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Efficacy Study: Quinine Plus Doxycycline Vs. Quinine Plus Clindamycin Vs. Artemisinin Combination Therapy in the Cases of Severe P.faciparum Malaria At Tertiary Care Hospital

Medical Science

KEYWORDS : P.Falciparum Malaria, 28 days cure rate, FCT, PCT

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ABSTRACT

Malaria is one of the major public health problems of the country. The emergence of resistance to standard antimalarial drugs by Plasmodium falciparum represents a major public health threat. The main aim of study is to determine therapeutic efficacy between a different regimens (Quinine plus Doxycycline & Quinine plus Clindamycin & Artemisinin combination therapy) in management of patients with severe P.Falciparum Malaria at Guru Govindsingh Hospital, Jamnagar (saurashtra region, Gujarat) and to find out the treatment outcome that will guide in choosing the right treatment regimen , helping to reduce morbidity and mortality in patients with severe P.Falciparum Malaria.

INTRODUCTION:

Malaria is one of the major public health problems of the country. Around 1.5 million laboratory confirmed cases of malaria are reported annually by the National Vector Borne Disease Control Programme (NVBDCP). Out of the total malaria cases, around 50% cases are due to Plasmodium falciparum (P.falciparum).[1,2,3]

One of the reasons to rise in the cases of P.falciparum cases is resistance to chloroquine, which was used for a long time as the first line of treatment. The artesunate sulfadoxine-pyrimethamine combination has become the standard therapy in India, but is hampered by lingering concerns of costs. Second-line treatment in India is quinine and 1st line treatment in many centres due to unavailability of artemisins and cost constraint. Tetracycline & clindamycin antibiotics demonstrate synergistic action with quinine when used in combination.[1,2,3]

In the view of increasing antimalarial drug resistance in the background of high endemicity in our region, high amount of severe malaria cases and high case fatality rate of severe malaria particularly in young children, there is a felt need of more efficacious treatment regimen for management of severe malaria. In a view of multiple recommendations and guidelines put forwarded at present, it becomes necessary to evaluate their comparative efficacy and safety profile. Hence this study was conceived to comparatively evaluate the efficacy of three treatment options in severe P.falciparum Malaria as recommended in Drug Policy for treatment of severe Malaria by National Vector Disease Control Programme (NVBDCP) with consideration to mortality, treatment failure in geographical area of Saurashtra:

1. Quinine and clindamycin combination therapy
2. Quinine and doxycycline combination therapy
3. Artesunate and pyrimethamine-sulfadoxin combination (AS+SP) therapy

AIMS & OBJECTIVES:

1. To determine therapeutic efficacy between regimens containing Quinine and doxycycline vs. Quinine and clindamycin vs. artemisinin based combination therapy (aretesunate and pyrimethamine-sulfadoxin combination) in management of patients with severe P.Falciparum Malaria.
2. To find out cure rate (treatment outcome) among treatment regimens.

MATERIALS & METHODS:

This prospective cross sectional study was carried out on 112 patients admitted in general wards, emergency ward and Intensive Care Unit under the domain of Department of Medicine, G. G. Hospital, Jamnagar.

Study observation was till the patient was discharged minimum 48 hours after laboratory investigations for P.falciparum malarial parasites was negative and follow up after 28 days as per protocol.

All patients were given treatment according to malaria guidelines defined by WHO[6] and national drug policy on malaria[3,4,5.]

Inclusion criteria:

- Age>12 years of either sex (except pregnant women)
- Slide positive severe malaria cases (P.falciparum) with/ without complication as defined by WHO
- Absence of any other systemic illness as determined by history and physical examination
- Absence of any other concomitant illness or medication

Exclusion criteria:

- Patients with clinical symptoms of malaria but smear negative
- Mixed malaria infection by giemsa stain.
- Patients who had taken ant malarial drugs before coming to the hospital or in previous 42 days.

Note: Severe form of P.falciparum malaria characterized by:

(As Defined by National Policy for Malaria Diagnosis and Treatment – 2011)

- Impaired consciousness/coma
- Repeated generalized convulsions
- Renal Failure (s.creat > 3)
- Jaundice (s.bilirubin > 3 mg)
- Severe anaemia (Hb < 5 g/dl)
- Pulmonary oedema/ ARDS
- Hypoglycaemia
- Metabolic acidosis
- Circulatory collapse/ shock (systolic BP< 80mm hg)
- Abnormal Bleeding & Disseminated Intravascular Coagulation(DIC)
- Haemoglobinuria

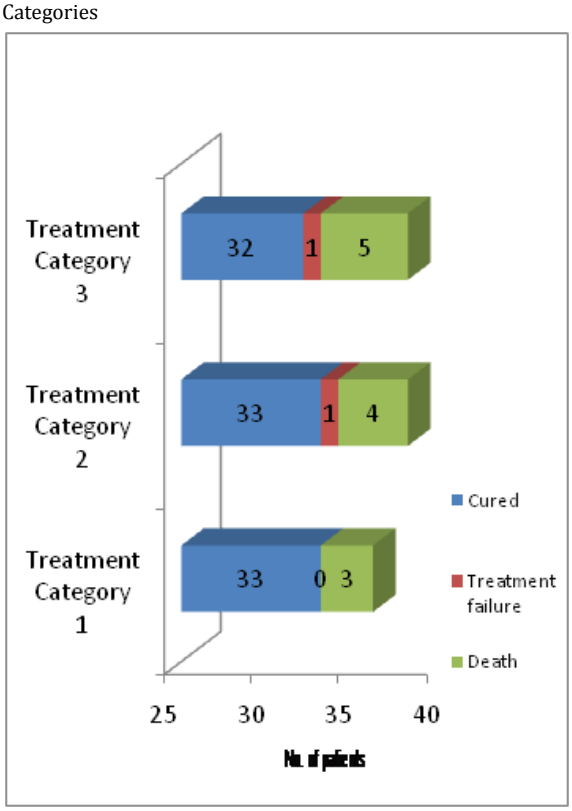
- Hyperpyrexia (t> 106)
- Hyperparasitemia (>5% Parasitized RBC's)

RESULTS:

The study was conducted on 112 hospitalized patients presenting with smear positive malaria parasite P.falciparum which could be classified in the category of severe malaria as per definition of NVBDCP & WHO. Out of which 36 patients were in treatment category I (Quinine and clindamycin) and 38 patients in each of the treatment category II (Quinine and doxycycline) and III (Artesunate and pyrimethamine-sulfadoxin combination).

It was observed that all patients included in the study had fever (100%) with chills and rigors (96%) at the time of presentation. The next common symptom was nausea and vomiting (84%) followed by anorexia, prostration, headache, Convulsions, altered sensorium, Breathlessness and abnormal bleeding. Tachycardia (61%) was commonest sign followed by pallor(36%), icterus(32%), spleenomegaly(32%), hepatomegaly(28%),hypo tension(21%) and petechia(9%).

Figure 1: Comparison of 28 days cure rate among Treatment Categories



It was observed that in treatment category I, 33 patients were declared cured as they achieved treatment objective of 28th day and 3 died during treatment and there was no failure. In treatment category II, 33 patients were declared cured as they achieved treatment objective of 28 day cure, 1 treatment failure and 4 died. In treatment category III, 32 patients were declared cured as they achieved treatment objective of 28 day cure, 1 treatment failure and 5 died.

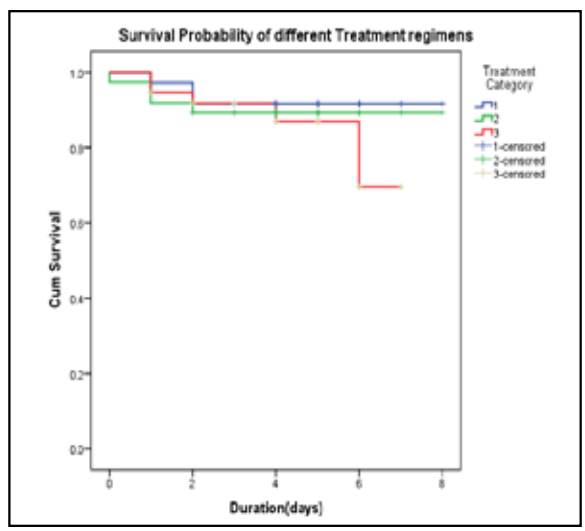
Table 1: Comparison of PCT (Parasite Clearance time) and FCT (Fever Clearance Time) among treatment categories.

PCT	Treatment category	I	II	III
	Mean PCT (hours)	37.50	42.18	36.36
	SD	16.34	17.26	14.22
	Standard Error of Mean (SEM)	2.88	3.00	2.47
	'P' value (ANOVA)	0.299*		
FCT	Treatment category	I	II	III
	Mean FCT (hours)	21.56	23.45	24.48
	SD	9.09	9.47	10.18
	Standard Error of Mean (SEM)	1.60	1.65	1.77
	'P' value (ANOVA)	0.46*		

*=not statistically significant, p>0.05

It is observed from the table 1 that the mean parasite clearance time (PCT) for the patients included in treatment category 1 was 37.50 hours, for Category 2 was 42.18 hours & for category 3 was 36.36 hours and the mean fever clearance time (FCT) for the patients included in treatment category 1 was 21.56 hours, for Category 2 was 23.45 hours & for category 3 was 24.48 hours. The difference in parasite clearance time (PCT) and fever clearance time (FCT) between three treatment categories was not statistically significant.

Figure 2: KAPLAN MEIER curve for survival:



Kaplan Meier survival analysis showed insignificant variation in survival. Though most number of deaths was seen in Category 3(5), the survival when checked on the anvil of Chi Square test, it was found to be statistically insignificant. Most (6 out of 12) of the deaths occurred in 48 hours of admission. Only 4 out to 12 patients had Positive smear at the time of death, others perished due to setting in of multiple organ failure which could not be contained in spite of optimum treatment available at our setup.

Cerebral Malaria remains the most common cause of death, followed by hepatopathy, ARDS and nephropathy. However all 12 patients had more than one complication at the time of presentation.

In category I 11(30.55%) patients, in treatment category II 17(44.73%) patients and in treatment category III 8(21.05%) patients developed Adverse Drug Reactions (ADRs).

DISCUSSION:

In our study 28 day cure rate is defined as clearance of the asexual parasites (erythrocyte stage of parasites) within 7 days without recrudescence by day 28[7,8]. In present study there were 12 mortality, two treatment failure and rest 98 patients were declared cured after 28 days.

Another meta-analysis done by Pittler MH et al[9] reported that no significant difference in mortality rate between recipients of artemether vs. quinine for severe malaria. All trials conducted in sub-Saharan African countries suggest the absence of a significant difference between artemether and quinine.

In present study mean Fever Clearance Time (FCT) was shortest in category I (Quinine and clindamycin) that was 21.56 hours

and mean Parasite Clearance Time (PCT) was shortest in category III (Artesunate and pyrimethamine-sulfadoxin combination) that was 36.36 hours. The difference in Fever Clearance Time (FCT) and Parasite Clearance Time (PCT) between three treatment categories was statistically not significant.

Similar results Moyou-Somo R et al[8] reported that the difference in cure rate, fever clearance time (FCT) and parasite clearance time (PCT) were non-significant between β-arteether group and quinine group. Another meta-analysis done by Kyu HH et al[10] reported that there was no statistically significant difference between artemisinin derivatives and quinine in preventing deaths. Another study done by Haroon et al[11] reported that the difference in cure rate is non-significant whereas the difference in FCT and PCT is significant between artesunate group and quinine group in the treatment of severe malaria.

CONCLUSION:

- We can deduce that in terms of efficacy all the three groups have equal effect. So the selection of drugs should be done on the basis of patient profile and local resistance pattern.
- There were total 2 treatment failures. One each in category 2 & 3. 1st patient (Cat 2) came out to be positive for P.falciparum Malaria (Low grade) at 28th day of smear most likely explained by re–infection due to high transmission rate in our region instead of true recrudescence which is rarely seen with quinine and doxycycline combination. 2nd patient (Cat 3) had early treatment failure as smear showed increased grading for parasitemia with persistence of fever at 48 hours.
- Kaplan Meier survival analysis and Chi Square analysis applied for cure rates at 28th day of study showed insignificant variation in survival and cure rates between three categories.
- In present study artesunate + Sulfadoxine-pyrimetahmine is well tolerated as compared to quinine + doxycycline or quinine + clindamycin.
- Artemisinin-based combinations with a short plasma half-life merit further attention for use in regions in which the rate of transmission of malaria is high.
- Characterized by slow but thorough antimalarial activity, clindamycin exhibits remarkably good safety and tolerability profile in antimalarial therapy.
- Clindamycin & doxycycline demonstrate synergistic action with quinine when used in combination so by using combination therapy we can reduce the emergence of resistance to monotherapy.

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