, efficacy, and cost - effectiveness of artesunate therapy as a treatment option for severe malaria. Severe malaria remains a significant global health challenge, with high mortality rates, especially among children. Artesunate, a derivative of artemisinin, has demonstrated remarkable efficacy in parasite and fever clearance times compared to quinine - based regimens. The article delves into the intricate mechanisms of action of artesunate, highlighting its interaction with Plasmodium parasites and the inhibition of key enzymes. Furthermore, it presents findings from various clinical trials, including comparisons with quinine treatments, emphasizing the shorter parasite clearance times and clinical benefits associated with artesunate. In addition, a comprehensive cost analysis reveals the cost - effectiveness of artesunate therapy, making it a promising choice for resource - limited settings. The study concludes that artesunate is not only a potent therapeutic option for severe malaria but also a cost - effective solution, warranting further exploration and implementation.***

Keywords: Artesunate, severe malaria, efficacy, cost - effectiveness, Plasmodium, treatment

1. Introduction

Malaria is one of the most dangerous diseases because it causes a lot of death in the world. Malaria is an infectious disease caused by parasites (protozoa) of the genus plasmodium, which can be transmitted by the bite of female anopheles mosquitoes containing Plasmodium in it. Plasmodium which is carried through the bite of a mosquito will live and multiply in human red blood cells (1) (2).

The cause of Malaria is the plasmodium parasite which is transmitted through the bite of a female anopheles mosquito. Known 5 (five) species, namely: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi. The last mentioned parasite has not been widely reported in Indonesia (2).

Malaria cases in 2017, an estimated 219 million cases of malaria occurred worldwide (95% confidence interval [CI]: 203–262 million), compared with 239 million cases in 2010 (95% CI: 219–285 million) and 217 million cases in 2016 (95% CI: 200–259 million). Although there were an estimated 20 million fewer malaria cases in 2017 than in 2010, data for the period 2015–2017 highlight that no significant progress in reducing global malaria cases was made in this timeframe. In 2017, there were an estimated 435.000 deaths from malaria globally, compared with 451.000 estimated deaths in 2016, and 607 000 in 2010. Children aged under 5 years are the most vulnerable group affected by malaria. In 2017, they accounted for 61% (266 000) of all malaria deaths worldwide (1).

The problem of malaria in Indonesia is mainly concentrated in the eastern part of Indonesia, namely, Papua, West Irian Jaya, Maluku, North Maluku and NTT. The most common parasites are Plasmodium vivax and Plasmodium falciparum. The endemic areas of Plasmodium falciparum are Papua, Kalimantan, North Sulawesi, Lombok and islands in Eastern Indonesia (2) .

Based on data the number of malaria cases that was very high in the world and Indonesia and the number of deaths caused by severe malaria, this makes the authors want to review related therapy of severe malaria, especially artesunate therapy as an artemisin derivative which serves as one of the options for treating severe malaria.

Epidemiology

Most malaria cases in 2017 were in the WHO African Region (200 million or 92%), followed by the WHO South - East Asia Region with 5% of the cases and the WHO Eastern Mediterranean Region with 2%. Fifteen countries in sub - Saharan Africa and India carried almost 80% of the global malaria burden. Five countries accounted for nearly half of all malaria cases worldwide: Nigeria (25%), Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%) (1).

The 10 highest burden countries in Africa reported increases in cases of malaria in 2017 compared with 2016. Of these, Nigeria, Madagascar and the Democratic Republic of the Congo had the highest estimated increases, all greater than half a million cases. In contrast, India reported 3 million fewer cases in the same period, a 24% decrease compared with 2016. Rwanda has noted estimated reductions in its malaria burden, with 430 000 fewer cases in 2017 than in 2016, and Ethiopia and Pakistan estimated decreases of over 240000 cases over the same period (1) (3).

The incidence rate of malaria declined globally between 2010 and 2017, from 72 to 59 cases per 1000 population at risk. Although this represents an 18% reduction over the period, the number of cases per 1000 population at risk has stood at 59 for the past 3 years. The WHO South - East Asia Region continued to see its incidence rate fall – from 17 cases of the disease per 1000 population at risk in 2010 to 7 in 2017 (a 59% decrease). All other WHO regions recorded either little progress or an increase in incidence rate. The WHO Region of the Americas recorded a rise, largely due to increases in malaria transmission in Brazil, Nicaragua and Venezuela (Bolivarian Republic of). In the WHO African

Region, the malaria incidence rate remained at 219 cases per 1000 population at risk for the second year in a row (1) (3).

Plasmodium falciparum is the most prevalent malaria parasite in the WHO African Region, accounting for 99.7% of estimated malaria cases in 2017, as well as in the WHO regions of South - East Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%). P. vivax is the predominant parasite in the WHO Region of the Americas, representing 74.1% of malaria cases (1) .

2. Mechanism

Artesunate (ART) is the semisynthetic derivative of artemisinin, developed from Artemisia annua L., which has been used in China as a traditional medicine for >2, 000 years

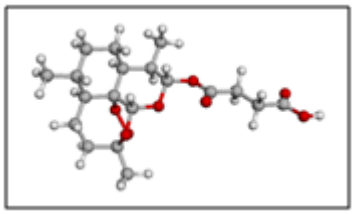

Figure 1: Structure Artesunate in 3D

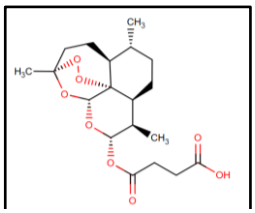

Figure 2: Structure Artesunate

The active moiety of artemisinin is a sesquiterpene lactone containing an endoperoxide bridge whose cleavage in the presence of ferrous iron in a Fenton - type reaction results in the generation of reactive oxygen species (ROS) such as hydroxyl radicals, superoxide anions, and carbon - centered free radicals. It has been suggested that free radicals are responsible for mediating the cytotoxic action of artemisinin derivatives in the parasites (4) .

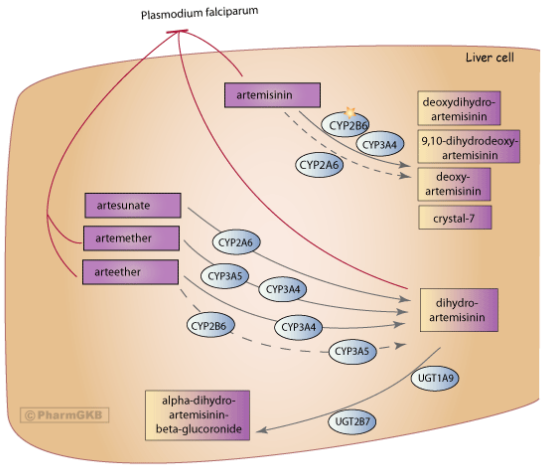

Figure 3: Genes involved in the pharmacokinetics of the antimalarial drugs artemisinin, arsenate, artemether, and arteether

Artemisinin has a poor bioavailability limiting its effectiveness. Therefore semisynthetic derivatives of artemisinin; artesunate, artemether, and arteether; have been developed. The mechanism of action of artemisin derivate was initially on the peroxide bridge, the artemisinin derivates drug was known to work specifically during the erythrocytic stage. The structure of the peroxide artemisinin bridge is broken by Fe2 + ions (iron ions II) to be reactive free radicals. These artemisin radicals then inhibit and modify various kinds of molecules in the parasite which cause the parasite to die. The intracellular iron II ion source is heme (an important component in hemoglobin), during its growth and multiplication in erythrocytes, the parasite eats and destroys up to 80% of host hemoglobin cells in food vacuoles. This will release Fe2 + - hem, oxidize it to Fe3 + - ematine, and then settle in food vacuola to form a Crystal pigment called hemozoin. The antimalarial effects of artemisin derivate are caused by the entry of this molecule into the parasitic food vacuole and then interact with Fe2 + - hem. Interactions produce free radicals that destroy the vital components of the parasite so that the parasite dies (4) (5) (6).

The new mechanism of action proves that Artemisin derivates works by inhibiting calcium - dependent ATPase enzyme (PfATP6). PfATP6 is similar to mammalian ATPase located in an intracellular compartment wrapped in a membrane called the endoplasmic reticulum. In this parasite the compartment is spread in the cytoplasm outside the parasitic food vacuole (4) (6)

Artemisin derivates encased in membrane bubbles is transported from erythrocytes into parasites. Once in the Artemisin parasite it is activated by free iron ions or other iron - dependent processes close to PfATP6 in the endoplasmic reticulum. The free radicals produced by artemisin derivates bind and inhibit PfATP6 irreversibly and specifically It is likely that free radicals modify the various sides of a single target and can also bind several other types of parasitic proteins. The function of ATPase in the pump complex system of Na + / K + ions is to regulate ion levels in the cell. The failure of the PfATP6 function results in a drastic decrease in potassium ions in cells that are very deadly to the parasite. Artesunate is a sodium artemisinin succinyl salt that dissolves well in water but is not stable in solution. While the artemeter is fat - soluble methyl ether artemisin. The artemeter is immediately absorbed and reaches peak levels in 2 - 3 hours. This drug undergoes demethylation in the liver to be dihydroartemisinin. The half - life of artemeter elimination is around 4 hours, while dihydroartemisinin is around 10 hours. Plasma protein bonds vary among species, in humans around 77% are bound to proteins (4) (5) .

3. Discussion

From 2006 to 2014 a total of 185 patients with severe malaria treated in 12 European countries wereincluded. Three patients died, resulting in a 28 - day survival rate of 98.4%. The majority of infections were acquired inWest Africa (109/185, 59%). The proportion of patients treated with intravenous artesunate increased from 27% in2006 to 60% in 2013. Altogether, 56 different combinations of

intravenous and oral drugs were used across 28 study centres. The risk of acute renal failure (36 vs 17% p = 0.04) or cerebral malaria (54 vs 20%, p = 0.001) was significantly higher in patients ≥60 years than in younger patients. Respiratory distress with the need for mechanical ventilation was significantly associated with the risk of death in the study population (13 vs 0%, p = 0.001). Post – artemisinin delayed haemolysis was reported in 19/70 (27%) patients treated with intravenous artesunate (3) .

Based on research conducted by Abdallah, et al in 2014, there was a need to investigate the treatment (artesunate and quinine) of severe malaria, as this will influence the outcome of morbidity and the mortality of the disease. The methodology was open randomized trial conducted at Kassala, Sudan. Patients with severe P. falciparum malaria were randomly assigned to either intravenous artesunate at 2.4 mg/kg at 0, 12, and 24 hours, then daily, or intravenous quinine at a 20 mg/kg loading dose, then 10 mg/kg three times a day. Fever and parasite clearance and coma resolution time were compared between the two groups. The results were the two groups (47 in each group) were well matched in the clinical and biochemical characteristics. Hypotension, convulsions, severe anemia, hypoglycemia, cerebral malaria, and jaundice were the predominant manifestations of severe malaria. The mean (SD) of the fever clearance (10.8 [5.5] vs.14.0 [8.1] hours, p = 0.028) and the parasite clearance time (16.5 [6.4] vs.21.7 [11.3] hours, p = 0.007) were significantly shorter in the artesunate - treated patients. In comatose patients, there was no difference between the two groups in coma resolution time. Following quinine infusion, ten patients developed tinnitus (p < 0.001), and four had hypoglycemia (p = 0.033). Tinnitus and hypoglycemia were not detected in the artesunate group. One patient in the artesunate group died (7) .

Based on research conducted by Byakika - Kibwika et al. in 2017 was Intravenous artesunate plus Artemisnin based Combination Therapy (ACT) or intravenous quinine plus ACT for treatment of severe malaria in Ugandan children. The methods was a randomized controlled clinical trial, we evaluated the 42 - day parasitological outcomes of severemalaria treatment with intravenous artesunate (AS) or intravenous quinine (QNN) followed by oral artemisinin based combination therapy (ACT) in children living in a high malaria transmission setting in Eastern Uganda. The results were we enrolled 300 participants and all were included in the intention to treat analysis. Baseline characteristics were similar across treatment arms. The median and interquartile range for number of days from baseline to parasite clearance was significantly lower among participants who received intravenous AS (2 (1–2) vs 3 (2–3), P < 0.001). Overall, 63.3% (178/281) of the participants had unadjusted parasitological treatment failure over the 42 – day follow - up period. Molecular genotyping to distinguish re - infection from recrudescence was performed in a sample of 127 of the 178 participants, of whom majority 93 (73.2%) had re - infection and 34 (26.8%) had recrudescence. The42 day risk of recrudescence did not differ with ACT administered. Adverse events were of mild to moderate severity and consistent with malaria symptoms (8) .

Based on research conducted by Maka et al. in 2015 was A randomized trial of the efficacy of artesunate and three quinine regimens in the treatment of severe malaria in children at the Ebolowa Regional Hospital, Cameroon. The methods was a randomized, open - label trial in children aged 3 months to 15 years, admitted in the hospital with severe malaria due to Plasmodium falciparum confirmed on microscopy after informed parental consent. Patients were randomized into four groups. Group 1 (ARTES) received parenteral artesunate at 2.4 mg/kg at H0, H12, H24 and then once daily; Group 2 (QLD) received a loading dose of quinine base at 16.6 mg/kg followed 8 hours later by an eight - hourly maintenance dose of 8.3 mg/kg quinine base; Group 3 (QNLD3) received 8.3 mg/kg quinine base every 8 hours; and, Group 4 (QNLD2) received 12.5 mg/kg quinine base every 12 h. All patients invariably received a minimum of 24 h parenteral treatment, then, oral drugs were prescribed. The endpoints were fever clearance time, time to sit unsupported, time to eat, parasite clearance time, and parasitaemia reduction rate at H24. Survival analysis was used to compare the outcomes. The results were One - hundred and sixteen patients completed the study: 29 in ARTES arm, 28 in QLD arm, 30 in QNLD3 arm, and 29 in QNLD2 arm. There was no major differences in baseline characteristics in the treatment groups. On analysis of endpoints, fever clearance time and parasite clearance time were significantly shorter for artesunate - treated patients than for quinine - treated patients. Parasitaemia reduction rate at H24 was also significantly higher for artesunate. Time to sit unsupported and time to eat were shorter with artesunate, but the difference was not statistically significant (9) .

Based on research conducted by Maka et al. in 2016 was Economic evaluation of artesunate and three quinine regimens in the treatment of severe malaria in children at the Ebolowa Regional Hospital-Cameroon: a cost analysis. The objective of the research was to conduct a cost - analysis of four different regimens used in the treatment from the perspective of the healthcare payer. The methods were An economic evaluation alongside a randomized comparative study was conducted in children aged 3 months to 15 years, admitted at the Ebolowa Regional Hospital with severe malaria due to Plasmodium falciparum. Patients were randomized to receive one of the four treatment alternatives. Group 1 (ARTES) received parenteral artesunate at 2.4 mg/kg at H0, H12, H24 and then once daily; Group 2 (QLD) received a loading dose of quinine base at 16.6 mg/kg followed 8 h later by an 8 - hourly maintenance dose of 8.3 mg/kg quinine base; Group 3 (QNLD3) received 8.3 mg/kg quinine base every 8 h, and Group 4 (QNLD2) received 12.5 mg/kg quinine base every 12 h. The main outcome measure for effectiveness of treatment was the parasite reduction rate. Based on a healthcare perspective, an evaluation of direct medical costs was done, including costs of anti - malarials, nursing care materials, adjuvant treatment, laboratory investigations, hospitalisation and professional fees. Guided by a cost minimalization approach, the relative costs of these treatment alternatives was compared and reported. The results were Overall cost was higher for ARTES group at $65.14 (95% CI $57.68–72.60) than for quinine groups ($52.49–$62.40), but the difference was not statistically significant. Cost of the anti - malarial drug was significantly

higher for artesunate - treated patients than for quinine - treated patients, whereas cost of hospitalization was significantly lower for artesunate - treated patients than for quinine - treated patients. Incremental analysis of ARTES against QLD as a baseline resulted in an ICER of $46.8/PRR24 and suggests ARTES as the most cost effective of all four treatment options (10) .

Based on several research journals related to the use of artesunate in severe malaria above, in my opinion the use of Artesunat is an effective choice of treatment for severe malaria compared to quinine, both in term of parasite and fever clearance time, in the age of children and adults, and in terms of cost effectiveness.

4. Conclusion

In summary, the research discussed in this article underscores the pivotal role of artesunate in treating severe malaria. Through its intricate mechanisms of action, including its interaction with Plasmodium parasites and inhibition of essential enzymes, artesunate has proven to be highly effective in rapidly clearing parasites and reducing fever. The clinical trials presented demonstrate its superiority over quinine - based treatments in terms of both parasite clearance times and clinical outcomes. Moreover, the economic evaluation reveals that artesunate is not only efficacious but also cost - effective, making it a viable solution for resource - constrained healthcare systems. As the fight against malaria continues, artesunate emerges as a potent and practical option for tackling the severe manifestations of this disease, contributing to improved patient outcomes and reduced healthcare burdens.

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