DOI: https://doi.org/10.54393/pjhs.v5i11.1919

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Efficacy of Artesunate versus a Combination of Artesunate and Quinine Di-Hydrochloride Given Intravenously for the Treatment of Malaria; A Comparative Study

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ARTICLE INFO

Keywords:
Artesunate, Efficacy, Malaria, Quinine Di-Hydrochloride, Treatment

How to Cite:
Akbar, A., Jabeen, I., Kanwal, K., Ilyas, S., & Ahmad, S. (2024). Efficacy of Artesunate versus a Combination of Artesunate and Quinine Di-Hydrochloride Given Intravenously for the Treatment of Malaria; A Comparative Study: Efficacy of Artesunate and Quinine Di-Hydrochloride for the Treatment of Malaria. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.1919

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Received Date: 29th August, 2024
Acceptance Date: 18th November, 2024
Published Date: 30th November, 2024

ABSTRACT

In developing countries, malaria is still one of the leading causes of morbidity and mortality. **Objectives:** To evaluate the efficacy of intravenous artesunate alone versus intravenous combination of artesunate and quinine. **Methods:** This randomized control trial was conducted in the Pediatric Medicine Unit-2, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan. The inclusion criteria were children of either gender, aged 2-14 years and admitted to the emergency department with the diagnosis of severe malaria. Children were randomly allocated to two treatment groups of equal size. The intravenous artesunate group received artesunate administered intravenously for a maximum of 7 days. The intravenous combination of artesunate and quinine group received artesunate intravenously combined with quinine di-hydrochloride intravenously for a maximum of 7 days. they were employing the lottery method. The outcome was measured as the number of hours elapsed for an individual to become fever-free (temperature below 36.8°C). **Results:** In a total of 104 children with severe malaria. the mean duration required to become fever-free was 28.3 ± 5.4 hours in intravenous artesunate alone versus 26.5 ± 6.4 hours in intravenous combination of artesunate and quinine groups (p=0.1242). The most frequent treatment-related side effects were nausea, loss of appetite, hypoglycemia, diarrhea, and rash, noted in 21 (20.2%), 13 (12.5%), 11 (10.6%), 5 (4.8%), and 2 (1.9%) patients, respectively. **Conclusions:** It was concluded that intravenous artesunate and quinine together did not provide any additional benefit or synergistic effect over intravenous artesunate alone in treating severe malaria in children.

INTRODUCTION

In developing countries, malaria is still one of the leading causes of morbidity and mortality. According to the WHO, there were 247 million cases of malaria worldwide in 2021, resulting in 619,000 deaths [1]. Although many zones of the world have been declared malaria-free, countries like Pakistan, India, Sri Lanka, Afghanistan, and many countries in Africa are still struggling against the crippling disease and continue to be endemic malaria [2]. All age groups are indiscriminately affected, but children, like any other disease, lie among the most vulnerable owing to their low immunity, dependency on caretakers for preventive measures, and repeated exposure. About three out of every four malaria victims happen to be children [3]. In a systematic review by Khan *et al.*, pooled malaria prevalence in Pakistan was estimated to be 23.0%. Severe malaria can be caused by any of the plasmodium species, but most commonly by vivax and falciparum species, as these species abundantly exist in the Indo-Pak region [4]. Classic clinical presentation, a high index of suspicion, and rapidly available diagnostic techniques rarely impart a diagnostic challenge in malaria but effective and time management are the real areas of concern. Regarding management, where supportive treatment plays a crucial role in immediate resuscitation and resolution of vitals, specific treatment remains the cornerstone for limiting morbidity and mortality [5]. The treatment of severe malaria varies according to age, immunity status, and local susceptibility patterns. Currently, the WHO recommends artesunate as the drug of choice for the treatment of severe malaria [6]. A study done by Botta *et al.*, from Italy, reported that the

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efficacy of IV Artesunate (IVA) alone or in combination with IV quinine (IVQ) was 83.3% versus 47.0% (p=0.002) respectively, favouring IV artesunate alone [7]. The efficacy of this single drug as compared to the combined drug regimen in severe malaria remains questionable. Therefore, we intended to evaluate the efficacy of only IVA versus IVA+IVQ in the treatment of severe malaria in children. The findings of the study were thought to help know whether the two drugs, when given together, have considerable benefits over single-drug therapy when given for the same. This is the first research comparing two treatment regimens in severe malaria in Pakistan so the findings of this study may bring very important insights about the treatment and outcome-related aspects of severe malaria in children.

This study aims to evaluate the efficacy of IVA alone versus IVA in combination with IVQ in the treatment of severe malaria in children.

METHODS

This randomized controlled trial was conducted in the indoor settings of the Pediatric Medicine Unit-2, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan, from 16th May 2024 to 25th June 2024. Approval from the institute's ethical committee was obtained (Letter number: PM.U-II/0011/58). Considering the efficacy of IVA at 83.3% versus IVA plus IVQ at 47% in severe malaria [7], with a 95% confidence level and 97% power of the study, the sample size was calculated to be 104 (52 in each group). A simple random sampling technique was adopted. The inclusion criteria were children of either gender, aged 2-14 years and admitted to the emergency department with the diagnosis of severe malaria as defined by the WHO [6]. The exclusion criteria were patients with chronic kidney disease, chronic liver disease, immunosuppressive disorders, hematological disorders, malignancies, and congenital heart disease (as per medical history). Before taking informed and written consent from the parents or caregivers, the study objective and safety aspects related to this study were explained. This clinical trial (NCT06472258) was registered. At the time of enrollment, gender, age, residential address, and maternal educational status were noted. Mothers who could read and write, and went to any form of formal education were labelled as literate, or illiterate otherwise. Laboratory evaluation of the involvement of plasmodium species was performed using an immune-chromatographic test (ICT) malarial parasite antigen. Patients were randomly allocated to two treatment groups employing the lottery method. The IVA group (n=52) received IVA with a weight-appropriate dosage at 0, 12, 24, and 48 hours and continued 12 hours for a maximum duration of seven days, with each dose diluted in normal saline and given as an infusion. The IVA+IVQ group (n=52) received IVA with a weight-appropriate dose at 0, 12, 24, and 48 hours, combined with IVQ by weight, with a loading dose of 20mg/kg in a 10% dextrose infusion, followed by a 10mg/kg infusion every 8 hours for 2 days and every 12 hours onwards for a maximum of 7 days. All the patients were provided symptomatic supportive therapy as needed, along with the mentioned specific drugs. All the patients were followed for the resolution of fever. The primary outcome was measured as the number of hours elapsed for an individual to become fever-free (temperature below 36.8°C). During their stay, children were monitored and their parents/caregivers inquired about the common treatment-related side effects. All the study data were recorded on a pre-designed proforma. The data were analyzed through IBM SPSS Statistics, version 26.0. Qualitative data like gender, age groups, residence, maternal education, plasmodium species, and treatment-related side effects were represented as frequency and percentages. Quantitative data like age and time to get fever-free were described as mean and standard deviation (SD). Comparison of categorical data in between study groups was done employing the chi-square test. Independent sample t-test was applied to compare quantitative data between study groups. For all statistical analyses, $p<0.05$ was taken as significant.

RESULTS

In a total of 104 children with severe malaria, 58 (55.8%) children were male. The mean age was 6.35 ± 3.61 years, ranging between 2-14 years. Plasmodium vivax was the most common plasmodium species, noted in 65 (62.5%) children. A comparison of characteristics of children is shown between both study groups and no significant differences was observed in terms of gender (p=0.6929), age (p=0.2748), residence (p=0.4201), maternal education (p=0.6759), and plasmodium species (p=0.5268).

Table 1: Comparison of Characteristics of Patients in Both Study Groups (n=104)

Characteristics		Groups		p-value
		IVA (n=52)	IVA + IVQ (n=52)	
Gender	Male	28 (53.8%)	30 (57.7%)	0.6929
	Female	24 (46.2%)	22 (42.3%)	
Age Groups (Years)	2-5	27 (51.9%)	21 (40.4%)	0.2748
	6-14	25 (48.1%)	31 (59.6%)	
Plasmodium Species	Vivax	32 (61.5%)	33 (63.5%)	0.5268
	Falciparum	14 (26.9%)	10 (19.2%)	
	Vivax and Falciparum	6 (11.5%)	9 (17.3%)	

The outcome was measured in the number of hours elapsed for an individual to become fever-free. The mean duration required to become fever-free was 28.3±5.4 hours versus 26.5±6.4 hours in IVA alone versus IVA plus IVQ groups, respectively, and the difference was found to be statistically insignificant (p=0.1242) (Figure 1).

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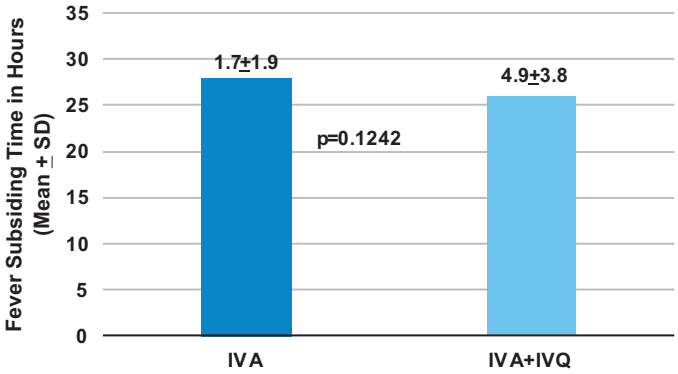

Figure 1: Fever Subsiding Time in Both Study Groups

The most frequent treatment-related side effects were nausea 21(20.2%), loss of appetite 13(12.5%), hypoglycemia 11(10.6%), diarrhea 5 (4.8%), and rash 2 (1.9%). Nausea was significantly associated with IVA alone group (p<0.01). Hypoglycemia was reported in 10.6%, and all these belonged to the combination group (p=0.01). Diarrhea was significantly associated with the combination group as all 4.8% who had diarrhea belonged to the combination group (p=0.0219). Frequency and comparison of treatment-related side effects in both study groups are shown. All 104 patients, whether receiving a single or combined drug regime, were successfully treated and discharged (Table 2).

Table 2: Frequency and Comparison of Treatment-Related Side Effects in Both Study Groups

Side effects	IVA	IVA + IVQ	p-value
Nausea (n=21)	19 (36.5%)	2 (3.8%)	2 (3.8%)
Loss of Appetite (n=21)	7 (13.5%)	6 (11.5%)	0.7668
Hypoglycemia (n=11)	-	11 (21.2%)	<0.01
Diarrhea (n=5)	-	5 (9.6%)	0.0219
Rash (n=2)	2 (3.8%)	-	<0.01

DISCUSSION

Malaria remains one of the leading causes of illness and death in Pakistan, while intense transmission occurs mainly in districts located in regions bordering Iran and Afghanistan, as well as the coastal belt in Sindh and Baluchistan provinces [8]. In the current study, 85.6% of children with severe malaria had involvement of either plasmodium vivax or falciparum and these findings are consistent with the recent trends as plasmodium vivax or falciparum are considered to be the most common-causing species of malaria in this region [9]. The ideal drug for the treatment of severe malaria remains a topic of interest, especially in endemic countries like Pakistan, where the susceptibility patterns continue to vary rapidly owing to emerging resistance due to multiple factors. Severe malaria in the pediatric age group remains one of the most commonly dealt with emergencies. Currently, WHO recommends intravenous artesunate for the treatment of severe malaria followed by artemether and quinine, respectively [10, 11]. However, the synergistic effect of giving combination drugs together in severe malaria is often questioned [12]. The present study fulfilled the desired purpose by answering the question. The outcome was measured in the number of hours elapsed for an individual to become fever-free. The mean duration required to become fever-free was 28.3 ± 5.4 hours versus 26.5 ± 6.4 hours in the intravenous artesunate group versus intravenous artesunate plus intravenous quinine group, respectively, and the difference was found to be statistically insignificant (p=0.1242). A similar study was conducted by Newton *et al.*, comparing parenteral artesunate alone with combined intravenous artesunate and intravenous quinine in the treatment of severe malaria. However, the study only enrolled the disease caused by plasmodium falciparum, while our study included both falciparum and vivax species leading to the disease. Nevertheless, the results of both studies supported each other and proved that there was no additional benefit to combining the two drugs and no synergistic effect was noted [13]. The combination of intravenous artesunate and intravenous quinine has been administered to severe malaria patients along the Thai-Myanmar border, where P. falciparum showed widespread resistance to artemisinin derivatives [14]. The authors suggested that adding intravenous quinine empirically to intravenous artesunate could be a precautionary measure in these cases. The WHO's latest malaria guidelines of July 2021 recommend the combined use of parenteral artesunate and quinine in full doses for treating severe malaria in regions with established artemisinin resistance [15]. Although combination therapy with intravenous artesunate plus intravenous quinine could be a last-resort option for patients from areas at risk of artemisinin resistance, further data on the combined use of these drugs would be valuable [16, 17]. In the present study, hypoglycemia was a dominant treatment-related side effect among children treated with intravenous artesunate plus intravenous quinine. Contemporary literature has highlighted a relatively higher incidence of hypoglycemia among cases treated with intravenous quinine when compared to those administered intravenous artesunate so caution is advised for regular monitoring among this set of children [18-20]. The current study had some limitations. Due to a lack of appropriate microscopy facilities, species confirmation was possible only through ICT malarial parasite antigen. Treatment-related side effects reported in this study were subjective complaints other than hypoglycemia which was confirmed through blood glucose level monitoring.

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CONCLUSIONS

It was concluded that intravenous artesunate and quinine together did not provide any additional benefit or synergistic effect over intravenous artesunate alone in the treatment of severe malaria in children. Being rapid in action and safe and cost-effective, intravenous artesunate alone outweighs the benefit of giving an intravenous combination of artesunate and quinine di-hydrochloride.

Authors Contribution

Conceptualization: AA
Methodology: AA, IJ, KK, SI, SA
Formal analysis: AA, IJ, KK, SI, SA
Writing review and editing: AA, IJ, KK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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