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Evaluation of Efficacy and Safety of Artemisinin Derivatives Comparison with Quinine in Paediatric Population for Treatment of Severe Malaria: A Meta-Analysis Approach

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ABSTRACT

Artemisinin and its derivatives such as artesunate, arteether and artemether are the primary and effective treatment of choice as per WHO malaria treatment guideline for the treatment of severe malaria although various endemic countries are using quinine for the treatment of severe malaria. The objective of this meta-analysis was to evaluate the efficacy and safety of artemisinin and its derivatives compared with quinine as parenteral antimalarial therapy for treating severe malaria in children. From the year 1990 to the year 2015, studies were identified using database searches, citation searches of selected articles. The electronic databases searched engines: Pubmed, Web of Science, Global Health, Medline & Cochrane review of Journals up to April 2015. We selected published randomized controlled clinical trials (RCTs) information comparing artemisinin derivatives with quinine and route of administration was either intravenous or intramuscular for treatment of severe malaria in paediatric population as per WHO malaria treatment guideline, any gender, age group up to 15 years of children who were diagnosed with confirmed malaria by RDT or slide test. The primary outcome was efficacy in terms of parasite clearance time (PCT) and fever clearance time (FCT) in paediatrics population. The secondary outcome was the mortality, coma resolution time (CRT) and neurological sequelae at the time of discharge in the paediatric population. We assessed identified articles on the basis of clinical trial eligibility, the risk of bias and extracted data as per objective of this research for the desired outcomes. We measured 95% confidence interval by the using of REVMAN software version 5.3 for meta-analysis and summarized the collected data on the basis of characteristics of inclusion criteria of articles such as risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes. We included total 17 RCTs, enrolling 7220 paediatric patients who were suffering from severe or complicated malaria and these trials were conducted in various countries in the world. Artemisinin derivatives showed mean PCT (MD -8.53 hours, 95% CI -9.44 to -7.62) and mean FCT (MD -9.42 hours, 95% CI -11.12 to -7.71) shorter and statistically significant (P<0.00001) as compared with quinine therapy. We evaluated secondary outcomes mortality, mean coma resolution time (CRT) and the risk of neurological sequelae at the time of discharge in paediatric malaria patients which was observed; (RR 0.82, 95% CI 0.72 to 0.93; 17 trials, 7220 participants, P=0.002), (MD -5.37 hours, 95% CI -7.70 to -3.05; nine trials, 591 participants, P<0.00001) and (RR 1.07, 95% CI 0.89 to 1.28; nine trials, 5939 participants, P=0.49), respectively. This meta-analysis of RCT addresses the evidence for various aspects in the treatment of severe malaria in the paediatric population although limitation of availability of published

information in studies furthermore research on paediatric malaria population is required to overcome from challenges drug resistance, patient compliance and less adverse effect.

Keywords: Artesunate, Arteether, Artemether, Antimalarial, Children, Malaria.

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INTRODUCTION

Malaria is one of the most important infectious diseases in the world and causing hundreds of millions of illnesses and mortality worldwide. Many deaths occur in malaria because of the severity of this infection especially for children who are admitted to hospital with severe malaria and receive parenteral antimalarial treatment. Despite challenges and extensive research malaria disease is a leading cause of morbidity and mortality in humans since many years. [1] Millions of people contract malaria each year an estimated 1.5–2.7 million deaths reported annually worldwide. [2] Malaria disease is caused by *Plasmodium* (intraerythrocytic protozoa) and its other species such as *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. Severe and fatal malaria is caused by *P. Falciparum* and *P. vivax* malaria is usually an uncomplicated disease which is rarely fatal. [3] This clinical hypothesis of the treatment has been challenged recently by several reports of disease severity or deaths due to *P. vivax* monoinfections. [4]

According to published research in 'The Lancet', Dhingra N *et al* [5] (2010) mortality at ages 1 month to 70 years, 2681 (3·6%) of 75 342 were attributed to malaria. Of these, 2419 (90%) were in rural areas and 2311 (86%) were not in any health-care facility. Death rates attributed to malaria correlated geographically with local malaria transmission rates derived independently from the Indian malaria control programme. The adjudicated results show 205000 malaria deaths per year in India before age 70 years (55000 in early childhood, 30000 at ages 5–14 years, 120000 at ages 15–69 years); 1·8% cumulative probability of death from malaria before age 70 years. Plausible lower and upper bounds (on the basis of only the initial coding) were 125000–277000. Malaria accounted for a substantial minority of about 1·3 million unattended rural fever deaths attributed to infectious diseases in people younger than 70 years. [6]

Many published studies have suggested that quinine was the mainstay of severe malaria treatment, though chloroquine resistance has emerged in Southeast Asia and spread to worldwide especially in endemic zones. So because of efficacy and ease of administration quinine was resumed to its primary role in the treatment of severe malaria. According to WHO malaria treatment guideline intravenous quinine administration needs a constant rate infusion with dosing three times a day because the intramuscular administration is painful and can cause sterile abscesses and predispose to lethal tetanus. The researcher showed that parenteral quinine has a narrow therapeutic ratio. [6] Although blindness and deafness may follow self-poisoning, these side-effects are observed in severe malaria including quinine-induced hyperinsulinaemic hypoglycaemia is a particular problem in patient management, especially in children and pregnant women. [7] Based on analysis descriptive studies of endemic countries such as Africa and Asia the World Health Organization defines clinical criteria for severe malaria term when asexual forms of *P. falciparum* are detected in peripheral blood smear and there is impaired consciousness or coma, prostration, multiple seizures, hyperlactatemia or metabolic acidosis, severe anaemia, dark urine, hypoglycaemia, jaundice, respiratory distress, persistent vomiting, abnormal bleeding, shock, and renal failure. [8-9] There are currently three recommended treatments for severe and complicated malaria: artesunate (AS), artemether (AM) and quinine (or quinidine), although in many countries only quinine is available. Primary objectives of these antimalarial therapies are the provision of prompt, effective therapy and concurrent supportive care to manage life-threatening complications of the disease. Quinine based therapy showed major serious side effects. The cardiac toxic effects of quinidine are a major concern, and intravenous therapy requires continuous cardiac monitoring, with slowing or discontinuation of the infusion for prolongation of the QT interval. [10] There are many published studies which have been proved the incomparability of quinine in the treatment of severe malaria has been challenged by the introduction of artemisinin derivatives. [10]

Today, Artemisinin-based combination therapy (ACT) is most recommended drug by the WHO for infants and paediatrics population. [9] Indian Academy of Paediatrics (IAP) followed the National Malaria Programme and recommended quinine and artemisinin derivates as preferred alternatives. [11] In the year 2008 treatment was modified artemisinin derivatives with tetracycline/clindamycin or doxycycline can be used as applicable in line with WHO malaria treatment guideline. In the year 2015, the WHO malaria treatment guideline strongly recommends artesunate in adults with severe malaria and suggests that quinine can be used as alternative therapy. There are less number of clinical trials are available on paediatric population to conclude the efficacy, safety and mortality rate by the treatment of quinine and artemisinin derivatives but on the basis of availability of information researcher suggested that in the treatment of malaria paediatric population mortality rate is increasing by the treatment of parenteral quinine therapy because of quinine resistance cases or high side effects. Artesunate is a semisynthetic derivative of artemisinin which provides an advantage as compared to other artemisinin derivatives because it can be formulated as oral, rectal, intramuscular, and intravenous preparations. Artesunate is rapidly hydrolyzed to dihydroartemisinin and most active schizonticidal metabolite. Injectable administration of artesunate results in a more rapid systemic availability of Artesunate compared with intramuscular Artemether. This pharmacokinetic advantage may provide a clinical advantage in the treatment of severe malaria. Rectal Artesunate has been shown to be absorbed rapidly, with a considerable inter-individual variability. Artesunate is highly effective against multidrug-resistant falciparum malaria and severe malaria in Vietnam, Thailand, China, and Myanmar. [8] Artesunate and its derivatives therapies shown good and safe clinical outcome during research in the treatment of malaria as compare to other antimalarial. [10] We performed this meta-analysis to obtain stronger evidence on treatment outcomes of malaria in children population. This systematic review and meta-analysis approach sharing the comparative outcome analysis of Artemisinin derivatives (intervention) and Quinine therapy (comparison) in the paediatric population. We evaluate clinical outcome in various aspects such as mortality, fever clearance time, parasite clearance time, coma recovery time and neurological sequelae disorder.

MATERIALS AND METHODS

Types of studies

Study searched; randomized clinical trials (RCT) of treatment comparator (either non-inferior trials or other published information), Abstracts or full article, Review article.

Types of participants

Patients who has complicated Malaria disease as per the definition of WHO malaria treatment guideline, Study subjects will belong to any gender, any country, Children with confirmed malaria infection through RDT or by blood slide test / microscopy age not more than 15 year and Patients will be excluded who were pregnant or lactating women, Adult, uncomplicated malaria.

Types of Interventions

We included only RCT or study in which treatment was the intramuscular or intravenous route of administration or both and followed by oral antimalarial treatment as applicable. We excluded trials where the patient was received antimalarial by other routes of administration as described above. Artemisinin drug or its derivative are dihydroartemisinin, artemisinin, artesunate, artemether, arteether) drug given as monotherapy versus Quinine.

Outcomes

Primary outcome was to evaluate the clinical characteristic of malaria symptoms; fever clearance time and parasite clearance time. FCT (time for the temperature to return to normal or equal to 98.6°F or 37°C); fever clearance within 48 hours of starting treatment; clinical treatment failure (patients given an alternative treatment because of no clinical improvement under the allocated regimen); other reported indicators of clinical improvement. Parasite clearance time which is parasite clearance after starting treatment showed no marked reduction in parasitaemia. The secondary outcome was to evaluate morality due to severe malaria during the treatment, coma resolution time and neurological sequelae at the time of discharge in the paediatric patient.

Studies inclusion and search methodology

From the year 1990 to the year 2015, studies were identified using database searches, citation searches of selected articles. The electronic databases searched engines: Pubmed, Web of Science, Global Health, Medline & Cochrane review of Journals. In this meta-analysis, each study is given a code name consisting of 'Name of the investigator, Initial three alphabet of Country code where the study was conducted, the year the study was published in the respective journal. Keywords were used for searching in the database; Antimalarial Drug, Quinine, Drug Resistance, Efficacy, Safety, and Tolerability, Malaria, Artemisinin, Dihydroartemisinin, Artesunate, Artemether, Arteether, severe malaria, complicated malaria, paediatrics and children.

Data extraction and management

We extracted complete data from the included RCT articles and collected in the datasheet as per predefined outcomes for meta-analysis. The primary measure of effectiveness was parasite clearance time and fever clearance time and secondary measure mortality, coma resolution time (CRT) and neurological sequelae at discharge. Depending on availability of data we

evaluated sensitivity analysis to explore the strength of the results.

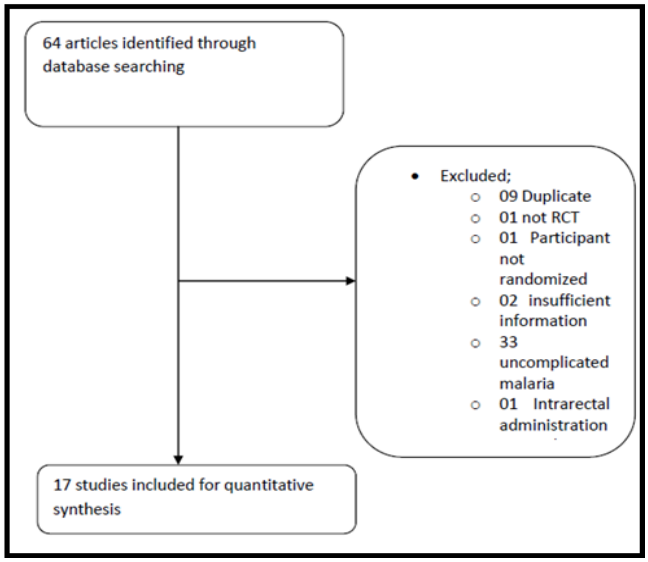

Fig. 1: Flow Chart for Identification and inclusion of studies

Data Synthesis

Analysis was done through Review Manager (updated software version Revman 5.3) pooling data where appropriate. Standard methods of Meta-analysis, e.g., Peto-Mantel-Haenszel method to test for differences in odds ratio or relative risk in terms of above-mentioned outcomes was used for this study. The mean difference was calculated for reported data of Parasite Clearance Time, Fever Clearance Time and coma resolution time. We included total seventeen RCT to evaluate for our outcome analysis which is summarized in figure 1.

RESULTS

All collected and evaluated seventeen RCT studies (7220 paediatric participants) showed comparative outcome in artemisinin derivatives and quinine group paediatric patient. We included RCT studies given mainly three intervention artemisinin derivatives; artesunate (three studies; ArjenAQUAMATAFR2010 [12], MohantyIND2004 [13], PhuongVIE1997 [14]), Artemether (twelve studies; AdamAFR2002 [15], AguwaNIG2010 [16], HudaIND2003 [17], MintaMLI2005 [18], MurphyKEN1996 [19], OjuawoNIG1998 [20], OlumeseNIG1999 [21], OsonugaNIG2009 [22], SattiSUD2002 [23], TaylorMAL1998 [24], VanhensbroekGAM1996 [25], WalkerNIG1993 [26]) and arteether (MoyouCAM2001 [27], ThumaZAM2000 [28]). These RCT conducted in various countries; Africa (02 studies), Nigeria (05 studies), India (02 studies), Sudan (01 studies), Malawi (01 studies), Mali (01 studies), Gambia (01 studies), Cameroon (01 studies), Kenya (01 studies), Vietnam (01 studies) and Zambia (01 studies) detail showed in table 1.

Dose and frequency

Included RCT studies showed variability in dose of artesunate derivatives and quinine as per WHO malaria guideline, ArjenAQUAMATAFR2010 [12]; Artesunate was given either intramuscular (i.m.) or intravenous (i.v.) starting dose 2·4 mg per kg at the time of admission at twelve hrs of interval by the following of once in a day until patient was conscious to take oral antimalarial though Quinine was given 20 mg per kg starting dose in 5% of dextrose three times in a day until patient was conscious to take oral antimalarial. In case of intramuscular administration, similar doses were given as in intravenous though quinine was diluted in normal saline and administered into the anterior thigh of patients. MohantyIND2004 [13]; first group of patient received quinine 20 mg/kg as starting dose by the following of 10 mg per kg at every eight hrs of interval until the patient was conscious to take oral antimalarial though the second group of patients were administered artesunate 2.4 mg per kg iv by the following of 1.2 mg per kg at every six hrs of interval by the following of once daily for next 5 days. PhuongVIE1997 [14]; Artemisinin therapy administered 40 mg at time of initial dose by the following of 20 mg at every specified time of interval as per WHO malaria treatment guideline with 750 mg mefloquine or Artesunate 3 mg per kg at time of initial dose by the following of 2 mg per kg at every 12 hrs of interval with 750 mg of mefloquine though Quinine was administered 20 mg per kg by the following of 10 mg per kg at every 8 hrs up to 7 days. AdamAFR2002 [15]; loading dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg once daily up to four days though loading dose of intravenous quinine was given 20 mg per kg in 5% of dextrose solution by the following of 10 mg per kg of quinine in 5% dextrose solution infused up to four hours for specified time of interval i.e. every eight hrs for three days by the following oral quinine up to seven days. AguwaNIG2010 [16]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg once in a day for two days through intravenous or intramuscular quinine was given 20 mg per kg at the time of admission as initial dose by the following of 10 mg per kg at every specified time of interval i.e. eight hrs. HudaIND2003 [17]; Loading dose of intramuscular artemether was given 1.6 mg per kg two times in a day at the time of admission by the following of 1.6 mg per kg one times in a day for five days though initial dose of quinine was given 20 mg per kg by the following of 10 mg per kg at specified time of intervals i.e. eight hrs until patient was conscious to take oral antimalarial. MintaMLI2005 [18]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg one times in a day for four days though initial dose of intravenous quinine was given 20 mg per kg at the time of admission by the following of 10 mg/kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient was conscious to take oral antimalarial.

Table 1: Characteristics of Included Trials

Intervention	S. No	Trial	Country	Study Population	Inclusion Criteria	N (A/Q)	ROA	Outcome
Artesunate	1	ArjenAQUAMATAFR2010	Africa Multicentre	<15 Yrs	PS+CF of severe malaria	2712/2713	A=i.m./I.V.Q=I.M.	Mortality, Neurological sequelae, CRT
	2	MohantyIND2004	India	Paediatric, Age; NS	PS+CF of severe malaria	40/40	A=I.V., Q=I.V.	Mortality, PCT, FCT, CRT, AE
	3	PhuongVIE1997	Vietnam	<15 Yrs	PS+CF of severe malaria	37/35	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT
Artemether	4	AdamAFR2002	Africa Multicentre	Paediatric, Age; NS	PS+CF of severe malaria	20/21	A=I.M., Q=I.V.	Mortality, PCT, FCT
	5	AguwaNIG2010	Nigeria	<12 Yrs	PS+CF of severe malaria	44/46	A=I.M., Q=I.V./I.M.	Mortality, PCT, FCT
	6	HudaIND2003	India	<14 Yrs	PS+CF of severe malaria	23/23	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT, AE, Neurological Sequelae
	7	MintaMLI2005	Mali	<15 Yrs	PS+CF of severe malaria	33/34	A=I.M., Q=I.V.	Mortality, PCT, FCT
	8	MurphyKEN1996	Kenya	<12 Yrs	PS+CF of severe malaria	89/71	A=I.M., Q=I.V.	Mortality, Neurological sequelae, CRT
	9	OjuawoNIG1998	Nigeria	<6 Yrs	PS+CF of severe malaria	18/19	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT, AE, Neurological Sequelae
	10	OlumeseNIG1999	Nigeria	<5 Yrs	PS+CF of severe malaria	54/49	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT, AE, Neurological Sequelae
	11	OsonugaNIG2009	Nigeria	<12 Yrs	PS+CF of severe malaria	16/16	A=I.M., Q=I.V.	Mortality, PCT, CRT
	12	SattiSUD2002	Sudan	<15 Yrs	PS+CF of severe malaria	38/39	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT, AE, Neurological Sequelae
	13	TaylorMAL1998	Malawi	Paediatric, Age; NS	PS+CF of severe malaria	83/81	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT, AE, Neurological Sequelae
	14	VanhensbroekGAM1996	Gambia	<10 Yrs	PS+CF of severe malaria	288/288	A=I.M., Q=I.V.	Mortality, PCT, FCT, AE
	15	WalkerNIG1993	Nigeria	<5 Yrs	PS+CF of severe malaria	25/29	A=I.M., Q=I.V.	Mortality, PCT, FCT, AE, Neurological Sequelae
Arteether	16	MoyouCAM2001	Cameroon	<10 Yrs	PS+CF of severe malaria	51/51	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT, AE, Neurological Sequelae
	17	ThumaZAM2000	Zambia	<10 Yrs	PS+CF of severe malaria	48/44	A=I.M., Q=I.V.	Mortality, PCT, FCT, CRT, AE, Neurological Sequelae

A = Artemisinin derivative, AE = adverse events, CF = clinical features, CRT = coma resolution time, FCT = fever clearance time, im = intramuscular, iv = intravenous, N = number of participants, NS = not specified, PCT = parasite clearance time, PS = peripheral smear showing asexual forms of Plasmodium

MurphyKEN1996 [19]; initial dose of intramuscular artemether was given 3.2 mg per kg by the following of 1.6 mg per kg one time in a day up to three doses by the following of sulfadoxine-pyrimethamine though initial dose of intravenous quinine was given 20 mg per kg administered up to four hours by the following of 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient

was conscious to take oral antimalarial by the following of sulfadoxine-pyrimethamine.

OjuawoNIG1998 [20]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg at every 12 hrs of intervals by the following of 1.6 mg per kg once in a day for 48 hrs though initial dose of intravenous quinine was given 10 mg per kg administered up to two hours by the following of 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient was conscious to take oral antimalarial for a total of seven days.

OlumeseNIG1999 [21]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg once in a day for four days though initial dose of intravenous quinine was given 20 mg per kg administered up to four hours by the following of 10 mg per kg administered up to two hours at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient was conscious to take oral antimalarial for a total of seven days or twenty-one day's administration.

OsonugaNIG2009 [22]; initial dose of intramuscular artemether was given 1.6 mg per kg two times in a day at the time of admission by the following of 1.6 mg per kg once in a day up to four days though initial dose of intravenous quinine was given 10 mg per kg administered up to four hours by the following of 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient was conscious to take oral antimalarial for a total of seven days.

SattiSUD2002 [23]; loading dose of intramuscular artemether was given 1.6 mg per kg two times in a day by the following of 1.6 mg per kg once in a day up to four days though initial dose of intravenous quinine was given 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient was conscious to take oral antimalarial.

TaylorMAL1998 [24]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg once in a day up to three doses by the following of oral sulfadoxine-pyrimethamine when patients are able to take oral antimalarial though initial dose of intravenous quinine was given 20 mg per kg administered up to four hrs by the following of 10 mg per kg administered up to two hrs at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy by the following of oral sulfadoxine-pyrimethamine.

VanhensbroekGAM1996 [25]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of daily doses of 1.6 mg per kg for three days though initial dose of intravenous quinine was given 20 mg per kg by the following of 10 mg per kg at every 12 hrs of interval and switched to oral antimalarial at the time of patient able to take, quinine for a total of five days by the following of oral dose of 1.25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine.

WalkerNIG1993 [26]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg for four days though initial dose of intravenous quinine was given 20 mg per kg administered up to four hrs at the time of admission by the following of 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy.

MoyouCAM2001 [27]; Arteether was administered intramuscular 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg once in a day up to four days though Quinine 20 mg/kg was administered intravenously initial dose up to 4 hrs by the following of 10 mg per kg at every 8 hrs up to six days by the following of oral quinine 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy and recrudescent cases were treated with sulfadoxine-pyrimethamine in this RCT.

ThumaZAM2000 [28]; intramuscular artemotil was administered as initial dose of 3.2 mg per kg by the following of daily doses of 1.6 mg per kg though intravenous quinine was given 20 mg per kg initial dose in 5% dextrose solution by the following of 10 mg per kg in 5% dextrose solution given at every specified time of intervals i.e. eight hrs followed by oral antimalarial quinine therapy continued for a total of 7 days.

Primary Outcomes

Parasite clearance time: We performed a meta-analysis of thirteen RCT (1048 participants) to evaluate mean parasite clearance time in paediatric patients (figure 2) and it was observed 8.5 hours less with artemisinin derivatives (MD -8.53 hours, 95% CI -9.44 to -7.62). Forest plot shows the statistical difference and significant improvement though we excluded trials which were observed the unclear or high risk of selection bias. The mean parasite clearance times were 30.24 and 36.71 hours for artemisinin derivatives and quinine therapy respectively (P<0.00001).

Fever Clearance Time: Total thirteen RCT studies reported mean fever clearance time with a statistically significant reduction of about nine hours with artesunate derivatives overall (MD -9.42 hours, 95% CI -11.12 to -7.71; thirteen trials, 1048 participants, figure 3). The mean fever clearance times for artesunate derivatives and quinine were 40.12 and 42.23 hours respectively (P<0.00001).

Secondary Outcomes

Mortality: We evaluated total seventeen clinical trials for mortality outcomes in Artemisinin derivatives compared with quinine. Forest plot metaanalysis (figure 4) confirmed that artemisinin or its derivatives showed a statistically significant mortality reduction as compared with quinine. There was the overall difference (RR 0.82, 95% CI 0.72 to 0.93; 17 trials, 7220

participants) *p*=0.002 shown in all-cause mortality in artesunate derivatives as compared with quinine. However, the number of articles needed to be evaluated to detect clinically important differences though overall meta-analysis remains significantly under power to prove equality. None of the collected trials was blinded in this meta-analysis. Risk of bias showed with forest plot that masking of allocation and low or insufficient outcome data or less than 10% due to increasing lost to follow-up observed in evaluable patients.

Coma Resolution Time (CRT): We evaluated total nine RCT and 591 paediatric patients to evaluate coma resolution time which showed less CRT in patients who were received artemisinin or its derivatives as compared to quinine. The mean difference was estimated five hrs shorter (MD -5.37 hours, 95% CI -7.70 to -3.05) *P*<0.00001 was observed in figure 5. In included RCTs risk of bias was high or unclear because of observed outcomes was largest in clinical trials without sufficient allocation concealment and during sensitivity analysis, we excluded these clinical trials which observed the negligible considerable difference between artemisinin and quinine.

Neurological sequelae at the time of discharge (such as blindness, deafness, hemiplegia and others): We evaluated nine trials (5939 participants) and didn't observe overall difference in the risk of neurological sequelae at the time of hospital discharge between artemisinin derivatives and quinine (RR 1.07, 95% CI 0.89 to 1.28) *P*=0.49 which is shown in figure 6 though included clinical trials were too small in the same size to conclude or confidently or exclude which can be shown clinically important differences between treatments arms.

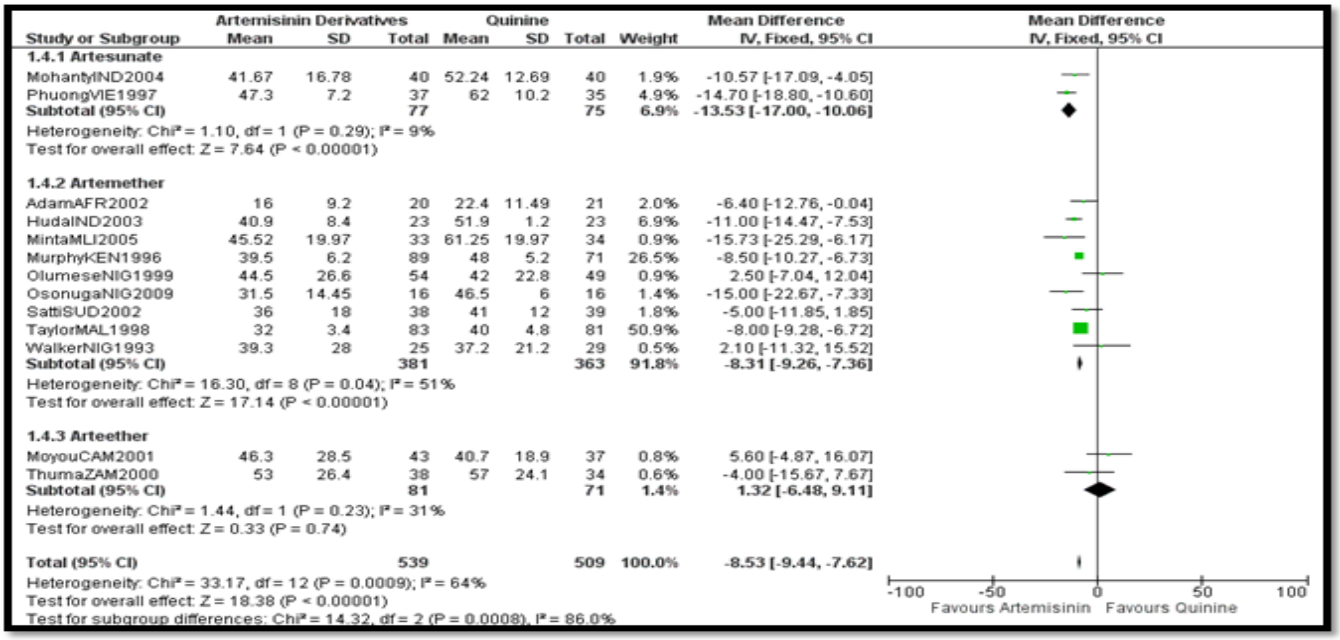

Fig. 2: Forest Plot Parasite Clearance Time

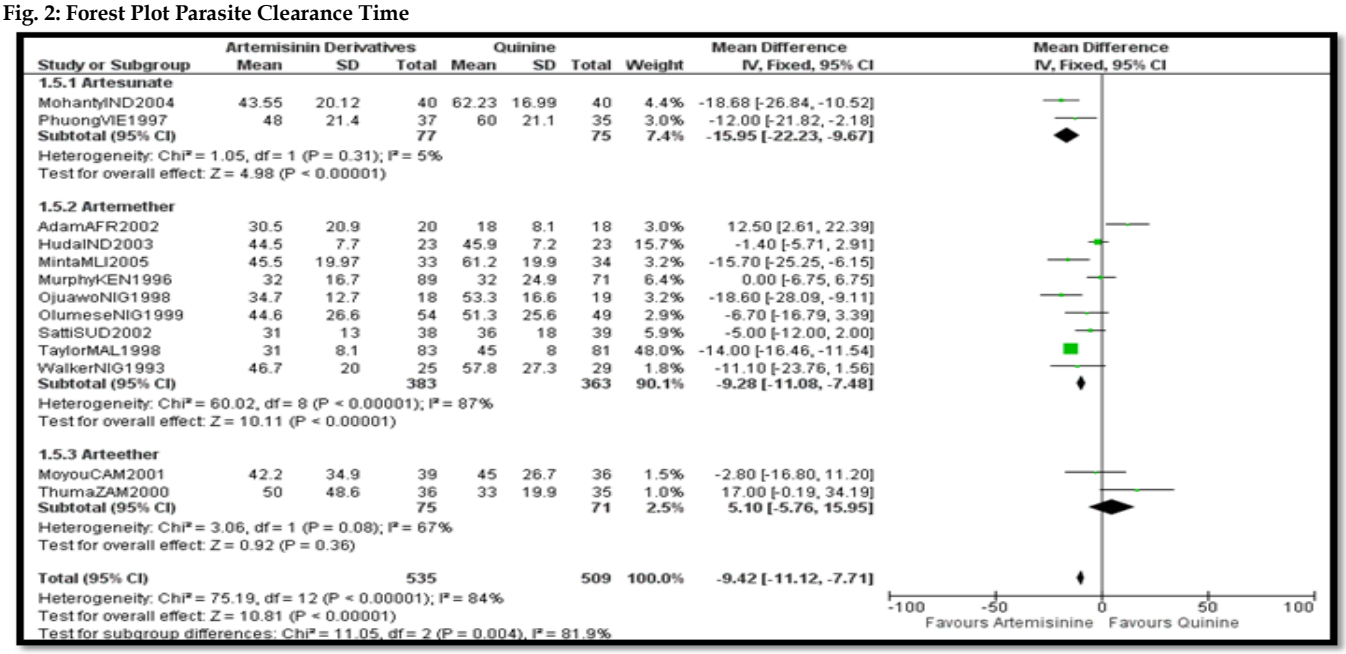

Fig. 3: Forest Plot Fever Clearance Time

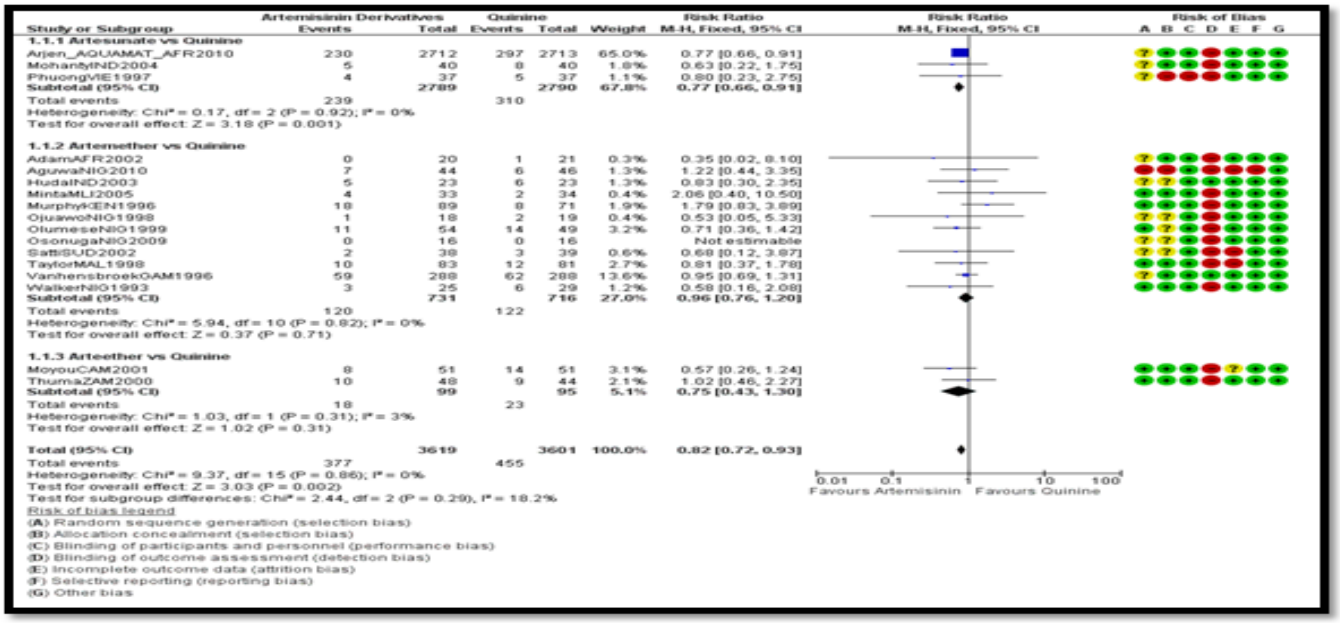

Fig. 4: Forest plot and risk of bias summary; Mortality Artesunate Derivatives versus Quinine in severe paediatric malaria and Risk of bias

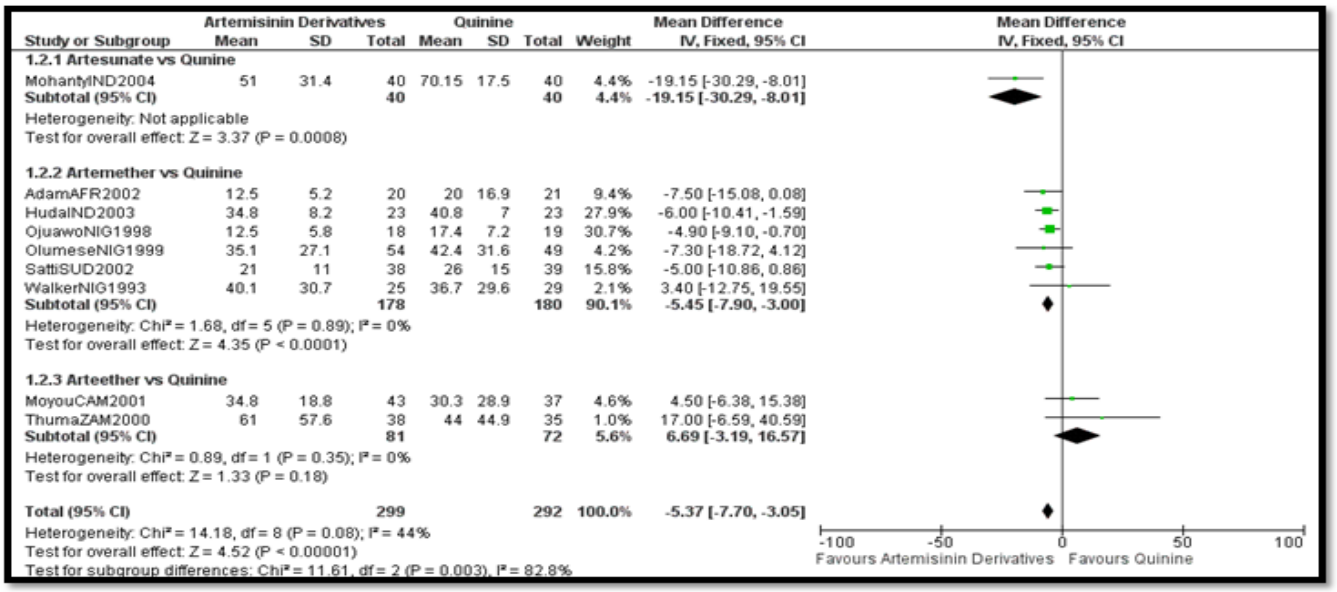

Fig. 5: Forest Plot Coma Resolution time

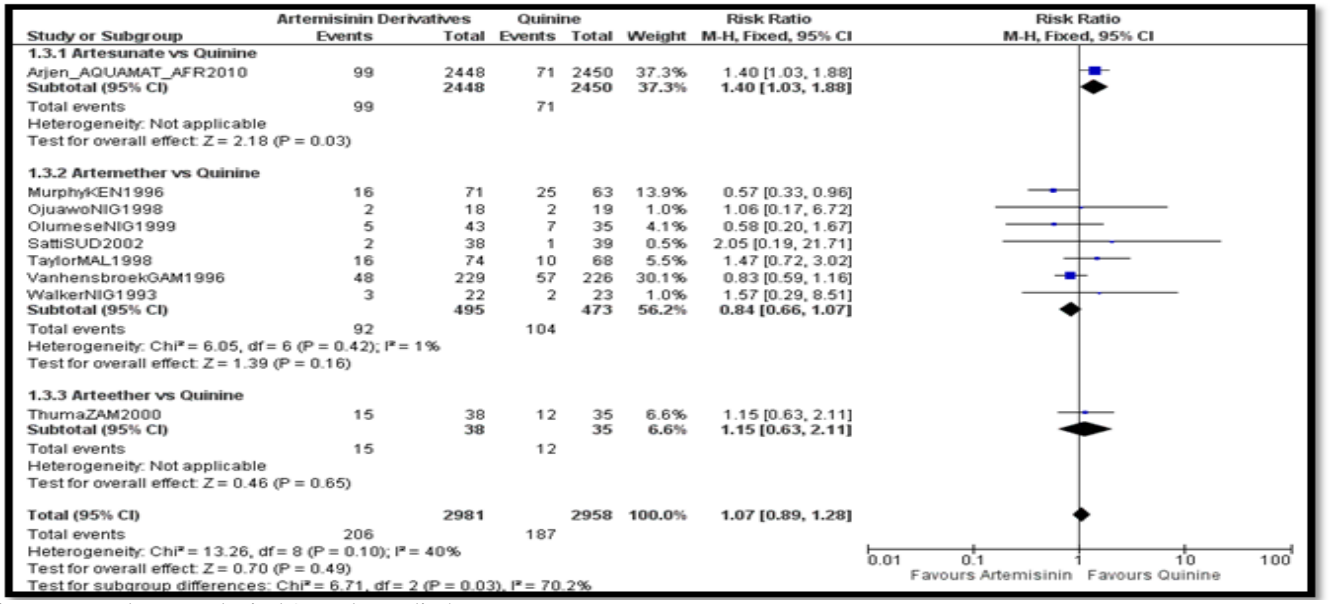

Fig. 6: Forest Plot Neurological Sequelae at discharge

DISCUSSION

For paediatrics RCT mostly conducted in Africa, regions showed the minor or negligible difference in the risk of mortality between artemisinin derivative and quinine which showed moderate or reasonable quality evidence. In this meta-analysis, heterogeneity was determined using the I^2 which defines a measure of the percentage of total variability due to among-study heterogeneity. Values of I^2 =50% suggest a lack of significant heterogeneity. In this meta-analysis, there was substantial heterogeneity (I^2 > 80%) for all outcome except mortality (I^2 =18.2%) and neurological sequelae at discharge (I^2 =70.2%) which is shown in forest plots. Coma is thought to be due to massive sequestration in the brain and this is related to convulsion. In conducted paediatric clinical trial and published report by Dondrop *et al* (2010) observed 230 patients died with artesunate antimalarial as compared with quinine treatment 297 patients. The odds ratio for study site was 0·75, 95% CI 0·63–0·90 and relative reduction 22·5%, 95% CI 8·1–36·9; p=0·0022. The incidence of neurological sequelae did not differ significantly between groups, but the development of coma with artesunate and with quinine showed marked significant OR 0·69 95% CI 0·49–0·95; p=0·0231. [12] Mohanty *et al* (2004) conducted study in paediatric malaria patients in India and research suggested that the CRT, FCT and PCT were significantly less in the artesunate group (50.4 ± 31.49 hrs; 43.55 + 20.12 hrs, and 41.67 ± 16.78 hrs respectively) as compared to the quinine group (70.15 + 17.56 hrs, 62.23 + 16.99 hrs, and 52.24 ± 12.69 hrs respectively) (p<0.05) No side effects were observed in the artesunate treated group. [13] Phuong *et al* (1997) studies showed parasite clearance times were significantly faster in artemisinin and artesunate-treated patients than in those who received quinine (P<0.0001). [14]

Artemisinin derivative may shorten the coma resolution time by about five hours which is low-quality evidence and may reduce the number of children with subsequent neurological sequelae which is low-quality evidence. Artemisinin derivative probably shortens the parasite clearance time by about nine hours (moderate-quality evidence) and may shorten the fever clearance time by about nine hours (moderate-quality evidence). For older children (> 15 years) Artemisinin derivatives probably reduce deaths compared with quinine (*moderate-quality evidence*) though there is a limitation in the availability of more evidence or need more RCT for favouring artemisinin derivatives in severe childhood malaria. However, artemisinin derivatives showed comparable effect across all outcomes. Many conducted studies suggest that either therapy could be equally efficacious though quinine administration requires close monitoring in a hospital setting and treatment of severe malaria in the real-world setting is often empirical and required urgent treatment so artemisinin may result in greater effectiveness, despite equivalent efficacy. [1-2] Published studied suggest that in Southeast Asia regions treatment with artemisinin derivatives might reduce mortality by 50%. [8]

Although there the limitation of availability for more number of evidence comparing artemether with artesunate and this meta-analysis showed that artemether is possibly less effective as compare to artesunate to preventing mortalities in severe malaria though where artesunate is not available artemether could use an alternative to quinine. Although this meta-analysis showed non-inferiority in terms of efficacy which allow better use of artemisinin derivatives because of its simpler administration and potentially improved safety for better patient care for the treatment of malaria in paediatrics.

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