Original Research Article

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Study clinical response and parasite clearance response to Artemisinins in severe malaria in children

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ABSTRACT

Background: The research was conducted to study the clinical response and parasite clearance response to Artesunate therapy, in children admitted with severe malaria at a tertiary care centre in Central India.

Methods: It is a prospective analytical study. 18 microscopy positive children diagnosed with severe malaria were included. Baseline blood samples collected for microscopy and biochemical tests. All patients were administered standard intravenous Artesunate therapy and were watched every 12 hourly for: 1. Resolution of clinical signs and symptoms. Clinical parameters included level of consciousness in form of GCS, vital signs like pulse rate, respiration, signs of bleeding, development of icterus, pallor, urine output and laboratory parameters included blood sugar levels, renal and liver function tests. 2. Time taken for conversion of microscopic Smear positive to Smear negative.

Results: The mean age was 8.34±4.35 years. Males and females were equally affected. 61% of severe malaria patients were infected by *P. falciparum* and remaining were infected by *P. vivax*. The most common clinical features were Pallor: 100%, Respiratory distress: 66.7%, Cerebral malaria: 55.6%. After giving Artesunate therapy, Mean GCS in Cerebral malaria patients showed improvement (on admission: 9±1.15, at 72 hours: 12.5±3.7). Effect was marginally better in *P. vivax* cases. Respiratory distress and tachycardia improved in majority of patients (75% and 80% respectively). The number of patients with icterus progressively increased. Improvement in liver function and renal function was minimal. 100% parasite clearance was achieved. The mean parasite clearance time is 46±9.43 hours. 72.2% were successfully discharged, 22.2% took Leave Against Medical Advice (LAMA) and 5.6% certified dead

Conclusions: Artesunate is an effective drug in severe malaria patients in terms of rapid improvement of cerebral function, improvement and stabilization of vitals, parasite clearance with favorable long-term outcome. There is no evidence of plasmodium resistance to Artesunate currently as per the present study.

Keywords: Artesunate, Parasite Clearance Time, Severe malaria

INTRODUCTION

According to the latest WHO estimates, there were 212 million cases of malaria in 2015 and 4,29,000 deaths. The incidence rate of malaria is estimated to have decreased by 41% globally between 2000 and 2015, and by 21% between 2010 and 2015. Malaria mortality rates are

estimated to have declined by 62% globally between 2000 and 2015 and by 29% between 2010 and 2015. In children aged less than 5 years, malaria mortality rates are estimated to have fallen by 69% between 2000 and 2015 and by 35% between 2010 and 2015. In India, the malaria incidence and deaths due to malaria have reduced significantly in recent years. During the period 2000 to

2015, cases declined by 44% from 2.03 million to 1.13 million and deaths declined by 69% from 932 to 287. The API (Annual Parasite Index) has also been declining from 3.29 in 1995 to 0.9 in 2015. Though the incidence is on decline, malaria still continues to be a major health problem. Madhya Pradesh, the state situated in central India, is one of the worst affected states by malaria. Pediatric population is especially vulnerable to this preventable and curable illness.

Artemisinin has been a very potent and effective antimalarial drug, especially when used in combination with other malaria medicines. Combining an artemisinin drug with a partner drug that has a longer half-life was found to improve the efficacy of the artemisinin. Resistance has been documented to all classes of antimalarial medicines, including the artemisinin derivatives, and it is a major threat to malaria control.³ Artemisinin resistance in *P. falciparum* is now prevalent in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. There is currently no evidence for artemisinin resistance outside these areas. Hence in our study we are assessing the Clinical Response and Parasite Clearance Response after administration of Artesunate in children presenting with severe malaria. This will help us to gain information about therapeutic efficacy and detect (if any) emergence of Artesunate resistance in Jabalpur and surrounding districts of Madhya Pradesh in Central India.

METHODS

It is a Prospective observational study conducted between March 2016 and August 2017 at the Department of Pediatrics, NSCB MCH, Jabalpur (Madhya Pradesh). Children admitted with c/o Fever (high grade) fulfilling the criteria for severe malaria as per WHO Guidelines for the treatment of malaria, third edition 2015 and who were positive for malaria parasite on microscopy were included in the study.3 Those allergic to Artesunate, who had already taken Anti-malarial therapy prior to admission and whose attenders were not giving consent for treatment with Artesunate were excluded from the study. Ethical clearance was obtained from the Institutional Review Board. Informed written consent was obtained from the parents of the study subjects. Strict confidentiality of data was maintained throughout the study.

18 children satisfying inclusion and exclusion criteria were recruited into the study. Information regarding demographic profile was taken from the parents or relatives including name, age, sex, residence, contact number, place of referral, and date of admission. Complete history was taken enquiring about history of fever, chills and rigors, headache, vomiting, convulsions, oliguria or haematuria, jaundice, or any other complaints, and duration of illness. Thorough clinical examination was done to assess the vitals, temperature, blood pressure, pallor, icterus, per abdominal examination to

look for organomegaly. Complete systemic examination including neurological examination to rule out meningitis and other causes of convulsions was done.

Artesunate therapy

Above patients were administered intravenous Artesunate for at least 24 hours (minimum 3 doses) and until they could tolerate oral medications. Treatment was completed with 3 days treatment with oral ACT (artemether + lumefantrine) + single dose of Primaquine.

Dose of parenteral Artesunate

Children ≤20 Kg: 3 mg/kg/dose
Children >20 Kg: 2.4 mg/kg/dose

Patients were watched every 12 hours for the following

Resolution of clinical signs and symptoms

Clinical parameters (level of consciousness in form of GCS, vital signs like pulse rate, respiration, signs of bleeding, development of icterus, pallor, urine output) and laboratory parameters (blood sugar levels, renal and liver function tests)

Time taken for conversion of microscopic peripheral blood Smear positive to Smear negative

To assess the parasitological clearance response, (as per the recommendations of WHO Guidelines for the treatment of malaria, third edition 2015) blood smears were prepared and examined by microscopy every 12 hours for monitoring of parasite during first 3 days of treatment. The observations were then recorded in a predesigned and pretested proforma.

Statistical analysis plan

The data of the present study was recorded/fed into the computers and after its proper validation, check for error; coding and decoding was compiled and analyzed with the help of SPSS 20 software for windows. Appropriate univariate and bivariate analysis and the descriptive statistics was carried out. All means are expressed as mean±standard deviation and the proportion as in percentage (%).

RESULTS

Out of 18 microscopy positive severe malaria cases, 5 were in the age group 1 month to <5 years, while 4 were between 5 to <10 years and 9 cases were between 10 to 14 years. There was only 1 patient who was <1 year of age. Mean age calculated was 8.34 ± 4.35 years. Among them 9 were males and 9 were females (M:F = 1:1) i.e. males and females were equally affected. Out of 18 cases, 12 were from rural area and 6 were from urban area. Maximum (n = 11) were having *P. falciparum* malaria

and remaining were having P. vivax malaria. There was no case of mixed (P. falciparum + P. vivax) infection.

Table 1: Clinical presentation of microscopy positive severe malaria cases.

Clinical feature	Cases (n)	
	P. Falciparum	P. Vivax
Cerebral malaria	6	4
Respiratory distress	7	5
High pulse rate	10	5
Bleeding	3	1
Icterus	8	0
Oliguria	4	0
Hematuria	2	0
Pallor	11	7
Hypoglycemia	1	0
Deranged LFT	9	3
Deranged RFT	5	1

Pallor (n = 18), high pulse rate (n = 15), respiratory distress (n = 12), deranged LFT (n = 12), cerebral malaria (n = 10) were most common findings. More cases were caused by P. falciparum in each clinical feature as compared to P. vivax.

Table 2: Course of GCS in microscopy positive severe (cerebral) malaria cases on Artesunate therapy.

Follow- up time	Mean GCS	GCS change in cerebral malaria cases (n=10)		
		Static	Improved	Deteriorated
On admission	9±1.15			
12 hours	10.4±2.2	2	6	2
24 hours	11.1±2.6	4	5	1
36 hours	11.9±2.8	7	3	0
48 hours	12.2±3.6	4	4	2
60 hours	12.5±3.7	7	3	0
72 hours	12.5±3.7	10	0	0

In Cerebral malaria cases, mean GCS on admission was 9±1.15 which showed improvement every 12 hours and mean GCS at 72 hours was 12.5±3.7.

Mean GCS in P. falciparum improved from 9 ± 1.4 on admission to 12 ± 3.9 at 72 hours. Mean GCS in P. vivax improved from 9 ± 1 on admission to 13 ± 3.9 at 72 hours.

Out of 7 cases of respiratory distress in P. falciparum malaria cases, 5 improved by 36 hours. Out of 5 cases of respiratory distress in P. vivax malaria cases, 4 improved by 36 hours.

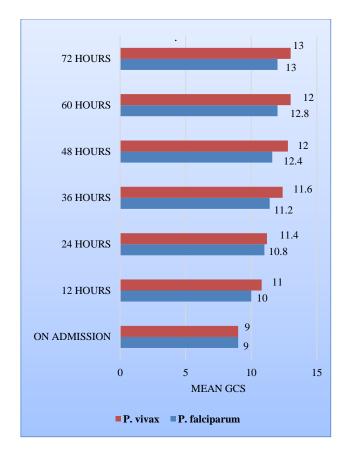


Figure 1: Course of GCS in cerebral malaria cases (according to parasite species) on Artesunate therapy.

Out of 18 cases, 15 (10 P. falciparum + 5 P. vivax) had abnormal high pulse rate on admission. At 72 hours only 3 (2 P. falciparum + 1 P. vivax) cases had high pulse rate.

Table 3: Course of respiratory distress in microscopy positive severe malaria cases on Artesunate therapy.

Follow up hours	Cases with respiratory distress (n)	
	P. falciparum	P. vivax
On admission	7	5
12 hours	6	5
24 hours	4	3
36 hours	2	1
48 hours	2	1
60 hours	2	1
72 hours	2	1

Out of 18 cases, 4 (3 P. falciparum + 1 P. vivax) had bleeding initially, which increased to 7 (6 P. falciparum + 1 P. vivax) at 24 hours and decreased to 5 (4 P. falciparum + 1 P. vivax) at 72 hours.

Out of 18 cases, 8 (8 P. falciparum + 0 P. vivax) had icterus initially and it persisted in all of them. Another 6 cases (2 P. falciparum + 4 P. vivax) developed icterus later at 48 hours.

Table 4: Course of pulse rate in microscopy positive severe malaria cases on Artesunate therapy.

Follow up hours	Pulse (mean±sd)	Cases with high pulse rate (n=15)	
		P. falciparum	P. vivax
On admission	111.22±25.66	10	5
12 hours	111.22±20.90	10	5
24 hours	106.89 ± 20.06	10	5
36 hours	107.33±21.24	9	5
48 hours	100.78±22.86	6	3
60 hours	97.00±21.62	4	1
72 hours	94.00±23.34	2	1

Table 5: Course of bleeding in microscopy positive severe malaria cases on Artesunate therapy.

Follow up hours	Cases with bleeding (n)	
	P. falciparum	P. vivax
On admission	3	1
12 hours	5	1
24 hours	6	1
36 hours	5	1
48 hours	4	1
60 hours	4	1
72 hours	4	1

Table 6: Course of icterus in microscopy positive severe malaria cases on Artesunate therapy.

Follow up hours	Cases with icterus (n)	
	P. falciparum	P. vivax
On admission	8	0
12 hours	8	0
24 hours	9	2
36 hours	9	4
48 hours	10	4
60 hours	10	4
72 hours	10	4

Out of 18 cases, 4 (all P. falciparum) had low urine output initially, only 1 of them improved at 60 hours. Low urine output persisted in 3 cases.

Out of 18 cases, 2 cases (both P.falciparum) had hematuria on admission, 3 cases (all 3 P.falciparum) at 12 hours, 4 cases (3 P. falciparum + 1 P. vivax) at 24, 36, 48 and 60 hours and 5 cases (4 P. falciparum + 1 P. vivax) at 72 hours.

All 18 cases (11 P. falciparum + 7 P. vivax) had pallor on admission which did not change during the observation period. Only 1 (P. falciparum) had low blood sugar initially which was found normal at 12 hours. Among 18 cases, 12 (9 P. falciparum + 3 P. vivax) had deranged

liver function initially and 12 (8 P. falciparum + 4 P. vivax) had deranged liver function till 72 hours.

Table 7: Course of urine output in microscopy positive severe malaria cases on Artesunate therapy.

Follow up hours	Cases with low urine output (n)	
	P. falciparum	P. vivax
On admission		
12 hours	4	0
24 hours	4	0
36 hours	4	0
48 hours	4	0
60 hours	3	0
72 hours	3	0

Table 8: Course of hematuria in microscopy positive severe malaria cases on Artesunate therapy.

Follow up hours	Cases with hematuria (n)	
	P. falciparum	P. vivax
On admission	2	0
12 hours	3	0
24 hours	3	1
36 hours	3	1
48 hours	3	1
60 hours	3	1
72 hours	4	1

Out of 18 cases, 6 (5 P. falciparum + 1 P. vivax) had deranged renal function on admission which reduced to 5 (4 P. falciparum + 1 P. vivax) at 48 hours.

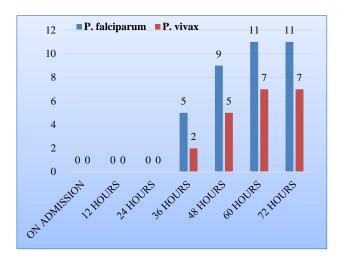


Figure 2: Effect of Artesunate on parasite clearance.

Out of 18 PSMP positive cases, 7 cases (5 P. falciparum + 2 P. vivax) turned negative at 36 hours, 7 cases (4 P. falciparum + 3 P. vivax) turned negative at 48 hours and remaining 4 cases (2 P. falciparum + 2 P. vivax) turned negative at 60 hours.

Table 9: Effect of Artesunate on parasite clearance.

Follow up hours	Parasite clearance achieved (n)	
	P. falciparum	P. vivax
On admission	0	0
12 hours	0	0
24 hours	0	0
36 hours	5	2
48 hours	9	5
60 hours	11	7
72 hours	11	7

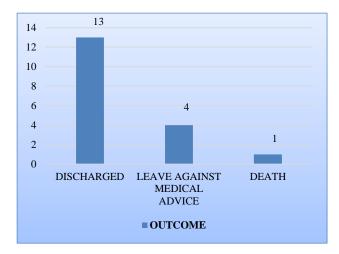


Figure 3: Outcome of microscopy positive severe malaria cases.

Out of 18 cases, most of them (13) were successfully Discharged. 4 took Leave Against Medical Advice (LAMA) and 1 was certified dead.

DISCUSSION

This study was conducted on a prospective basis from March 2016 to August 2017. A total of 18 cases of severe malaria positive by microscopy were included.

In the present study, 27.8% (n = 5) were in the age group 1 month to <5 years, 22.2% (n = 4) between 5 to <10years, 50% (n = 9) between 10 to 14 years and only 1 patient <1 year of age. Mean age calculated was 8.34±4.35 years. In a study by Singh N et al, the slide P. falciparum rate increased from 12.6% to 26.9% in children ≤1 year of age (infants) to 35.6% in >1-4 years of age to 39.4% in >4-8 years of age, and then decreased to 31.3% in those >14 years of age.4 In the present study also, maximum (50%) of microscopic slide positive cases were between 10-14 years age group. Males and females were equally affected (n = 9 each). There were more cases from rural areas (66.7%, n = 12) as compared to urban areas (33.3%, n = 6). In a study by Gohiya P et al, 80% severe malaria cases were admitted from adjacent rural area which explains the patient drainage of tertiary centres.⁵ Maximum (61.1%, n = 11) were having P. falciparum malaria and remaining (38.9%, n = 7) P. vivax malaria. In another study by Ganguly T et al it was observed that *P. falciparum* was the predominant causative agent of severe malaria, causing 85% of cases.⁶

In the present study, the most common clinical features of severe malaria cases were Pallor: 100% (n = 18), respiratory distress: 66.7% (n = 12), cerebral malaria: 55.6% (n = 10) and icterus: 44.4% (n = 8). Bleeding: 22.2% (n = 4), oliguria: 22.2% (n = 4) and hematuria: 11.1% (n = 2) were less common. The most common biochemical abnormality was deranged liver function: 66.7% (n = 12) and deranged renal function: 33.3% (n = 6). In all the above clinical and biochemical manifestations, P. falciparum was more dominant as compared to P. vivax. In the study by Gohiya P et al, pallor was the most common (in 96% cases) clinical finding, cerebral Malaria in 50%, oliguria in 13% and hematuria in 8% cases.⁵ In another similar study by Murmu MC et al, Pallor was the most common sign (in 84% cases). These above observations are comparable to the present study.

We had 18 microscopy positive cases. All cases were reported negative by microscopy after initiating artesunate therapy, out of which 7 cases turned negative at 36 hours, 7 cases became negative at 48 hours and remaining 4 cases turned negative at 60 hours. The response was comparable in *P. falciparum* and *P. vivax* cases. The mean parasite clearance time in the present study is 46±9.43 hours.

Table 10: Parasite clearance time in similar other Indian studies.

Author	Place of study	Parasite clearance time
Huda SN et al ⁸	Jawaharlal Nehru Medical College, AMU, Aligarh, U.P.	40.9±8.4 hours
Mohanty AK et al ⁹	SCB Medical College and SVP PG Institute of Pediatrics, Cuttack, Orissa	41.67±16.78 hours
Shambhunath K et al ¹⁰	KMCH, Katihar, Bihar	42.88 hours
Singh D et al ¹¹	Rajendra Institute of Medical Sciences, Ranchi, Jharkhand	42.88 hours
Present study	N.S.C.B Medical College, Jabalpur, M.P.	46±9.43 hours

Cerebral malaria is the most severe neurological complication of Severe Malaria. Parasite sequestration in cerebral microvasculature and cytokine mediated inflammatory response to parasite antigens released at schizogony are proposed to be the underlying mechanism.¹²

In our study, 55.6% (10 out of 18 cases) were admitted with cerebral malaria. Out of them, 60% (n = 6) had shown improvement in GCS as soon as 12 hours after initiation of Artesunate therapy. Mean GCS on admission was 9 ± 1.15 which showed improvement every 12 hours and mean GCS at 72 hours was 12.5 ± 3.7 . This can be explained due to rapid schizonticidal effect of Artesunate leading to inhibition of cytokines and ultimately release of nitric oxide (which is neurotoxic).

In a study by Gehlawat VK et al, among children with cerebral malaria, 62.5% had improvement in sensorium within 48 hours. ¹³ In another study by Desai PD et al, 90% patients with cerebral malaria recovered after getting injectable Artesunate. ¹⁴ This highlights dramatic clinical response to Artesunate in cerebral malaria. Mean GCS in *P. falciparum* severe malaria cases improved from 9±1.4 on admission to 12±3.9 at 72 hours while Mean GCS in *P. vivax* severe malaria cases improved from 9±1 on admission to 13±3.9 at 72 hours (Table 8). This highlight better response of P. vivax severe malaria to Artesunate.

Respiratory distress improved in 75% (9 out of 12) patients, after administration of Artesunate which is expected because of reduction in parasitemia and also due to supportive measures to correct acidosis. Out of 7 cases of respiratory distress in P. falciparum severe malaria cases, 5 (71%) improved by 36 hours. Out of 5 cases of respiratory distress in P. vivax severe malaria cases, 4 (80%) improved by 36 hours. Similarly, abnormally high pulse rate was normalised in 80% patients (12 out of 15) after initiating artesunate therapy and other supportive measures. In the study by Gehlawat VK et al, all 18 children with severe malaria who were treated with intravenous Artesunate followed by a course of combination artemether-lumefantrine showed reasonable clinical response with no evidence of early or late treatment failures. 13 Bleeding was observed in 22% (n = 4) patients at the time of admission. 11.1% (n = 2) of them improved whereas bleeding persisted in 11.1% (n = 2) patients and 22.2% (n = 2) started bleeding later. It can be due to thrombocytopenia and/or disseminated intravascular coagulation. In a study by Gehlawat VK et al, 16.7% (3 out of 18) patients had bleeding manifestations which is comparable to our observation. But no research could be found to establish relation between artseunate therapy and malaria-induced bleeding. 13 So this observation needs further validation.

Number of patients with Icterus on admission (44.4%, n = 8) was high in the present study. Kochar DK et al studied malaria hepatitis, its multifactorial etiology and found jaundice is the commonest sign of hepatic dysfunction.¹⁵ The number of patients with Icterus in the present study progressively increased which can be attributed to ongoing hemolysis and hepatocyte dysfunction. This also led to persistently deranged Liver function in 83.3% cases. Oliguria or low urine output was observed in 22.2% (n = 4) cases during initial hours. This is comparable to study by Murmu MC et al who found

low urine output in 17.16% cases initially. In the present study, only 1 of the patients improved at 60 hours and low urine output persisted in remaining patients. According to Bodi JM et al recovery of renal function does not appear to be correlated with parasitemia. 16 This explains minor effect of Artseunate on oliguria. A study by Panwar S et al has observed P. vivax as important cause of nephropathy.¹⁷ But in the present study all oliguric patients were P. falciparum severe malaria cases. Hematuria was a less common (11.1% cases) finding in our study. Similar results have been observed by Kumar A et al where hematuria was noticed in 6.6% of cases. 18 It may be due to DIC or thrombocytopenia. Pallor was observed in 100% (n = 18) cases included in the present study. We observed Hypoglycaemia (blood glucose <40mg/dL) in 5.6% (1 out of 18) cases. In the study by Ganguly T et al, similar incidence of hypoglycemia (8.5% cases) was reported.⁶ This case was *P. falciparum* infection and hypoglycemia improved within 12 hours.

Improvement in Liver Function Test (LFT) and Renal Function Test (RFT) reports on 12 hourly follow-up testing after initiating Artesunate therapy was minimal in our study. This is explainable as recovery of liver and renal function takes time.

In the present study, out of 18 cases, 72.2% (13/18) were successfully discharged. 22.2% (4/18) took Leave Against Medical Advice (LAMA) and 1 (5.6%) was certified dead. All 18 cases had shown parasite clearance to intravenous Artesunate given in appropriate doses as per WHO guidelines. The case which was certified was *P. vivax* severe malaria case, having Multi Organ Dysfunction Syndrome (MODS), evidenced by septicaemia (CRP positive), renal and hepatic failure (severely deranged RFT and LFT), thrombocytopenia (platelet count 40,000/microlitre), gastrointestinal bleed and shock. The overall mortality rate in a similar study by Huda SN et al was 10.86%. Hence we can say that clinical outcome following Artesunate was favourable in severe malaria cases in the present study.

The small sample size of study (n = 18) was a major limitation as we could not see the effects of Artesunate on a larger number of cases.

CONCLUSION

Artesunate is an effective drug in severe malaria patients in terms of rapid improvement of cerebral function, improvement and stabilization of vitals, parasite clearance with favourable long-term outcome. There is no evidence of plasmodium resistance to Artesunate currently as per the present study.

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Institutional Ethics Committee

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