JMSCR Volume||2||Issue||5||Pages 1030-1037||May 2014 2014

www.jmscr.igmpublication.org Impact Factor-1.1147
ISSN (e)-2347-176x

Journal Of Medical Science And Clinical Research
IGM Publication An Official Publication Of IGM Publication

Comparative study on clinical efficacy between Artesunte and Quinine in the treatment of Cerebral Malaria

Authors

Shafat Imam Siddiqui[1], PK Agarwal[2], Tabassum Yasmin[3], Syed Touseef Nawaz[4]

[1]Assistant Professor, Department of Medicine, Katihar Medical College, Katihar, Bihar
[2]Professor, Department of Medicine, Katihar Medical College, Katihar, Bihar
[3]Assistant Professor, Department of Biochemistry, Rama Medical College, Pilakhua, Hapur, U.P.
[4]M.Sc. Student, Medical Pharmacology, Department of Pharmacology, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, U.P

Corresponding Author
Shafat Imam Siddiqui
Assistant Professor
Department of Medicine, Katihar Medical College Katihar
Bihar INDIA

Abstract:
Malaria remains a serious helath problem in tropical regions causing 0.86 million death in 2009. Quinine is still effective against Plasmodium falciparum (P.f) but in recent years rising trends of resistance is emerging in sense of response time, and fever clearance time. The objective of the study was to compare the clinical efficacy of Artesunate with Quinine in the treatment of cerebral malaria. The study was conducted on 50 confirmed patients of cerebral malaria in the Department of Medicine in Katihar Medical College, Katihar, Bihar. Diagnosis was confirmed clinically on the basis of World Health Organization (WHO) criteria, positive blood films and by Parahit total rapid dipstick for malaria. Patients were randomized to receive either Artesunate or Quinine. Our study shows that 68% of patients treated with Artesunate improved with in 8-24 hrs against 16% from Quinine. There were no serious side effects noted in patients who are treated with Artesunate while 44% of the patients who are treated with Quinine developed side effects. Our study suggests that Artesunate is a good alternative to Quinine in the treatment for cerebral malaria and can be used as first line treatment.
Key words: Artesunate, Quinine, Cerebral Malaria, Plasmodium falciparum

Introduction

Malaria is a protzoal disease caused by infection of erythrocytes with any four of the parasite of the genus PLASMODIUM – falciparum, vivax, malariae and ovale. It is transmitted by the bite of female anopheles mosquito[1]. Malaria remains a serious helath problem in tropical regions causing 0.86 million death in 2009, with annual death rate of upto 93% of affected severe malaria[2]. As per the National Vector Borne Disease Control Programme (N.V.B.D.C.P)[3] data in 2007, 14,76,562 malaria cases (of which 7,25,502 were caused by *Plasmodium falciparum*) and 1,173 deaths were reported from India.

In the classic malarial paroxysysm, fever spikes, chills and rigors occur at regular interval.

Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specially associated with falciparum malaria and may herald the development of encephalopathy (cerebral malaria), leading to coma[4].

Quinine is still effective against Plasmodium falciparum (P.f) but in recent years rising trends of resistance is emerging in sense of response time, and fever clearance time. Quinine can be given intramuscularly but its potential disadvantage is local toxicity. It can cause severe hypoglycaemia[5,6]. The recommended first line therapy for cerebral malaria is intravenous Quinine but the case fatality rate is 10-30% despite treatment. Because of its potential toxicity it is ideally administered by carefully controlled intravenous infusion, a procedure that is impractical in rural areas.

Qinghaosu (Artemisinin) derivatives are synthetics of Chinese plant Artemisa annua which has been used in for centuries. Since 1979 several derivatives of Artemisinin (artesunate, artemether, dihydroartemisinin, artilinic acid and artemotil) have been synthesized and studied in China[7,8,9]. Artemisinin compounds have gained importance from the fact it is highly effective, rapid in parasite clearance as compared to Quinine, and significantly less toxic. It is better than Quinine in rapid coma resolution and fever clearance there by reducing mortalities[10].

South East Asian Quinine Artesunate Malaria Trial (S.E.A.Q.A.M.A.T) Group concluded that Artesunate should be the treatment of choice[10]. The drug is more effective than Quinine, easy to administer and is safe. It is a potential candidate for use in rural areas of India that comprises of about 70 % of India and where health care facilities are not adequate. Hence in the light of current available information, an urgent need was felt to conduct a careful controlled prospective and comparative study regarding the efficacy of Artesunate and Quinine in the management of cerebral malaria.

Materials and Methods

After obtaining clearance from the ethical committee of the institution, the study was carried out in the Department of Medicine, Katihar Medical College and Hospital, Katihar. The study was conducted from 2006 to 2009. A total no of 50 patients, irrespective of age and sex who were

suffering from fever with rigor, headache and altered consciousness were included in the study. The cases were confirmed on the basis of positive blood films and supported by Parahit Total Dipstick Rapid Malaria Test. The diagnosis of cerebral malaria caused by P.f was made by W.H.O criteria (2000)[11].

1. Unarousable coma not attributable to any other cause in a patient with falciparum malaria. The coma should persist for at least one hour after generalized convulsions to make the difference from transient postictal coma. Coma was assessed using the Blantyre Coma Scale[12] in children and Glasgow Coma Scale[13] in adults

2. Clinically by intermittent fever with chills, headache, drowsiness, convulsion and palpable spleen.

Finger was punctured with a sterile lancet which is provided in the kit. The blood was aspirated into the heparinized glass capillary and transferred immediately into the test strip on the absorbent pad. Test strip was placed into the reaction tube containing 200 picolitre of reaction buffer provided with the kit. After 15 minutes the dipstick was taken out from the sample tube and then the result was interpreted. Results should not be read beyond thirty minutes as this can give false positive results.

The patients were randomized to receive either Quinine or Artesunate with the following schedule. Artesunate is given as 2.4 mg/kg body weight stat by intravenous (i.v) route, then 2.4 mg/kg bodyweight i.v. after 12 hours(hrs) then repeated at 24 hrs in same dose, followed by 2.4 mg/kg body weight once a day for 7 days. Quinine dihydrochloride is given as a loading dose of 20 mg/kg body weight in 500 ml 5% dextrose i.v over 4 hours infusion, then followed by 10 mg/kg body weight every 8 hourly for 7 days[4]. Oral quinine is started as soon as the patient is able to take orally. The patients were assessed for – fever clearance time and coma resolution time and all side effects occurring during and after giving drugs. Median values of fever clearance time (F.C.T) and coma clearance time (C.C.T) were calculated for the two drugs using the formula.

$$\text{Median} = L1 + \frac{N/2 - C.f}{f} \times I$$

Median Class = N/2th item, L1 = lower limit, N= no of observations, C.f = cumulative frequency of the above class interval, f = frequency of median class, I = class interval.

Results

Our study shows that 68% of patients treated with Artesunate improved within 8 – 24 hrs against 16% from Quinine. The median coma clearance time (C.C.T) in patients treated with Artesunate was 20 hrs and in Quinine treated patients it was 34 hrs. (Table 1)

Table 1 – The coma clearance time (in Hrs) in patients treated with Quinine (n = 25) and Artesunate (n = 25)

Time (in Hrs)	**Quinine**		**Artesunate**		
	No. of cases	%	No. of cases	%	
8-24	4	16	17	68	Median Coma clearance Time (Q)-34H
>24-48	9	36	4	16	
>48-72	5	20	1	4	Median Coma clearance Time (A)-20H

Majority of cases improved within 48 to 72 hrs, in both the test groups, but the percentage of Artesunate was slightly higher (60%) in comparison to the Quinine (48%). Death recorded in Artesunate was 12% in contrast to 28% in Quinine. The median clearance time in Artesunate treated patients was 58 hrs and in Quinine treated patients it was 60 hrs. (Table 2)

Table 2 – Fever clearance time (in Hrs) in patients treated with Quinine (n = 25) and Artesunate (n =25)

Time (in Hrs)	**Quinine**		**Artesunate**	
	No. of cases	%	No. of cases	%
24-48	3	12	6	24
>48-72	12	48	15	60
>72-96	3	12	1	4

There was no serious side effects noted in Artesunate patients but 44% of patients had developed side effects with Quinine among which the commonest was nausea and vomiting in 16% followed by hypoglycaemia in 80% of cases (Table 3)

Table 3 – Drug toxicity found in patients of cerebral malaria undergoing treatment with Quinine and Artesunate.

Toxicity	Cases on Quinine		Cases on Artesunate	
	No. of cases	%	No. of cases	%
Intolerance	1	4	Nil	Nil
Local pain Reaction, Necrosis	1	4	Nil	Nil
Hypoglycemia	2	8	Nil	Nil
Cardiac Toxicity	1	4	Nil	Nil
Neurotoxicity (phychosis)	1	4	Nil	Nil
Nausea & vomiting	4	16	Nil	Nil
Tinnitus	1	4	Nil	Nil

Overall mortality was 20%. Only 3 patients died in group receiving Artesunate compared with Quinine in which 7 patients died during treatment (Table 4)

Table 4 – No of deaths occurring due to cerebral malaria in groups treated with Artesunate (n=25) and Quinine (n=25)

	NO OF DEATHS	PERCENTAGE
Artesunate	3	12 %
Quinine	7	28 %
Total	10	20 %

No side effects occurred with Artesunate, but Quinine showed various side effects as hemiplegia and ataxia both seen in 8% of the cases. (Table 5)

Table 5 – Residual neurological deficient in cases of cerebral malaria treated with Quinine and Artesunate (4 weeks after recovery)

Neurological Deficit	Quinine		Artesunate	
	No. of cases	%	No. of cases	%
Hemiplegia	2	8	Nil	Nil
Ataxia	2	8	Nil	Nil
Any Other	Nil	Nil	Nil	Nil

Discussion

No disease is static. Its clinical profile keeps changing with time. Newer diagnostic techniques and resistance to conventional drugs throw up fresh challenges requiring major reappraisals at frequent intervals. This comment also hold true for malaria. This has played a major role in human history and has caused more harm to more people than any other infectious disease.

In our study we found that fever and unconsciousness was present in 100% cases and apart from central nervous system (CNS), abdomen was the most common system involved in complicated malaria. Splenomegaly was present in 92% of the patients. Whereas Mohanty et al [14] found splenomegaly in 80% cases. Cerebrospinal fluid examination was done in all cases of cerebral malaria and it was normal in all the cases. Many other authors have also reported normal CSF in all the cases[12,15,16].

Glasgow coma scale was < 7 in 50% cases, 7-10 in 32% cases and > 10 in 18% of cases.

Primary end point of study was to see duration of fever clearance, duration of coma resolution in hours and mortality in both study groups. The median coma clearance time in Artesunate treated patient was 20 hrs and in Quinine treated patient it was 34 hrs. Only 16% patients gained consciousness in first 8-24 hrs while 68% of the patients treated with Artesunate gained consciousness in first 8-24hrs.

Taylor WR et al [17] observed in their study that patient treated with quinine consistently developed side effects and incidence of hypoglycaemia and cardiac toxicity were higher. They also found that artemisinin derivatives have no dose related adverse side effects and only very rarely produce allergic reactions.

Dandrop A et al [10] in their study (which was largest ever clinical trial) found artemisinin derivatives (artesunate) to be safe and very well tolerated. Baird JK [18] in 2005 had found higher side effects with quinine.

Rolling T et al[19] found that adverse effect in patients treated with Artesunate were limited to delayed haemolysis and temporary deterioration in renal function that too only in 60% of the patients while those treated with Quinine it was 71%. Most common adverse effect with Quinine was hearing tinnitus (37%), hypoglycaemia (32%) and cardiotoxicity (14%).

Jones KL et al [20] observed that treatment with Artesunate significantly reduced the risk of death (RR 0.62, 95% CI 0.51-0.75), reduce parasite clearance time (MD 8.14 hrs) and hypoglycaemia.

Conclusion

Our study suggest that Artesunate is a good alternative to Quinine in cerebral malaria as the fever clearance time was not significantly shorter but the percentage of patients becoming afebrile was greater in Artesunate group and coma clearance time was shorter with Artesunate than with Quinine. And also Artesunate is simple to administer, safe, continuous monitoring is not required, minimal or no side effect. So it is well suited for rural areas and in the setting of poor infrastructure. By contrast Quininie is locally toxic after intramuscular use, cannot be used as

bolus i.v. required three times daily infusion and is associated with potentially serious side effects like hypoglycaemia necessitating continuous monitoring.

As per W.H.O Artesunate can be used as a good Alternative therapy for cerebral malaria and in cases which are resistant to Quinine. The present study favours that Artesunate should be used as a first line treatment over Quinine for cerebral malaria.

References

1. Park K. Park's Textbook of Preventive and Social Medicine. 21st ed. Jabalpur: Banarsidas Bhanot; 2011. Chapter 5, Epidemiology of communicable diseases-Malaria; p. 231-244
2. WHO. World Malaria Report 2009. World health organization: Geneva, Switzerland. 21 Feb 2010. ISBN 9789241563901. Available on line: http:// www.who.int/malaria/publications/atoz//9 789241563901/en/index.html
3. National Vector Borne Disease Control Programme 2007. Directorate General of Health Services, Ministry of Health and Family Welfare, Govt of India. Malaria situation in India. Available from http://www.nvbdcp. gov.in/malaria
4. Dan Longo et al. Harrison's Text book of Internal Medicine. 18th ed. New York: McGraw Hill; 2011. vol 1, p1688-1705
5. White NJ, Warrell DA, Chanthavanich P, Looareesuwan S, Warrell MJ, Krishan S et al. Severe hypoglycaemia and hyperinsulinimeia in falciparuum malaria. N Engl J Med. 1983;309: 61-66
6. White NJ, Miller KD, Marsh K, Berry CD, Turner RC, Williamson DH, Brown J. Hypoglycaemia in African children with severe malaria. Lancet. 1987;1(8535):708-711
7. You-You T, Mu-Yun N, Yu-rong Z. Studies on the constituents of Artemiesia annua. Part II. Planta Medica. 1982;44(3):143-145
8. Ding GS. Recent studies on antimalarials in china: A review of literature since 1980. Int J Exp Clin Chemother.1988;1:9-22
9. Posner GH, Parker MH, Northrop J, Elias JS, Ploypradith P, Xie S, Sharpio TA. Orally active, hydrolytically stable, semisynthetic, antimalarial trioxanes in the artemisinin family. J Med Chem. 1999;42(2):300-304
10. Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Aretsunate Malaria Trial (SEAQUAMAT) group. Artesunate versus Quinine for treatment of severe falciparum malaria: a randomised trial. Lancet. 2005;366(9487):717-725
11. WHO, Communicable Diseases Cluster. Severe falciparum malaria. Trans R Soc Trop Med Hyg. 2000;94(Suppl 1):51-90
12. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose

Malawian children. QJM. 1989;71:369-371

13. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81-84
14. Mohanty AK, Rath BK, Mohanty R, Samal AK, Mishra K. Randomized control trial of quinine and artesunate in complicated malaria. Indian J Pediatr. 2004;71(4):291-295
15. Kochar D, Kumawat BL, Karan S, Kochar SK, Agarwal RP. Severe and complicated malaria in Bikaner (Rajasthan), western India. Southeast Asian J Trop Med Public Health. 1997;28(2):259-267
16. Ahmad SH, Moonis R, Kidwai T, Khan TA, Khan HM, Shahab T. Cerebral malaria in children. Indian J Pediatr. 1986;53:409-413
17. Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf. 2004;27(1):25-61
18. Baird JK. Effectiveness of antimalarial drugs. N Engl J Med. 2005;352:1565-1577
19. Rolling T, Wichmann D, Schmiedel S, Burchard GD, Kluge S, Cramer JP. Artesunate versus quinine in the treatment of severe imported malaria: comparative analysis of adverse events focussing on delayed haemolysis. Malar J. 2013;12:241
20. Jones KL, Donegan S, Lalloo DG. Artesunate versus Quinine for treating severe malaria. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005967. DOI: 10.1002/14651858.CD005967.pub2

.