Artesunate versus Quinine in the Treatment of Severe *Plasmodium falciparum* Malaria at North Eastern of Democratic Republic of Congo: Parasites and Fever Clearance

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**Abstract**

Severe malaria is one of the leading causes of death in sub-Saharan African countries and Artesunate is the first-line choice recommended treatment by the World Health Organization. The objective of this study was to identify biological and clinical advantages of Artesunate compared to Quinine in the treatment of severe malaria in children. This study was a randomized and analytical study focused on children admitted to Pediatric Hospital Center Village of Kisangani with severe *falciparum* malaria, from January 1, 2015 to December 31, 2017. We assigned individuals children intravenous Artesunate 2.4 mg/kg given as a bolus (n=34) at 0, 12, 24 hours and then daily or Quinine 20 mg/kg infused in 5 or 10% Dextrose over 4 hours than 10 mg/kg infused every 8 hours (n=83). During our study period, a total of 117 children were included in the study, 34 were treated with Artesunate while 83 were treated with Quinine. The higher malaria parasites clearance average 1063174 Parasites/µL (971 Parasites/µL - 1563 400 Parasites/µL) concerned the preschool age. The malaria parasites clearance on 12 hours after administration of Artesunate was similar (79.1%) compared with 79.1% clearance obtained by using quinine. The fever clearance of children treated with Artesunate and Quinine was higher in the Artesunate group (91.2%) than in the Quinine group (88%) on 12 hours with significant statistic difference. This study concluded that Artesunate and Quinine present a similar clinic and biologic efficiency.

**Keywords:** Efficiency; Malaria; Antipaludic

**Introduction**

Severe malaria is one of the medical emergencies in endemic countries where, if it’s not treated; results in 100% mortality [1]. Malaria is a major morbidity and mortality in the world [2]. In 2016 approximately 1.2 billion people in the world were exposed at high-risk malaria; 216 million cases of malaria globally estimated; 445 000 deaths from malaria globally estimated; 446 000 deaths from malaria annually estimated; 1063174 Parasites/µL (971 Parasites/µL - 1563 400 Parasites/µL) in children intravenous Artesunate 2.4 mg/kg given as a bolus (n=34) at 0, 12, 24 hours and then daily or Quinine 20 mg/kg infused in 5 or 10% Dextrose over 4 hours than 10 mg/kg infused every 8 hours (n=83). During our study period, a total of 117 children were included in the study, 34 were treated with Artesunate while 83 were treated with Quinine. The higher malaria parasites clearance average 1063174 Parasites/µL (971 Parasites/µL - 1563 400 Parasites/µL) concerned the preschool age. The malaria parasites clearance on 12 hours after administration of Artesunate was similar (79.1%) compared with 79.1% clearance obtained by using quinine. The fever clearance of children treated with Artesunate and Quinine was higher in the Artesunate group (91.2%) than in the Quinine group (88%) on 12 hours with significant statistic difference. This study concluded that Artesunate and Quinine present a similar clinic and biologic efficiency.

**Materials and Methods**

**Study area and duration**

This study was conducted from January 1, 2015 to December 31, 2017, at the Pediatric Hospital Center Village of Kisangani, located in the North-Eastern of Democratic Republic of Congo. This is a heavily malaria-infected area. The centre was chosen because it is the only pediatric health facility the highest referral centre and also has better Pediatric service in the state (Figure 1).

**Participants:** Patients were included in the study were older than 6 months to 15 years presenting with one or more general danger signs of severe or complicated malaria based on the WHO criteria of severe malaria [16] and had a positive rapid diagnostic test (RDT) for *Plasmodium falciparum* (SD Biotine Malaria Antigen Pf/ Pan Standard Diagnostic) and positive Giemsa-Stained thick blood smear on admission. The eligible patients were randomly assigned to treatment with either intravenous Artesunate or Quinine. The first group of children (n=34) received 2.4 mg body weight of intravenous Artesunate given at H0, H12, H24.
The second group children (n=83) received three doses of Quinine infusion 20 mg/kg body weight over 4 hours every 8 hours than 10 mg/kg body weight every 8 hours. Quinine regimes were diluted in 10 ml/kg body weight of 5% or 10% dextrose. Oral antimalarial Artemether- Lumefantrine was prescribed for 3 days to complete the Artesunate treatment and oral Quinine at 10 mg/kg three times a day for 5 days to complete Quinine parenteral treatment.

Patients were excluded if they had a known serious adverse reaction to Quinine and for Artemisinin derivatives; patient without any manifestations of severe malaria; patients with severe malnutrition; children below 6 months and those above 15 years were not included.

Variables: The clinical outcome variables were fever clearance time from the onset of treatment until normalization temperature down to 37.5°C. The body temperature was taken to the electronic thermometer in respecting carefully the procedure of taking pediatric temperature [17]. The biological outcome variables were parasite clearance time from the onset of treatment to the time of the first of two negatives blood smears.

Parasitological methods: Thick and thin films were prepared and stained with 10% Giemsa and the parasite counts were obtained by counting the number of asexual parasites per 200 leukocytes, assuming a leukocytes count of 8000 leukocytes/µL or thick films per 1000 red blood cells for thin films. Blood films were considered negative if no parasites were detected in 100 oil immersion fields of a thick blood film. At presentation, 5 ml of venous blood samples were taken for a completed blood count. Was systematically précised the density parasite at Hour 0 (H0), Hour 12 (H12); Hour 24 (H24) and Hour 36 (H36) for every patient. The rapid test of paludism diagnostic used was on the bases of antigens of Plasmodium falciparum: Histidine Rich Protein II and PLDH (Lactate Dehydrogen), this test was systematically done to all patients from the admission [16-18].

Data collection and treatment

A survey form has helped us in the collection of different variables in this study which were the age, sex, clinical signs and biologic signs. The data obtained were analyzed with the SPSS 20.0 and Excel 2010 software.

Ethical considerations

Necessary clearance was obtained from the Village Pediatric Hospital Center authorities and Hospital ethics committee and written consent were also obtained from the children's caretakers. Moreover confidentiality was maintained during data collection and processing and procedures did not endanger or have adverse effects on the patients.

Data and statistical analysis

Data missing at random was dealt with by partial case-wise deletion. Statistical analysis was performed using SPSS statistics 20.0. Levels of parasitaemia were log-transformed before analysis. The significance of differences in prevalence was explored using Pearson’s Chi-square or Fisher's Exact test whereas differences in group means were assessed using student's tests. A difference giving a P-value<0.05 was considered statistically significant.

Results

During our study period, a total of 117 children were included in the study. 34 were treated with Artesunate while 83 were treated with Quinine. Males was 66 (56.4%) and females 51 (43.6%) without significant difference X²=3.918, Ddl=1; p>0.05.

It clearly appear (Figure 2) that high malaria parasites clearance average 106374 Parasites/µL (971 Parasites/µL-1563 400 Parasites/µL) concerned the preschool age. The malaria parasites clearance (Figure 3), on 12 hours after administrating of Artesunate was similar (79.1%) compared with 79.1% clearance obtained by using quinine, However, parasitaemia clearance was 99.7% with Artesunate and 99.8% with quinine one 36 hours without significant statistic difference (Figure 4).
In our study males was 66 (56.4) and females 51 (43.6) without significant difference $X^2=3.918$, Ddl=1; $p>0.05$ and boys presented higher malaria parasites clearance average of 864924 Parasites/µL (2961 Parasites/µL-1 563 400 Parasites/µL) (H0) compared to girls admitted who had a malaria parasites clearance average of 34705 Parasites/µL (971 Parasites/µL-528 700 Parasites/µL). Malaria parasites clearance decrease in a proportional way to 12, 24 and 36 hours after administration of doses of Artesunate and Quinine (Table 1).

The fever clearance of children treated with Artesunate and Quinine was higher in the Artesunate group (91.2%) than in the Quinine group (88%) on 12 hours with significant statistic difference $X^2=0.254$, Ddl=1; $p<0.05$ and was 100% in both drug group on 48 hours later.

<table>
<thead>
<tr>
<th>Hours</th>
<th>Artesunate</th>
<th>Quinine</th>
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<tbody>
<tr>
<td>&gt;37.5°C</td>
<td>&lt;=37.5°C</td>
<td>&gt;37.5°C</td>
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<tr>
<td>n=34</td>
<td>n=34</td>
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<td>H0</td>
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<td>31 (91.2)</td>
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<td>H24</td>
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<td>H36</td>
<td>01 (02.9)</td>
<td>33 (97.1)</td>
</tr>
<tr>
<td>H48</td>
<td>0 (0.00)</td>
<td>34 (100)</td>
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</table>

Table 1: Fever clearance.

The parasite clearance

Three independent processes contribute to the clearance of malaria parasites from the peripheral blood circulations: Host-defence mechanisms; anti-malarial drug as Artesunate or Quinine effects and sequestration [22,23]. Rapid malaria parasite clearance in our study (Figure 2), on 12 hours was similar (79.1%) both in Artesunate and Quinine groups. Parasite clearance time was also not found to be different between Artesunate and Quinine in the treatment of severe Plasmodium falciparum malaria in children. Eltahir et al. was found the same result in Central Sudan [24] however, Ndour et al. Observed rapid malaria parasite clearance with Artesunate in the treatment of severe malaria in Malian children [25]. Artemisinin derivatives and its derivatives are first-line treatment for severe and uncomplicated Plasmodium falciparum worldwide. Artemisinin and derivatives are typical schizontocides for all forms of Plasmodium; also they act on the gametocytes of some plasmodia by delaying their formation and destroying them in the blood. These two pharmacodynamics effects, which are not achieved by Quinine, are explained advantages of Artesunate to reduce rapidly malaria parasite density [26,27].

Distribution and evolution of malaria parasites density according to gender

In our study males was 66 (56.4%) and females 51(43.6%) without significant difference $X^2=3.918$, Ddl=1; $p>0.05$. Others authors get similar results [21,28]. According to gender and malaria parasites density, boys presented higher malaria parasites density average of...
864924 Parasites/µL (2961 Parasites/µL-1563400 Parasites/µL) at admission compared to girls admitted who had a malaria parasites density average of 34705 Parasites/µL (971 Parasites/µL-528 700 Parasites/µL). Parasites density decrease in a proportional way to 12, 24 and 36 hours after administration doses of Artesunate and Quinine both in male and females’ gender. Males and females differ in their ability to cope with infection, beyond physiological mechanisms, immune differences from an adaptive point of view in relation to sex-specific reproductive strategies; genotype and phenotype of pathogens. Generally, male traits exhibit large sensitivity to extrinsic changes than female [1,2].

Fever clearance

Artesunate is more effective than Quinine in term of fever clearance in the treatment of Plasmodium falciparum malaria in the North-Eastern of Democratic Republic of Congo. In Artesunate group fever clearance was observed in (91.2%) than in the Quinine group (88.0%) on 12 hours after treatment with significant statistic difference X2=0.254, Ddl=1 p<0.05 and the fever clearance were 100% in both drug groups on 48 hours later. Tajeldin M et al, get a similar result in Sudan at Kassala Hospital [29].

Conclusion

The current study showed that Artesunate and Quinine are comparable alternatives in the treatment of severe malaria in children. Artesunate is as effective as Quinine in terms of parasite clearance in the North-Eastern of DRC. The fever clearance of children treated with Artesunate and Quinine is higher in the Artesunate group (91.2%) than in the Quinine group (88%) on 12 hours with significant statistic difference X2=0.254, Ddl=1 p<0.05. However, we recommend permanent surveillance of malaria parasite charge at look different molecules of Artesunate proposed on market, also the observance of individual and collective prophylactic measures mainly at the children in preschool age.

Competing Interests

The authors declare that they have no competing interests.

Authors’ Contributions

Ngbonda NG conceived the study and all authors participated to collect the data, performed the statistical analysis; wrote the draft of the paper and were involved in critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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