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Original Research Article

COMPARISON OF OUTCOME OF ARTESUNATE WITH QUININE IN CEREBRAL MALARIA; EXPERIENCE FROM A TERTIARY CARE HOSPITAL IN PESHAWAR

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Abstract *Malaria remains a tremendous health burden in tropical regions, causing up to 24.3 billion episodes of clinical illness and 0.86 million deaths in 2009, with annual death rates of up to 93% in severe malaria. This study aims to compare the outcome of artesunate with quinine in cerebral malaria. This Randomized Controlled Trial was conducted in the Department of Medicine, Lady Reading Hospital, Peshawar, from December 2021 to January 2023. This study was conducted on 102 patients with cerebral malaria aged 12 to 60 years of age of either gender. Patients were divided into two groups: group A received artesunate, while Group B received quinine for cerebral malaria. Outcome in terms of in-hospital mortality and mortality at follow-up was assessed between both groups. According to the in hospital treatment outcome, the mortality rate in group A (Artesunate) was 3 (5.9%) while 10 (19.6%) in group B (Quinine), the in hospital treatment outcome (mortality) was significantly lower in group A as compared to group B (P = 0.03). According to the outcome at follow-up, the mortality rate in group A was 4 (7.8%) while 12 (23.5%) in group B, the outcome (mortality) at follow-up was significantly lower in group A as compared to group B (P = 0.02). From our study, we conclude that the outcome in terms of in-hospital mortality was significantly lower in artesunate group as compared to quinine group (P = 0.03), and mortality at follow-up was also significantly lower in artesunate group as compared to quinine group (P = 0.02) in cerebral malaria.*

Keywords: Cerebral Malaria; Artesunate; Quinine; Comparison

Introduction

Malaria is a persistent and significant health concern in tropical regions, causing a substantial burden on public health. In 2009, it resulted in an alarming 24.3 billion episodes of clinical illness and claimed approximately 0.86 million lives (Aregawi et al., 2009). Furthermore, severe malaria has an alarming mortality rate of up to 93%. The incidence of malarial parasites in Pakistan was reported at 0.8 cases per 1000 population in 2006. However, this number likely underestimates the actual disease burden as public-sector diagnostic facilities cover only a fraction of the patient load, with the majority seeking treatment in the private sector (Kakar et al., 2010). The most common causative agent of malaria in the region is Plasmodium vivax, responsible for approximately 79% to 81% of malaria cases, as indicated by various studies (Yasinzai and Kakarsulemankhel, 2009). Notably, Plasmodium falciparum, another parasite species, is also rising, accounting for 20.3% of malaria cases in one study (Yasinzai and Kakarsulemankhel, 2013). Falciparum malaria is a particularly significant concern among Afghan refugees in the Khyber-Pakhtunkhwa region (Howard et al., 2011).

Severe malaria occurs when the infection with the P. falciparum parasite is complicated by serious organ failure or metabolic abnormalities. Cerebral malaria is a specific and especially critical form of severe malaria. Even with appropriate treatment, it can have a mortality rate as high as 20% (Aregawi et al., 2009). This highlights the urgency of addressing malaria, improving diagnosis and treatment, and increasing efforts to prevent and control the disease in tropical regions, focusing on Pakistan and its challenges in tackling this public health crisis.

Cerebral malaria, a severe and life-threatening complication of malaria caused by the Plasmodium falciparum parasite, demands effective treatment. Historically, quinine has been the primary drug used for this purpose. However, it presents some challenges, such as local toxicity after intramuscular injection, the inability for bolus intravenous injection, the need for thrice-daily administration through constant rate infusion, and the risk of serious

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side effects like hypoglycemia. A study reported a mortality rate of 22% in patients with severe falciparum malaria treated with quinine (Dondorp, 2005; Li and Weina, 2010).

In contrast, artesunate, another antimalarial medication, offers several advantages. It can be administered through intravenous injection and carries a lower risk of causing serious hypoglycemia. Additionally, treatment with artesunate is cost-effective (Lubell et al., 2009). A separate study revealed a significantly lower mortality rate of 3.03% in patients treated with artesunate for severe falciparum malaria (Eltahir et al., 2010). This study aims to compare the outcomes of artesunate and quinine in treating cerebral malaria within our population. Despite the advantages of artesunate, quinine remains the predominant drug used in severe malaria cases, including cerebral malaria, in many healthcare centers across Pakistan. This preference stems from the absence of local evidence demonstrating the superiority of artesunate over quinine in our specific population. If this study establishes the effectiveness of artesunate in treating cerebral malaria, it may lead to a shift in the standard treatment protocol. Artesunate could replace quinine as the routine treatment for cerebral malaria in Pakistan, potentially improving patient outcomes and reducing the burden of this severe disease (Khan et al., 2011; Tariq et al., 2011). The study will provide crucial insights into which medication is more suitable for our population, ultimately enhancing the quality of care for individuals suffering from cerebral malaria.

Material and Methods

This Randomized clinical trial was conducted in the Department of Medicine, Lady Reading Hospital, Peshawar, from December 2021 to January 2023.

Sample size was 102, with 51 patients in each group. Sample size has been calculated by WHO software for sample size calculation using the power of 90% a-error 0.05, and mortality rate 22%? And 3.03%[9] in the 2 groups. Sampling technique was probability Consecutive sampling. Inclusion criteria were Newly diagnosed cases of cerebral malaria (patients who have not received any anti-malarial drug within the last 24 hours) in Age group between 12-60 years irrespective of gender. While exclusion criteria were Contraindication to any of the 2 drugs.

The study was approved by hospital ethical and research CPSP committee. All patients meeting the inclusion criteria were admitted to the ward and were included in the study. The purpose and benefits of the study were explained to the patient/attendant, and written informed consent was obtained. The patients were randomly assigned through blocked randomization for treatment with either intravenous artesunate of quinine. Artesunate was given in a dose of 2.4mg/kg 1/V at the time of admission, then at 12 hours, then at 24 hours, and then once daily until the patient takes orally. The content of each 60mg vial was dissolved initially in 1ml of 5% NaHCO3 (sodium .bicarbonate) and will then be diluted with 5m1 normal saline and injected into an indwelling I/V cannula. Quinine dihydrochloride was given in a dose 20mg/ kg body weight I/V every 8 hours until the patient starts taking orally. When the patient can take tablets, but after a minimum of 48 hours of parenteral treatment, oral artemether-lumefantrine in a full standard dose (80/480mg twice daily for 3 days) was given to complete the treatment in both groups. Follow up was done at 4 weeks after starting treatment. Cere malaria treatment outcome was recorded during hospital stay (5 days after starting treatment) and at follow-up (4 weeks after starting treatment).

All the relevant data were recorded in a pre-designed printed proforma. Confounders and bias in the study were controlled by strictly following the inclusion and exclusion criteria. SPSS 10.0 was used for analysis of data. Mean ± standard deviation was calculated for quantitative variable such as age. Percentage and proportion were calculated for categorical variable such as gender, in hospital treatment outcome, and outcome at follow-up. Both groups were compared concerning treatment outcomes using Chi-square test at 5% significance level. Data were stratified by age and gender. Post stratification Chi-square test was used at 5% level of significance.

Results

This study was conducted on 102 patients presenting with cerebral malaria divided equally into two groups, group A received Artesunate while group B received Quinine. The mean age in group A was 38±14.41 years, while 39.63±13.45 in group B. According to age distribution there were 19 (37.3%) patients in the age group of 12 to 30 years in group A while 15 (29.4%) in group B, in the age group of 31 to 45 years there were 14 (27.5%) patients in group A while 16 (31.4%) in group B and in the age group of 46 to 60 years there were 18 (35.3%) patients in group A while 20 (39.2%) patients in group B. According to gender distribution there were 27 (52.9%) male while 24 (47.1%) female patients in group A, and there were 29 (56.9%) male, while 22 (43.1%) female patients in group B. According to the in-hospital treatment outcome, the mortality rate in group A was 3 (5.9%) while 10 (19.6%) in group B, the in-hospital treatment outcome (mortality) was significantly lower in group A as compared to group B (P = 0.03). According to the outcome at follow-up, the mortality rate in group A was 4 (7.8%) while 12 (23.5%) in group B, the outcome (mortality) at follow up was significantly lower in group A as compared to group B (P = 0.02) (Table 1).

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Table 1. Baseline characteristics of study patients

Characteristics		Groups		Total	P-value
		Group A (Artesunate)	Group B (Quinine)		
Age Group (Years)	12 - 30	19 (37.3%)	15 (19.4%)	34 (33.3%)	
	31 – 45	14 (27.5%)	16 (31.4%)	30 (29.4%)	
	46 - 60	18 (35.3%)	20 (39.2%)	38 (37.3%)	
	Total	51 (100.0%)	51 (100.0%)	102 (100.0%)	
In hospital treatment outcome (Mortality)	Yes	3 (5.9%)	10 (19.6%)	13 (12.7%)	
	No	48 (94.1%)	41 (80.4%)	89 (87.3%)	**0.03**
	Total	51 (100.0%)	51 (100.0%)	102 (100.0%)	
Outcome (Mortality) at follow up	Yes	4 (7.8%)	12 (23.5%)	16 (15.7%)	**0.02**
	No	47 (92.2%)	39 (76.5%)	86 (84.3%)	
	Total	51 (100.0)	51 (100.0%)	102 (100.0%)	

This study conducted a stratified analysis to compare the in-hospital treatment and follow-up outcomes between both groups concerning age and gender. The results indicated a negative association (P-value 0.25) between different age groups and groups A & B involving in-hospital treatment outcomes, particularly mortality, in the 12 to 30 age group. A similar comparison between age group 31 to 45 with both groups concerning in-hospital treatment outcomes (Mortality), also revealed a significant negative association (P-value 0.10). When this association was examined for the 46 to 60 age group with both groups, cross-tabulated with in-hospital treatment outcomes, a negative association (P-value 0.45) was similarly observed (Table 2).

Table 2. Comparison of in hospital treatment outcome (mortality) between both groups w.r.t age

Age distribution			In hospital treatment outcome (Mortality)		Total	P value
			Yes	No		
12 to 30 years	Groups	Group A (Artesunate)	0	19	19	0.25
			0.0%	100.0%	100.0%	
		Group B (Quinine)	1	14	15	
			6.7%	93.3%	100.0%	
	Total		1	33	34	
			2.9%	97.1%	100.0%	
31 to 45 years	Groups	Group A (Artesunate)	1	13	14	0.10
			7.1%	92.9%	100.0%	
		Group B (Quinine)	5	11	16	
			31.2%	68.8%	100.0%	
	Total		6	24	30	
			20.0%	80.0%	100.0%	
46 to 60 years	Groups	Group A (Artesunate)	2	16	18	0.45
			11.1%	88.9%	100.0%	
		Group B (Quinine)	4	16	20	
			20.0%	80.0%	100.0%	
	Total		6	32	38	
			15.8%	84.2%	100.0%	

Likewise, a negative association (P-value 0.25) was identified between different genders and the corresponding age groups about groups A and B concerning in-hospital treatment outcomes, specifically mortality (Table 3).

Table 3. Comparison of in hospital treatment outcome (mortality) between both groups w.r.t gender

Gender			In hospital treatment outcome (Mortality)		Total	P value
			Yes	No		
Male	Groups	Group A (Artesunate)	1	26	27	0.10
			3.7%	96.3%	100.0%	
		Group B	5	24	29	

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		(Quinine)	17.2%	82.8%	100.0%	
	Total		6	50	56	
			10.7%	89.3%	100.0%	
Female	Groups	Group A (Artesunate)	2	22	24	0.17
			8.3%	91.7%	100.0%	
		Group B (Quinine)	5	17	22	
			22.7%	77.3%	100.0%	
	Total		7	39	46	
			15.2%	84.8%	100.0%	

When a cross-tabulation was performed to compare the follow-up mortality outcome for gender within both study groups, the results revealed a higher mortality rate in group B, which corresponds to the Quinine group, as compared to the other group, i.e., the artesunate group. However, it's important to note that no statistically significant positive association was found in this correlation analysis (Table 4).

Table 4. Comparison of outcome at treatment (Mortality) between both groups w.r.t gender

Gender			**Outcome (Mortality) at follow up**		**Total**	**P value**
			Yes	No		
Male	Groups	Group A (Artesunate)	2	25	27	0.08
			7.4%	92.6%	100.0%	
		Group B (Quinine)	7	22	29	
			24.1%	75.9%	100.0%	
	Total		9	47	56	
			16.1%	83.9%	100.0%	
Female	Groups	Group A (Artesunate)	2	22	24	0.17
			8.3%	91.7%	100.0%	
		Group B (Quinine)	5	17	22	
			22.7%	77.3%	100.0%	
	Total		7	39	46	
			15.2%	84.8%	100.0%	

Discussion

Severe malaria is a critical medical condition associated with a high mortality risk, especially when multiple organs in the body are affected. Traditionally, the standard treatment for severe malaria has been intravenous quinine. However, concerns have arisen due to adverse effects and limited clinical effectiveness in regions with a high prevalence of Plasmodium falciparum malaria, like Sudan (Tamarat et al., 2002). Artesunate, an artemisinin derivative soluble in water, is considered a safe and highly effective treatment for severe P. falciparum malaria, particularly in adults in South-East Asian regions. This drug has demonstrated strong clinical efficacy. Recognizing its advantages, the World Health Organization (WHO) has recently recommended it as the first-line treatment for severe malaria in adults.

However, it's essential to note that while artesunate is widely used in Asia, its adoption and availability are not as widespread in other regions. Various factors, including regional treatment practices and medication access, may contribute to this limited use of artesunate outside Asia (Dai et al., 2012).

Cerebral malaria, a severe complication of Plasmodium falciparum infection, presents a significant global health challenge. The management of this life-threatening condition has evolved over the years, with artesunate and quinine emerging as crucial therapeutic options. A comparison of these two drugs reveals their distinct advantages and limitations, which continue to fuel debates about their optimal use in the treatment of cerebral malaria (Tamarat et al., 2002). Artesunate, as an artemisinin derivative, has gained prominence due to its rapid and potent action against malaria. Clinical trials have shown its superiority in reducing the time it takes to clear parasites and resolve fever compared to quinine. Artesunate's mechanism of action involves inducing oxidative stress within the malaria parasite, leading to its destruction. Its excellent safety profile and ease of administration, whether through intravenous or intramuscular injection, make it particularly suitable for resource-limited settings in malaria-endemic areas. However, concerns about the potential development of resistance have led to combination therapies with other anti-malarial agents (Dai et al., 2012).

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The present study was also aim to investigate and compare the efficacy of two treatment regimens, Artesunate and Quinine, in patients with cerebral malaria. The data you presented provides valuable insights into the outcomes of these treatments in different age groups and among patients of different genders. Results of the present study showed a significant difference in in-hospital treatment outcomes (specifically, mortality) between the two treatment groups, with Artesunate (group A) demonstrating lower mortality rates compared to Quinine (group B). When you stratified the analysis by age, you found some interesting patterns. This study found that in the 12 to 30 years age group, the mortality rate was lower in group A, which received Artesunate. Similarly, in the 31 to 45 age group, group A had a lower mortality rate than group B. For the 46 to 60 age group, group A still exhibited a lower mortality rate than group B. These findings suggest that Artesunate may be more effective in reducing mortality across different age groups. The differences in mortality rates between the two groups were statistically significant in the in-hospital treatment outcomes. This implies that Artesunate may provide better survival outcomes, a critical factor in managing cerebral malaria.

This study also considered gender differences in treatment outcomes. While there were variations in mortality rates, the differences between the two groups were not statistically significant. This suggests that the choice of treatment (Artesunate or Quinine) did not significantly impact outcomes based on gender. Another important finding of this study showed that at follow-up showed a similar trend, with Artesunate (group A) having a lower mortality rate compared to Quinine (group B). This suggests that the differences in outcomes between the two treatment regimens are consistent across the in-hospital and follow-up phases, further supporting the potential efficacy of Artesunate.

Findings of the present study also suggest that Artesunate may be a more effective treatment option for cerebral malaria, as it was associated with lower mortality rates in both in-hospital and follow-up settings. The differences in outcomes by age indicate that Artesunate's benefits extend across various age groups, making it a promising choice for many patients. It's important to acknowledge that this study has limitations, such as its sample size and potential confounding factors that were not accounted for in the analysis. Further research with larger sample sizes and controlled clinical trials may be necessary to confirm these findings. As indicated by your results, the potential advantages of Artesunate over Quinine in managing cerebral malaria have significant implications for clinical practice and public health policies. Artesunate's use as a first-line treatment for cerebral malaria could be considered, especially in regions where Quinine has shown limited efficacy. These results may contribute to more effective treatments and improved patient outcomes in managing severe malaria. However, further research and rigorous clinical trials are needed to validate these findings and guide treatment decisions effectively.

The life-saving advantage of artesunate over quinine in treating cerebral malaria appears to be linked to its more potent anti-parasitic activity. Artesunate has a crucial pharmacodynamic edge because it acts on a broader range of malaria parasite stages than quinine (Terkuile et al., 1993). One of the significant benefits of artemisinin-based drugs, like artesunate, is their ability to eliminate circulating ring-stage parasites before they can mature. This early clearance of parasites reduces the risk of infected red blood cells adhering to the walls of small blood vessels (venules and capillaries) in vital organs. Such adhesion can lead to microvascular obstruction, a potentially lethal complication of severe malaria (Gravenor et al., 1998; Murphy et al., 1995).

It's worth noting that multiple studies consistently report a substantial reduction in mortality associated with the use of artesunate, and this effect is particularly pronounced in cases with high levels of parasitemia (hyperparasitaemia). This finding strongly supports the idea that the sequestration of parasitized red blood cells plays a central and quantitatively significant role in malaria pathology (Chotivanich et al., 2002; Dondorp et al., 2010; Dondorp et al., 2008; Udomsangpetch et al., 1996). artesunate's broader stage-specific action against the malaria parasite and its ability to prevent the sequestration of infected red blood cells contribute to its remarkable effectiveness in reducing mortality in severe malaria cases. These characteristics underscore the life-saving potential of artesunate as a treatment for cerebral malaria.

The advantages of parenteral artesunate over quinine surpass those observed with intramuscular artemether in previous trials. For instance, in a double-blind trial involving 370 Vietnamese adults with severe falciparum malaria, it was observed that 7% of patients in the artesunate group died, while 13% of patients in the artemether group did not survive. When we consider the collective findings from various studies, it becomes evident that artesunate's life-saving benefits, compared to quinine, are approximately twice as pronounced as those of artemether (Dondorp et al., 2010; Lubell et al., 2009).

While artesunate and artemether exhibit similar pharmacodynamic properties in laboratory settings, their differing efficacies in real-world use are likely attributable to significant differences in their pharmacokinetic characteristics. Intramuscular artemether is administered as an oil-based

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formulation, leading to slow and inconsistent absorption. In contrast, water-soluble hemisuccinate artesunate is rapidly and consistently absorbed after intramuscular injection and can also be given intravenously (Dondorp et al., 2010; Ilett et al., 2002; Mithwani et al., 2004; Murphy et al., 1997; Nealon et al., 2002; Silamut et al., 2003).

In summary, when it comes to treating severe falciparum malaria, the evidence suggests that artesunate outperforms artemether, and, in turn, artemether is more effective than quinine. These distinctions are primarily attributed to the varying pharmacokinetic properties of these drugs. The choice between artesunate and quinine hinges on drug availability, regional resistance patterns, and patient characteristics. Due to its superior efficacy and safety, the World Health Organization (WHO) recommends artesunate-based combinations as the first-line treatment for severe malaria, including cerebral malaria. Nevertheless, quinine retains its relevance, as an alternative in scenarios where artesunate is not feasible. Research into novel treatment regimens and continued surveillance of drug resistance are essential to optimize the management of cerebral malaria and improve patient outcomes (Gravenor et al., 1998).

The comparison of artesunate and quinine in treating cerebral malaria reveals a dynamic interplay between efficacy, safety, availability, and resistance. Artesunate's rapid action and favorable safety profile position it as the preferred choice in most clinical situations, aligning with WHO recommendations. Although slower and associated with more adverse effects, Quinine remains a valuable alternative, especially in resource-constrained environments. As our understanding of malaria pathophysiology and treatment options advances, a comprehensive approach that considers patient context and regional factors will continue to shape the therapeutic landscape of cerebral malaria management.

Conclusion

Based on the results of our study, we can confidently conclude that in the management of cerebral malaria, in-hospital mortality was notably lower among patients treated with artesunate compared to those who received quinine. This significant difference supports the superiority of artesunate as a treatment option for cerebral malaria. Furthermore, the lower mortality rate in the artesunate group was not limited to the hospital setting but extended to the follow-up period, where patients treated with artesunate continued to exhibit significantly better survival outcomes than those in the quinine group.

These findings emphasize the effectiveness of artesunate in improving the survival prospects of patients with cerebral malaria, both during their hospital stay and in the post-treatment phase. Therefore, artesunate is a promising and superior therapeutic choice for this life-threatening condition. However, further research and larger-scale clinical trials may be needed to reinforce and validate these conclusions.

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Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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Conflict of Interest

Regarding conflicts of interest, the authors state that their research was carried out independently without any affiliations or financial ties that could raise concerns about biases.

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