Open Access Library Journal
2024, Volume 11, e10938
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Critical Analysis of the Literature Comparing Artemisinin-Based Combination Therapy and Quinine Treatments for Uncomplicated Malaria in Pregnancy

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How to cite this paper: Nsonizau, D.M.P., Kouzitissa, D.K., Wasadidi, N., Mazoba, T.K. and Damien, M.K.-M. (2024) Critical Analysis of the Literature Comparing Artemisinin-Based Combination Therapy and Quinine Treatments for Uncomplicated Malaria in Pregnancy. *Open Access Library Journal*, **11**: e10938.
https://doi.org/10.4236/oalib.1110938

Received: October 30, 2023
Accepted: January 9, 2024
Published: January 12, 2024

Abstract

In areas of high *P. falciparum* resistance, artemisinin derivatives and quinine are recommended as effective antimalarial drugs. In four randomized clinical trials, artemisinin- and quinine-based treatments (Quinine versus Artesunate-Atovaquone-Preguanil; Quinine versus Artesunate-Mefloquine; Quinine-Clindamycin versus Artesunate, Quinine versus Artemether-Lumefantrine) were compared to determine which regimen was more effective in treating uncomplicated malaria in pregnant women. It was not possible to make this choice as artemisinin derivatives in combination were compared with quinine alone and vice versa, as the WHO recommends dual therapy for the treatment of uncomplicated malaria in pregnant women. All regimens have been shown to be effective, with good tolerability and compliance, and less side-effects for artemisinin derivatives, and poor compliance and observance, as well as greater side-effects, for quinine. Balanced comparative studies will be useful in the future to settle this question.

Subject Areas

Clinical Medicine

Keywords

Artemisinin, Quinine, Comparison, Efficacy, Malaria, Pregnancy

1. Introduction

Malaria is a common disease in sub-Saharan Africa. In 90% of cases, it is caused by *Plasmodium falciparum* (Pf). This is the most formidable parasitic agent. It is responsible for the complicated form of malaria in pregnant women, and has also developed a high level of resistance to conventional antimalarial drugs in our region [1] [2] [3]. In our country, the Democratic Republic of Congo (DR Congo), the vast majority of malaria cases (around 98%) are caused by Pf. Malaria infection caused by other plasmodial species is exceptional [1] [4]. Pregnant woman runs a very high risk of contracting malaria and developing serious complications, as a result of their reduced immunity during pregnancy. Malaria during pregnancy is associated with an increased risk of maternal anemia, spontaneous abortion, prematurity, low birth weight and maternal-fetal mortality. Around 25 to 30 million pregnant women each year are exposed to this risk [1] [5]. Despite the emergence of Pf chemoresistance to conventional antimalarial drugs, artemisinin derivatives and quinine have remained effective [6]. Moreover, it has been observed that these molecules not only bring about a faster cure, but also prevent or delay the emergence of multidrug-resistant plasmodial strains [1] [3]. Quinine, which has been in use for 400 years since its efficacy was first demonstrated, retains its effectiveness to this day. However, its continued use is challenged by poor tolerance, poor compliance with complex dosage regimens and a growing risk of therapeutic failures [7].

The World Health Organization (WHO), to reinforce the efficacy of these rare and still effective antimalarial drugs, has opted for their use in dual therapy [3]. Thus, the DR Congo, through its National Malaria Control Program (PNLP), has chosen 4 groups of antimalarial drugs for oral treatment of uncomplicated malaria in pregnant women. These drugs are Artesunate-Amodiaquine (AS-AQ), Artemether-Lumefantrine (AL), Artesunate-Pyronaridine (AP) and Quinine-Clindamycin (QC) [1] [4]. However, for reasons of use's ease and compliance with the short duration of treatment, prescribers seem to prefer artemisinin-based combination therapy to quinine [8] [9].

In DR Congo, anti-malarial drugs are distributed free of charge to pregnant women during the prenatal visits. This free distribution of anti-malarial drugs is quite often confronted with supply shortages, particularly for artemisinin-based combination therapies (ACTs) [4] [10]. Thus, when the latter molecules are unavailable, quinine becomes the antimalarial drug of choice. Based on the available literature, this review sets out to establish a treatment strategy with a safer, more effective therapy, by determining which of artemisinin-based and quinine treatments would be more effective in treating uncomplicated malaria in pregnant women.

2. Methods

Using the PubMed, Cochrane, Medline, Google scholar and PMC Free databases, we searched between July and August 2023, without limitation of publication year or language, for available articles from interventional studies using artemi-

sinin and quinine derivatives to treat non severe malaria in pregnant women. In the process, we combined 4 main terms: artémisinine, quinine, efficacity, pregnancy with synonyms for artémisinine such as ACT, artemether. Eligible studies were selected on the basis of the following criteria: randomized clinical trial (RCT) in pregnant women evaluating the efficacy of artemisinin- and quinine-based antimalarials in the treatment of uncomplicated Pf malaria.

This research generated a total of 43 studies. After application of the criteria listed above, only 3 articles from Asia (Thailand) and 1 article from Africa (Uganda) were retained to support this review comparing the efficacy of artemisinin- and quinine-based treatments for uncomplicated malaria in pregnant women. Figure 1 provides information on study selection flow.

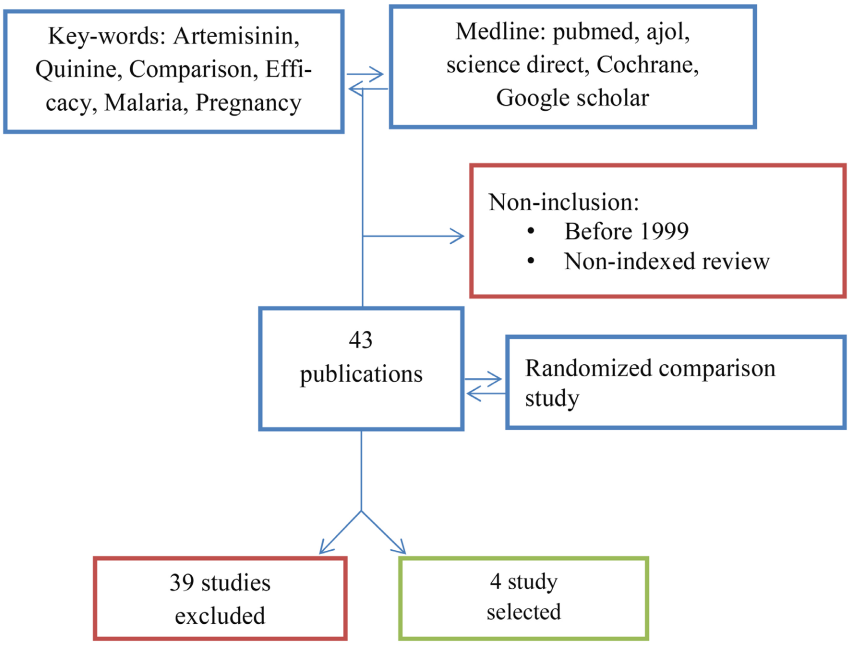

Figure 1. Chart of study selection flow.

3. Results

The summary of the critical analysis of the literature comparing artemisinin-based combination therapy and quinine treatments for uncomplicated malaria in pregnancy is shown in Table 1.

Table 1. Summary of the critical analysis of the literature comparing artemisinin-based combination therapy and quinine treatments for uncomplicated malaria in pregnancy.

Authors	Nature of study	Year	Sample size	Judgement criteria	Superiority	Dose	Duration
Rosa Mc Gready *et al.*	Randomized	2005	n = 41 (Q7) n = 39 (AAP3)	-	AAP3	Artesunate 4 mg/Kg/day, Atovaquone 20 mg/Kg/day, Proguanil 8 mg/Kg/day	3 days

Continued

Rosa Mc Gready *et al.*	Randomized	2000	n = 65 (MAS3) n = 41 (Q7)	cure rate on day 42, confirmed by PCR	MAS3	mefloquine 25 mg base/Kg (Total Dose) Artesunate 4 mg/Kg daily	3 days
Rosa Mc Gready *et al.*	Randomized	2001 (1997-2000)	n = 65 (QC7) n = 64 (A7)	cure rate on day 42, confirmed by PCR	None	Quinine (10 mg salt/Kg every 8 hours)/Clindamycin (5 mg/Kg every 8 hours) *versus* Artesunate 2 mg/Kg	7 days *versus* 7 days
Pola *et al.*	Randomized	2010	n = 138 (AL) n = 125 (Q)	cure rate on day 42, confirmed by PCR with a non-inferiority margin, a difference in cure rate of 5%	None	-	-

AAP3: Artesunate-Atovaquone-Proguanil in tritherapy; MAS3: mefloquine-Artesunate in biotherapy; AL: artemether-lumefantrine.

3.1. A Randomized Comparison of Artesunate-Atovaquone-Proguanil versus Quinine in Treatment for Uncomplicated Falciparum Malaria during Pregnancy

Published in 2005 by Rosa Mc Gready *et al.*, [11], this study was carried out between December 2001 and July 2003 on the western border of Thailand. It was an open randomized clinical trial on a global sample of 81 pregnant women presenting with the first episodes of uncomplicated multidrug-resistant Pf malaria in the second and third trimesters of pregnancy. Of these, 42 pregnant women were given a supervised quinine salt regimen (10 mg salt/Kg every 8 hours) for 7 days (SQ7), while the remaining 39 were given the artesunate-Atovaquone-Proguanil regimen (Artesunate 4 mg/Kg per day, Atovaquone 20 mg/Kg per day, Proguanil 8 mg/Kg per day) for 3 days (AAP3).

Fever, parasite clearance and duration of anemia were significantly better with AAP3; the treatment failure rate was seven times lower (5% [2/39] vs. 37% [15/41]; relative risk, 7.1 [95% confidence interval, 1.7 - 29.2]; p = 0.001). There were no significant differences in birth weight, duration of pregnancy or rates of congenital anomalies in neonates, or in growth and development parameters in infants followed up for 1 year. AAP3 is a well-tolerated, effective, convenient but costly treatment for multidrug-resistant falciparum malaria in the second or third trimester of pregnancy.

3.2. Comparison of Mefloquin-Artesunate versus Quinine in the Treatment of Multidrug-Resistant Falciparum Malaria in Pregnancy

An article, written by Rosa Mc Gready *et al.* [12], published in 2000, was an

open-label randomized controlled trial of supervised quinine (10 mg salt/Kg every 8 hours) for 7 days (Q7) versus mefloquine 25 mg base/Kg (Total Dose) plus Artesunate 4 mg/Kg daily for 3 days (MAS3). The study was conducted in Thailand (Asia) from 1995 to 1997 in 108 women with uncomplicated Pf malaria in the second and third trimesters of pregnancy.

Of the 108 pregnant women, 65 were treated with the MAS3 regimen and 41 with the Q7 regimen. The primary endpoint was the PCR-confirmed cure rate at day 42.

The 2 treatments were generally effective, but MAS3 was more effective than the Q7 regimen: cure rates at day 63 were 98.2% (95% CI 94.7 - 100) (n = 65) and 67.0% (95% CI 43.3 - 90.8) (n = 41) for Q7, P = 0.001. The MAS3 regimen was also associated with less gametocyte carriage; the average person-gametocyte-weeks for MAS3 was 2.3 (95% CI 0 - 11) and for Q7 was 46.9 (95% CI 26 - 78) per 1000 person-weeks, respectively (P < 0.001).

3.3. Comparison of Quinine-Clindamycin versus Artesunate in the Treatment of Falciparum Malaria in Pregnancy

This study, written by Rosa Mc Gready *et al.* [13], it was a randomized trial opened carried out in Thailand (Asia) between 1997 and 2000 with a sample of 129 pregnant women suffering from uncomplicated Pf malaria in the second and third trimesters of pregnancy. A total sample of 129 pregnant women with uncomplicated Pf malaria in the second and third trimesters of pregnancy was examined. The sample was divided into 2 cohorts: 65 women treated with supervised quinine (10 mg salt/Kg every 8 hours) combined with clindamycin (5 mg/Kg every 8 hours) for 7 days (QC7) and 64 pregnant women treated with the Artesunate 2 mg/Kg daily regimen for 7 days (A7).

The primary endpoint was the PCR-confirmed cure rate at D42. Cure rates at D42 in the 2 groups, QC7 (n = 65) and A7 (n = 64) regimens, were similar, *i.e.* 100% efficacy in the 2 cohorts, confirmed by parasite genotyping. The A7 regimen was associated with less gametocyte carriage, with mean gametocyte-weeks for A7 of 3 (95% CI: 0 - 19) and for QC7 of 39 (95% CI: 21 - 66) per 1000 person-weeks; p < 0.01.

3.4. Efficacy and Safety of Artemether-Lumefantrine Compared with Quinine in Pregnant Women with Uncomplicated Malaria

Piola *et al.* [14] had published in 2010; the article is entitled "Efficacity and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated malaria": an open-label, randomized, non-inferiority trial. The study is a randomized, open-label trial conducted between October 2006 and May 2009 at the antenatal clinics of the Mbarara University Hospital of Science and Technology in Uganda, Africa. Three hundred and four pregnant women were randomly assigned by computer-generated sequence to receive either quinine hydrochloride or artemether-lumefantrine as treatment for uncomplicated

Pf malaria, and were followed weekly until delivery. The primary endpoint was: cure rate and PCR confirmation at D42, with a non-inferiority margin of 5% difference in cure rate. The 304 women in the initial sample were randomized into 2 groups of 152 women each. In the artemether-lumefantrine (AL) group, 16 patients were lost to follow-up and 25 were excluded from the analysis at D42. The AL cohort totaled 138 patients, while the quinine (Q) cohort comprised 125 patients. At D42, 137 (99.3%) of the 138 patients on AL and 122 (97.6%) of the 125 on quinine (Q) were cured, with a difference of 1.7% (lower 95% limit IC: 0 - 9). There were 290 adverse events in the Q group and 141 in the AL group. These results lead to the conclusion that: artemisinin derivatives (dual therapy) are not inferior to oral quinine (monotherapy) for the treatment of uncomplicated malaria "during pregnancy". They may be preferable based on safety and efficacy.

4. Discussion

4.1. Artesunate-Atovaquone-Proguanil (Combination of 3 Antimalarials) Was Compared to Quinine Monotherapy

Artesunate-Atovaquone-Proguanil (combination of 3 antimalarials) was compared to Quinine monotherapy (article 1); Quinine-Clindamycin (combination of 2 antimalarials) compared to artesunate monotherapy (article 3); Quinine (antimalarial monotherapy) compared with Artesunate-Mefloquine (combination of 2 antimalarials), article 2 and Quinine (antimalarial monotherapy) compared with Artemether-Lumefantrine (antimalarial dual therapy), (article 4).

4.2. Others Combinations

The 4 randomized clinical trials [8] were aimed at treating uncomplicated multi-resistant *plasmodium falciparum* malaria during pregnancy in the second and third trimesters. Artemisinin-based treatment lasted 3 days, while quinine-based treatment, both mono- and dual-therapy, lasted 7 days.

Referring to WHO guidelines [3], which advise combining antimalarial drugs for best results in the treatment of uncomplicated *Pf* malaria, we note that this rule was not followed to the letter in the 4 randomized clinical trials analyzed. This leaves us wanting more. The question of which of artemisinin- and quinine-based treatments would be most effective remains unresolved in this critical analysis. Better-structured future studies are needed to answer this question. However, despite the non-compliance with the combination of antimalarial drugs, the 4 randomized clinical trials based on artemisinin and quinine were effective. Some were effective with good compliance over 3 days of treatment (artemisinin derivatives), while others were also effective, but with poor compliance and adherence due to the excessively long duration of 7 days of treatment (quinine-based treatment). Adverse effects were observed in both artemisinin- and quinine-based treatments, but were more numerous with quinine. Of course, the continued use of quinine is threatened by poor tolerance and poor

compliance. Studies are urgently needed to determine the minimum dose of quinine needed to guarantee both efficacy and compliance.

5. Limitations of Study

As limitations, the articles selected were carried out practically by the same teams. These articles are over 10 years old.

6. Conclusion

This study shows that quinine monotherapy offers lower efficacy and tolerance than ACTs, while artesunate monotherapy offers better tolerance but lower efficacy than quinine-clindamycin. The need for studies comparing ACTs and quinine in dual therapy has emerged, as has the need to determine the minimum effective dose and improve compliance with quinine-based antimalarial treatment.

Contribution of Authors

Mbanzulu Pita Nsonizau D: Conception of the study project, manuscript writing. Kiozi Kouzitissa D: Bibliographical research, participation in writing the text, Text input. Nekwei Wasadidi H: Discussion of project as a whole, choice of key words. Mazoba Tacite Kpanya: Data analysis, author correspondence. Mamanisini Kiaku-Mbuta Damien: English translation of summary. All authors have read and approved the text.

Conflicts of Interest

The authors declare no conflicts of interest.

Disclosures

All authors confirmed having participated.

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