IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 5 Ver. VIII (May. 2017), PP 115-119
www.iosrjournals.org

Observation on The Efficacy And Outcome of Artesunate Versus Quinine Therapy in Complicated Malaria

Dr. Divya Singh[1],Dr. Arun Kumar Sharma[2]
[1](Medical Officer,Ex-Senior Resident, Departement Of Paediatrics,RIIMS, Ranchi)
[2](Professor & Ex-H.O.D, Departement Of Paediatrics, RIIMS,Ranchi)

Abstract:
Background*: complicated malaria is the most dangerous and notorious complication of severe falciparum malaria. In the present study 100 cases with clinical features of complicated malaria (WHO criteria) were included and randomly allocated into two equal groups. One group received i.v. quinine and the other group received i.v. artesunate.*
Objective: *To find out the outcome in terms of relative efficacy and overall cure rate for both drugs, employed for therapy.*
Methodology: *The study was carried out in the Department of Pediatrics, Rajendra Institute of Medical Sciences, Ranchi in which Patients presenting with features of severe malaria and positive blood film for P. falciparum were taken for study,excluding those with no asexual form of P. falciparum or with multispecies forms of malarial parasite in peripheral smear, G6PD deficient cases and cases with hepatitis or renal failure due to other causes.*
result: *Maximum number of patients recovered from coma within 24- 48 hours in artesunate group (43%), while only 26% in quinine group . artesunate showed Faster fever clearance time (median = 49.66 hours) than with quinine (median= 63.78 hours).artesunate group showed significantly less parasite clearance time as compared to quinine group (median = 54.7 hours). Toxicity and side effects of drugs where much less in patients taking artesunate than those taking quinine with no significant difference in mortality.*
Keywords: *artesunate, quinine, cerebral malaria, outcome and efficacy.*

I. Introduction

Malaria continues to be a major health problem, affecting over 40% of world's population. Prevalence of malaria is estimated to be around 300 – 500 million people in some 101 countries with a global death rate of over 3.5 million per year. P. falciparum is responsible for the most severe, complicated often fatal form of the disease. The recent rise in the incidence of malaria has been associated with the spread of drug resistant strains of P. falciparum. Chloroquine is now ineffective in many parts of world including Asia and South America and resistance to drug is emerging in Asia, India and particularly so in Jharkhand. Quinine is still the mainstay of treatment in complicated malaria in children, but also is associated with several side effects. Because of the emergence of resistance to quinine, its effectiveness is declining in most parts of Africa and South East Asia.

According to WHO Regional publication of South East Asia Series no 9, P. falciparum and P.vivax account for more than 95% of the cases of malaria in the South East Asian region. In 1970, nearly 20% of confirmed cases were due to P. falciparum. However during subsequent years, P. falciparum showed a downward trend and in 1977 the percentage of P. falciparum was 12.90% of all confirmed cases of malaria. In 1987 and 1988 the same data stood at 38% and 37% respectively in the South East Asian Region. In India also percentage of P. falciparum cases decreased from 26.2% in 1965 to 14.1% in 1975 and then a continuous gradual increase to 37.1% in 1988. The levels remain alarming high with NMEP Survey report (1995) reporting a "National Average" of P. falciparum malaria to be 34.5%. The systematic review from Cochrane Library compared artesunate with quinine for treating complicated malaria. There is paucity of direct head to head trials of these drugs in severe malaria and more so in children. Moreover, the side effects, if any, of these drugs during therapy of severe malaria are not widely reported from India. The aim of the study is to compare the efficacy and outcomes in artesunate in relation to quinine therapy in complicated malaria, in reference to clinical and biochemical profile in children.

II. Methodology

The present study, "Observation on the efficacy and outcome of Artesunate versus Quinine therapy in complicated malaria" was carried out in the Department of Pediatrics, Rajendra Institute of Medical Sciences, Ranchi. Patients presenting with features of severe malaria and positive blood film for P. falciparum were taken for study from amongst the patients admitted to the Department of Pediatrics from 2008 TO 2011. The diagnosis of P. falciparum malaria was made on the basis of Clinical features, Demonstration of malarial parasite, P.

falciparum in thick & thin peripheral blood films taken . Investigations like TC, DC of WBC, Hb%, Blood urea, Serum Creatinine, Serum bilirubin- total, direct; SGPT, SGOT, Alkaline Phosphatase, CSF analysis, R/E of urine, RBC & casts, ECG after administration of drugs, X ray Chest PA view , Plasma glucose (R) were done to detect concomitant complications and to rule out other diseases with similar presumptions .The cases having no asexual form of P. falciparum in the peripheral smear , those showing multispecies forms of malarial parasite in peripheral smear, patients with known G6PD deficiency , cases with hepatitis due to other causes, cases with renal failure due to other causes were not taken into study. 100 patients of confirmed complicated malaria due to P. falciparum were allocated randomly into 2 groups, containing 50 patients each.

Group 1 – was given I.V. Quinine dihydrochloride 20 mg/kg (loading dose) in 10 ml of isotonic fluids/kg by infusion over 4 hours then 12 hours after the start of loading dose, a maintenance dose of 10 mg salt/kg was given I.V. over 4 hours, every 8 hourly, until the patient could swallow, then quinine tab, 10 mg/kg 8 hourly to complete 7 day course of treatment.

Group 2 – was given I.V. artesunate 2.4 mg/kg/ dose at 0, 12 and 24 hours, then once a day for total 7 days Patients were followed up in the hospital at regular intervals. Patients were discharged from hospital after completion of treatment, with instructions for follow-up in the out patient clinic on day 14, 21, and 28.

III. Result

In our study it was found that 24% cases were conscious at the time of admission (MGCS = 15), while 76% cases were either unconscious (35%) with MGCS < 8, or in altered sensorium (41%) with MGCS ≥ 8 but < 15 (Table-1).

Table-1 Level of conciousness at the time of admission among cases under study (n = 100)

Sl. No.	Level of conciousness at admission	No. of cases	Percentage
1.	Conscious	24	24
2.	Altered Sensorium	41	41
3.	Unconscious	35	35
	Total	100	100%

Maximum number of patients recovered within 24- 48 hours in artesunate group (43%), while only 26% in quinine group. Results show faster coma clearance time in patients treated with artesunate (40.64 hours) than the patients treated with quinine (52.94 hours), $p<0.05$., (Table-2)

Table_2 Showing coma clearance time in hrs, in patient treated with quinine & artesunate (n= 100)

Sl.No.	Time in Hrs	Quinine		Artesunate	
		No. of cases	%	No. of cases	%
1.	6 – 24 hours	3	8.82	6	18.75
2.	24 – 48 hours	9	26.47	14	43.75
3.	48 – 72 hours	22	64.70	12	37.50
	Total	34	100	32	100

Faster fever clearance time was noted with artesunate (median = 49.66 hours) than with quinine (median= 63.78 hours) In quinine group 66 % patients became afebrile by 72 hours while in artesunate group, 86 % became afebrile by 72 hours.
(Table-3).

Table no. 3 Showing The Fever Clearance Time In Hours In Patient Treated With Quinine & Artesunate (N = 100)

Sl.No.	Time in hours	Quinine		Artesunate	
		No.of cases	%	No. of cases	%
1.	24 – 48 hours	3	6	21	42
2.	48 – 72 hours	28	56	22	44
3.	72 – 96 hours	9	18	3	6
4.	96 – 120 hours	4	8	0	0
5.	Death	6	12	4	8
6.	Total	50	100	50	100

The parasite clearance time was significantly less in artesunate group (median=42.88 hours) as compared to quinine group (median = 54.7 hours)(Table4)

Table no. 4 showing the parasite clearance time in hours in patients treated with quinine & artesunate (n = 100)

Sl.No	Time in hours	Quinine		Artesunate	
		No. of cases	%	No. of cases	%
1.	6 – 24 hours	0	0	2	4
2.	24 – 48 hours	16	32	26	52
3.	48 – 72 hours	20	40	18	36
4.	72 - 96 hours	8	16	0	0
	Death	6	12	4	8
	Total	50	100	501	100

1.Median Parasite Clearance Time for quinine = 54.70 hours
2.Median Parasite Clearance Time for artesunate = 42.88hrs.

The above results shows that Parasite clearance time for artesuante was (42.88 hrs) which is lower than for quinine which was (54.70 hrs) ($p<0.05$). It shows that 82% slides were clear of parasite within 72 hours in cases treated by artesunate. Only 72% slides were clear of parasite in cases treated with quinine within 72 hours.

There was definite improvement of renal function and liver function after treatment with quinine and artesunate groups, but the difference of improvement was not statistically significant (Table 5 &6) .

Table No. 5 renal function tests on the basis of blood urea & serum creatinine among cases under study (n=13)

Group	No. of cases	Mean Blood Urea mg%		Mean Serum Creatinine mg/dl	
		BT	AT	BT	AT
Quinine		95	15	7	4
Artesunate		10	53	3	6

The table shows that there is definite improvement of renal function in both groups, but the difference of improvement was not statistically significant ($p >0.05$). Renal function is assessed on the basis of blood urea and serum creatinine. Both were estimated before treatment (BT) and after treatment (AT).

Table no. 6 Liver Function Tests On The Basis Of Serum Bilirubin & Sgpt Level Among Cases Under Study (n= 19)

Group	No.of cases	Mean Serum Bilirubin(mg/dl)		Mean SGPT(IU/l)	
		BT	AT	BT	AT
Quinine	10	3.87	2.17	93.3	60.2
Artesunate	10	3.67	2.07	92.7	57.6

The table shows the value of serum bilirubin and SGPT level before and after treatment with quinine and arteusante does not vary significantly. Improvement in liver function test is significant after treatment with both quinine and artesunate group($p>0.05$). In quinine treated group side effects like nausea (50%), vomiting (24%), headache (36%), tinnitus (18%), vertigo (8%), circulatory failure (2%), slurring of speech (4%) and hypoglycemia (4%) were observed, whereas no significant side effect was observed in artesunate group except for slurring of speech in one case and nausea in two cases.(table no.7)

Table no. 7 Showing Side Effects Of Drugs In Treatment Of Complicated Malaria (N=50)

Sl.No.	Toxicity	Quinine		Artesunate	
		No.of cases	%	No.of cases	%
1.	Nausea	25	50	2	4
2.	Vomiting	12	24	0	0
3.	Headache	16	36	0	0
4.	Tinnitus	8	18	0	0
5.	Vertigo	4	8	0	0
6.	Circulatory failure	1	2	0	0
7.	Hypoglycemia	2	4	0	0
8.	Slurring of speech	2	4	1	2

Mortality in relation to MGCS showed better survival rate in all patients treated with both artesunate and quinine. Six patients died in quinine group and 4 patients in the artesunate group, but the difference was not statistically significant (Table 8).

Table no.8: Table Showing The Mortality In Cases Under Study In Relation To Clinical Manifestations (N=10)

Sl.No.	Presentation	Quinine group	Artesunate group
1.	Anaemia only	0	1
2.	Cerebral malaria + anaemia	3	2
3.	Cerebral malaria+anaemia+jaundice	0	1
4.	Cerebral malaria+anaemia+ARF	1	0
5.	Cerebral malaria+anaemia+shock	1	
6.	DIC	1	0
	Total	6	4

With the present study we found that artesunate is a better drug in complicated malaria in terms of clinical improvement and tolerability.

IV. Discussion

Cerebral malaria is defined as diffuse symmetric encephalopathy characterized by unarousable coma persisting for more than 30 mins, after a generalized convulsion, not attributable to any other cause (eg: meningitis, encephalitis, stoke, head injury, heat stroke, hepatic encephalopathy and other metabolic encephalopathy etc.) in a patient with falciparum malaria.(WHO 1990 and White NJ 1996). It is the most dangerous and notorious complication of severe falciparum malaria.High fever and generalized convulsion is very common. In the present study 100 cases with clinical features of complicated malaria (WHO criteria), having asexual forms of P. falciparum in the peripheral smear, were included. The patients with complicated malaria were then randomly allocated into two equal groups. One group received i.v. quinine and the other group received i.v. artesunate. Relevant investigations were carried out for confirmation of diagnosis and to assess the prognosis. The aim of the study was to find out the outcome in terms of relative efficacy and overall cure rate for both drugs, employed for therapy. Males were affected more than the females and the highest incidence of malaria was seen amongst child between 1-10 years of age groups. 64% cases belonged from rural areas whereas only 36% were from urban areas. About 72% were from lower socioeconomic strata and 9% belong to upper class. 65% were from tribal population and only 35% from non tribal population. Fever(100%), pallor (90%), splenomegaly (85%), and hepatomegaly (70%) were the most common presentations at the time of admission. 55% patients had Haemoglobin level < 7 gram/dl. 76% patients were either unconscious or had altered sensorium, 38% had convulsion.

Coma clearance time varied from 6 – 72 hours for both group. With artesunate maximum number of cases 62.5% recovered from coma within 48 hours, whereas only 35% cases in quinine group recovered in 48 hours. Median coma clearance time for quinine was found to be 52.95 hours and for artesunate it was found to be 40.64 hours. The significant less coma resolution time in patients treated with artesunate could be due to its rapid schizonticidal effect leading to inhibition of cytokines and ultimately release of nitric oxide (which is neurotoxic). Also it prevents the rosette formation in the cerebral circulation 86% of cases became afebrile within 72 hours in artesunate group (median = 49.66 hrs). While only 74% patients recovered from fever in quinine group (median = 63.78 hrs). The significantly lower fever clearance time for artesunate could be due to its rapid schizonticidal effect leading to suppression of cytokines and TNF-α production, which are responsible for fever. The Parasite clearance time was significantly less in artesunate group (median = 42.88 hrs) as compared to quinine group (median = 54.70 hrs). There was definite improvement of renal function and liver function after treatment with quinine and artesunate groups, but the difference of improvement was not statistically significant. Several toxicities were seen in patients treated with quinine like nausea (50%), vomiting (24%), headache (36%), tinnitus (18%), vertigo (8%), circulatory failure (2%), slurring of speech (4%) and hypoglycemia (4%). Patients on artesunate developed almost no toxicity except for nausea (4%) and slurring of speech (2%). 12% patient died in quinine group and 8% in artesunate group, but the difference was not statistically significant. The mortality was highest amongst patients presenting with cerebral malaria, severe anaemia, acute renal failure, shock and DIC.

V. Conclusion

The study showed that Artesunate is a much better drug in complicated malaria in terms of rapid coma resolution, fever clearance, parasite clearance, is well tolerable with no significant side effects, has more rapid schizonticidal action than quinine, administration easy, no risk of fluid overload and consequent heart failure , and with less toxicities. So artesunate can be considered as a good alternative to quinine therapy in complicated falciparum malaria in our state and country as most of the cases are reported from rural and tribal areas where monitoring facilities do not exist and it is very easy to administer the drug and once daily dosing.

Bibiliography

[1]. WHO(2008), World Malaria Report 2008.
[2]. WHO Expert Committee on Malaria. Twentieth report. Geneva, World Health Organization, 2000 (WHO Technical Report Series, No: 892).
[3]. Govt Of India (2007), NRHM News letter, vol. 3, No.2, July-Aug.
[4]. 2007, National Rural Health Mission, Dept of Health and Family Welfare, New Delhi.
[5]. Preventive & Social Medicine – Park - ed.
[6]. Essential Pediatrics – TB – O.P. Ghai – 7th ed. Pg: 227-236.
[7]. I.A.P. TB of Pediatrics, Vol-I: Pg:423-439.
[8]. Nelson TB of Pediatrics Vol I; Pg: 1477- 1485.
[9]. WHO; Severe falciparum malaria. (Transactions of the Royal Society of Tropical Medicine and Hygiene) 2000:94 (Suppl. 1): 1-90.
[10]. China Cooperative Research Group on Qinhaosu and its derivatives as Antimalarials (1982) J. Trad. Chin. Med. 2, 3-8.
[11]. Cumming, J.N., Ploypradith, P. and Posner, G. H. (1997) Adv. Pharmacol. 37, 253-297.
[12]. DeVries PJ, Dien TK. Clinical Pharmacology and Therapeutic Potential Of Artemisinin and its derivatives in the treatment of malaria. Drugs 1996; 52: 818-836.
[13]. Eckstein – Ludwig U et al. Artemisinin target the SERCA of Plasmodium falciparum. Nature. 2003- 424: 957-61 (Medline).
[14]. Eskstein – Luwig U, et al – Artemisinins target SERCA of Plasmodium falciparum Pub Med – Nature 2003; Aug 21; 424 (66951) 887 – 9.
[15]. Facer, C.A. and Tanner, M. (1997) Adv. Parasitology, 39, 1-68.
[16]. Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Safety, 2004, 27:25-61.
[17]. Navaratnam V et al. Pharmacokinetics of artemisinin-type compounds. Clinical Pharmacokinetics, 2000, 39:255-270.
[18]. Ribeiro IR, Olliaro P. Safety of artemisinin and its derivatives. A review of published and unpublished clinical trials. Medicine Tropical (Mars), 1998, 58(3 Suppl.): 50-53.
[19]. Price R et al. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. American Journal of Tropical Medicine and Hygiene, 1999, 60:547-555.
[20]. Van Vugh M et al. A case-control auditory evaluation of patients treated with artemisinin derivatives for multidrug-resistant Plasmodium falciparum malaria. American Journal of Tropical Medicine and Hygiene, 2000, 62:65-69.
[21]. Kissinger E et al. Clinical and neurological study of the effects of multiple doses of artemisinin on brain-stem function in Vietnamese patients. American Journal of Tropical Medicine and Hygiene, 2000, 63:48-55.
[22]. Bethell DB et al. Pharmacokinetics of oral artesunate in children with moderately severe Plasmodium falciparium malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene, 1997, 91:195-198.
[23]. Newton PN et al. Antimalarial Boiavailability and disposition of artesunate in acute falciparum malaria. Antimicrobial Agents and Chemotherapy, 2000, 44: 972-997.
[24]. White NJ et al. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. American Journal of Medicine, 1982, 73: 564-572.
[25]. van Hensbroek MB et al. Quinine pharmacokinetics in young children with severe malaria. American Journal of Tropical Medicine and Hygiene, 1996, 54: 237-242.