

Intravenous Artesunate Reduces Parasite Clearance Time, Duration of Intensive Care, and Hospital Treatment in Patients With Severe Malaria in Europe: The TropNet Severe Malaria Study

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Intravenous artesunate improves survival in severe malaria, but clinical trial data from nonendemic countries are scarce. The TropNet severe malaria database was analyzed to compare outcomes of artesunate vs quinine treatment. Artesunate reduced parasite clearance time and duration of intensive care unit and hospital treatment in European patients with imported severe malaria.

Keywords. severe malaria; artesunate; quinine; *Plasmodium falciparum*; clinical study.

Intravenous artesunate has been shown to be a life-saving drug for patients with severe malaria in multicenter trials in Southeast Asia and Africa, improving survival compared with quinine by 34.7% and 22.5%, respectively. The survival benefit was most pronounced in hyperparasitemic patients [1, 2].

In nonendemic countries where nonimmune travelers with imported malaria may exhibit high parasite loads, introduction of intravenous artesunate into treatment practice has been slow because a formulation meeting standards of Good Manufacturing Practice (GMP) as well as prospective clinical safety data required for regulatory approval are not available. Intravenous artesunate is generally safe and well tolerated. A delayed self-limiting hemolytic reaction can occur several weeks after treatment, making follow-up examinations necessary [3–5].

Given the documented life-saving effect of artesunate in endemic countries, controlled clinical trials to confirm better survival for patients in nonendemic countries are no longer justified. Moreover, limited patient numbers and low case fatality of patients treated under intensive care standards in industrialized countries curtail their feasibility. Observational studies are therefore the only source of information on artesunate in this patient population.

The European Network for Tropical Medicine and Travel Health (TropNet) has conducted an observational multicenter study over 9 years (2006–2014) to monitor treatment practices and outcomes of severe malaria treatment across 12 European countries. For this brief report, data from study patients treated with intravenous artesunate or intravenous quinine were analyzed to compare clinical outcomes such as parasite clearance,

treatment duration in hospital (particularly in the intensive care unit [ICU]), and survival.

METHODS

All patients with confirmed severe *Plasmodium falciparum* malaria according to the 2006 World Health Organization criteria [6] treated at one of the 28 participating TropNet centers between 2006 and 2014 were eligible for inclusion. The treatment remained the responsibility of the treating physician. Demographic, travel, clinical, laboratory, and treatment data were collected retrospectively from clinical records at the treatment center, pseudonymized, and reported using an electronic case report form.

The primary objective of this analysis was to analyze differences among patients treated with intravenous artesunate vs intravenous quinine with regard to survival, duration of ICU and inpatient treatment, and 99% and complete parasite clearance time. The Mann–Whitney *U* test at a 2-sided significance level of $\alpha = .05$ was used for comparative analysis. Data are displayed as median (interquartile range). To further assess the association between treatment with artesunate and ICU treatment time, multiple regression analysis with backward elimination ($P < .05$) was performed, with duration of ICU treatment as a dependent variable including (1) known risk factors for longer treatment (age, renal failure, respiratory failure, coma, and the number of comorbidities); (2) variables with statistically significant association with ICU treatment time in univariate analysis; and (3) the year of treatment. The selected variables were used as independent variables in multifactor analysis of variance (ANOVA) of ICU treatment time using the *F* test.

Statistical analysis was performed using JMP software version 7.0 (SAS Institute Inc, Cary, North Carolina). The study was approved by the Ethics Committee of Charité University Hospital Berlin. Ethical clearance for transfer of pseudonymized patient data was sought at participating TropNet centers according to local regulations.

RESULTS

The TropNet severe malaria study comprises 185 cases with severe falciparum malaria. The majority of patients were European tourists (106/185 [57%]), followed by patients with a history of migration (68/185 [37%]) and tourists from endemic areas (11/185 [6%]). The overall 28-day survival rate was 98.4% (182/185). Of 3 patients who died, 2 had been treated with intravenous quinine and 1 with quinine and artesunate simultaneously. All deaths occurred within the first 4 days after admission. Due to the low number of deaths, a survival analysis was not performed. Adverse events in patients treated with quinine consisted of transient cinchonism and hypoglycemia and

were predominantly mild. In 70 patients who received intravenous artesunate, 19 episodes of delayed hemolysis were observed, a known adverse drug reaction [3–5].

For the following analysis of treatment duration and parasite clearance, patients who died ($n = 3$), who underwent erythrocyte apheresis ($n = 5$), who were treated with artesunate and quinine simultaneously ($n = 7$, 1 of whom also underwent apheresis and 1 of whom died), or who received oral antimalarial combination therapies as first-line treatment ($n = 21$) were excluded. Thereafter, 151 patients were available for comparative analysis, of whom 60 received intravenous artesunate and 91 received intravenous quinine as main first-line treatment.

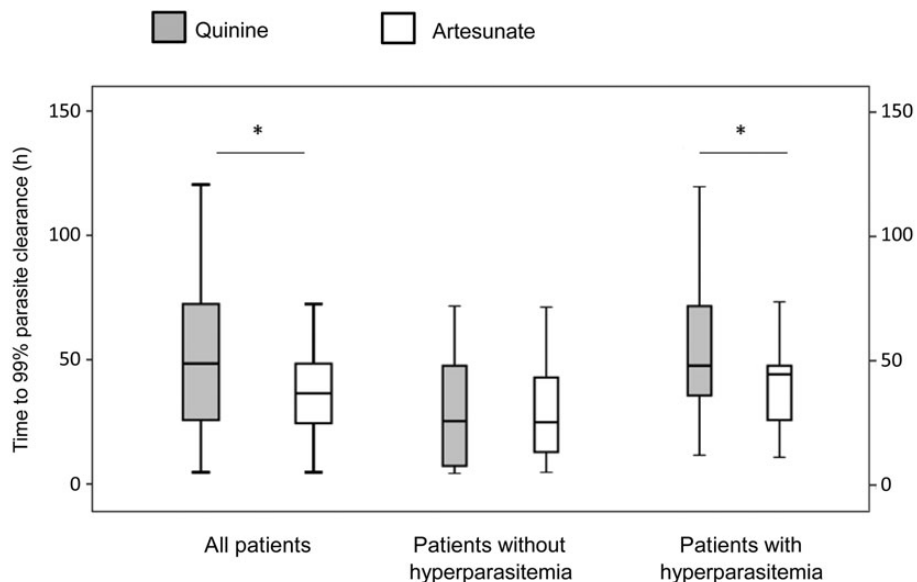
Patients treated with either artesunate or quinine showed similar baseline characteristics such as median age (44 vs 40 years; $P = .16$), median baseline parasitemia (5% vs 6%; $P = .4$), median number of criteria for severe disease (2 in both groups; $P = .3$), median proportion of patients with comorbidities (32% vs 39%; $P = .3$), median proportion of patients with European origin (60% vs 55%), history of migration (34% vs 39%), and visitors from endemic countries (6% in both groups; overall $\chi^2 = 0.62$, $P = .73$), respectively.

Patients treated with intravenous artesunate exhibited a faster 99% parasite clearance time (median, 36 vs 48 hours; $P = .02$, $n = 100$) and a faster complete parasite clearance time (median, 72 hours vs 96 hours; $P = .005$, $n = 84$) compared with patients treated with intravenous quinine.

Similarly, median length of ICU treatment (2 vs 3 days; $P < .05$, $n = 117$) and median length of hospital inpatient treatment (6 vs 7 days; $P < .01$, $n = 151$) were shorter for patients treated with artesunate compared to patients treated with quinine (Figure 1). Absence of signs of cerebral malaria (median 2 vs 4 days; $P < .0001$), absence of renal failure (median, 2 vs 4 days; $P < .0001$), and absence of respiratory failure (median, 2 vs 6 days; $P < .0001$) were equally associated with a shorter ICU treatment.

In multiple regression analysis, the same 4 variables were selected in the final model and showed independent statistically significant association with shorter length of stay at ICU in multifactor ANOVA ($F = 16.0$, $df = 4$, $P < .0001$): treatment with artesunate ($F = 6.1$, $P = .01$) compared with quinine, absence of cerebral malaria ($F = 4.33$, $P = .04$), absence of renal failure ($F = 20.0$, $P < .0001$), and absence of respiratory failure ($F = 12.2$, $P < .001$). Age, sex, citizenship (European/history of migration/visitor from endemic area), year of presentation, hyperparasitemia, presence of comorbidities, and multiplicity of criteria for severe malaria did not show significant association with duration of ICU treatment.

Subgroup analysis revealed that faster parasite clearance and shorter length of ICU and inpatient treatment for artesunate was only evident in patients presenting with hyperparasitemia $\geq 5\%$ (108/151), whereas in patients without



| | All patients | | | Patients without hyperparasitemia (parasitemia < 5%) | | | Patients with hyperparasitemia (parasitemia ≥ 5%) | | |
|--------------------------------------------------------|--------------|------------|---------------------------|----------------------------------------------------------------|------------|----------------|-------------------------------------------------------------|------------|-----------------------|
| | Quinine | Artesunate | <i>P</i> value | Quinine | Artesunate | <i>P</i> value | Quinine | Artesunate | <i>P</i> value |
| Median time to 99% parasite clearance in hours (IQR) | 48 (29–72) | 36 (24–48) | .02 n = 100 | 24 (6–48) | 24 (12–45) | .9 n = 23 | 48 (36–72) | 45 (24–48) | .02 n = 77 |
| Median time to total parasite clearance in hours (IQR) | 96 (72–120) | 72 (48–74) | .005 n = 84 | 56 (36–144) | 54 (42–72) | .7 n = 21 | 96 (72–120) | 72 (60–92) | .004 n = 63 |
| Median length of stay at ICU in days (IQR) | 3 (1–5) | 2 (1–4) | <.05 n = 117 | 2 (1–5) | 3 (1–5) | .5 n = 34 | 3 (2–5) | 2 (1–3) | .003 n = 83 |
| Median length of stay in hospital in days (IQR) | 7 (6–10) | 6 (4–8) | <.01 n = 150 | 7 (6–9) | 6 (4–9) | .25 n = 43 | 7 (6–10) | 6 (4–9) | .01 n = 107 |

Figure 1. Median time to 99% parasite clearance, median time to total parasite clearance, median length of stay in intensive care unit (ICU), and median length of stay in hospital in patients treated with either intravenous artesunate or intravenous quinine. Hyperparasitemia is defined as parasitemia $\geq 5\%$. *Statistically significant difference. Abbreviation: IQR, interquartile range.

hyperparasitemia (43/151), there was no statistically significant difference (Figure 1).

DISCUSSION

This TropNet study is the largest multicenter study outside endemic areas comparing intravenous quinine vs intravenous artesunate for the treatment of severe malaria. Only 1 single-center study from the United Kingdom reported similar data in a limited number of patients with artesunate treatment [7].

As an overwhelming benefit of artesunate treatment has already been shown in principle, controlled clinical trials are no longer justified. Regulatory approval in industrialized countries is therefore delayed, preventing patients from having regular access to the best treatment available. A GMP-compliant formulation is only available in the United States from the Centers for Disease Control and Prevention [8]. The present data may help to improve clinical decision making in nonendemic countries and provide useful information for regulatory authorities.

As observed in endemic countries, intravenous artesunate cleared high parasitemias in our patient population more rapidly than intravenous quinine. This is of particular relevance for nonimmune patients who carry a comparatively high risk of hyperparasitemia. Knowledge from malaria-endemic settings shows that survival benefit was most pronounced in hyperparasitemic patients [1, 2].

Our data demonstrate that intravenous artesunate reduces duration of ICU and hospital treatment. Both factors have relevant influence on outcome as many patients with severe malaria die from nosocomial complications rather than from malaria itself [9]. This applies in particular to patients in ICU treatment with respiratory failure (including comatose patients with cerebral malaria on mechanical ventilation), in whom the risk for ventilator-associated infections increases over time [10].

We did not find an association of sex, age, or comorbidities with duration of ICU treatment despite age being a known risk factor for increased mortality from severe malaria [11]. Shorter duration of ICU and hospital treatment was only found for patients with high parasitemia, underlining that rapid parasite clearance is likely to be a decisive factor for the clinical and overall benefit of artesunate.

This is a retrospective observational study on a heterogeneous patient population with inherent limitations. In particular, biases in physicians' judgment and patient selection may have occurred. The proportion of nonhyperparasitemic patients in our population was comparatively small. The absence of statistically significant different outcomes in these patients might therefore be caused by type II error. As postartemisinin delayed hemolysis was first described in the year 2011 [3], underreporting of this adverse reaction may have occurred in this retrospective study.

In conclusion, this analysis shows that the therapeutic benefit of artesunate to patients in nonendemic areas is beyond doubt. Faster parasite clearance is likely to be the relevant factor that reduces ICU treatment duration, hospital stay, and, therefore, the risk of nosocomial complications. Prospective collection of data—for example, in patient registries—should continue to improve the evidence base on the safety of artesunate in non-endemic countries.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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