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Original Research Article

Efficacy, safety and tolerability of three regimens of artemisinin combination therapy in the management of *Plasmodium falciparum* malaria: a comparative study

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ABSTRACT

Background: The WHO now recommends the use of artemisinin-based combination therapies for the first-line treatment of *Plasmodium falciparum* malaria to reduce the drug resistance. Hence, this study was designed to compare the efficacy, safety and tolerability of three regimens of artemisinin combination therapies in malaria diagnosed patients of Kamineni Institute of Medical Sciences Hospital, Narketpally.
Methods: Total of 104 subjects had been allocated to 3 different artemisinin-based combinations regimens in a period of 2 years during December 2013 - November 2015. Out of 104 subjects, 34 received artemisinin-sulphadoxine pyrimethamine regimen, 33 subjects received artemisinin-lumefantrine regimen, and 37 subjects received artemisinin-doxycycline regimen. All the three regimens were studied for their efficacy, safety and tolerability.
Results: The mean number of febrile days in artesunate-sulfadoxine pyrimethamine group (3.43±0.92) and artesunate-doxycycline group (3.51± 0.74) were comparatively less than artemether-lumefantrine group (4.33±0.77) which is statistically significant. The mean Hb%, RBC count, WBC count was not significantly different on day 7 in comparison to day 1 in all the three regimens of treatment groups. 14 subjects among the 104 had mild thrombocytopenia which was significantly improved on day 7 in all the three regimens of treatment groups.
Conclusions: Artesunate-sulfadoxine-pyrimethamine and artesunate-doxycycline regimens showed better efficacy, safety and tolerability than artemether-lumefantrine regimen.

Keywords: *Plasmodium falciparum* malaria, Artemisinin-based combination therapies, Febrile days, Thrombocytopenia

INTRODUCTION

Malaria is a protozoan disease transmitted by the bite of infected female *Anopheles* mosquitoes. It is present in 106 countries containing about 3 billion people and causes approximately 2000 deaths each day.[1] For the prevention of malaria, WHO recommends vector control (i.e. preventing mosquitoes from biting human beings) or chemoprevention (i.e. providing drugs that suppress infections) in specific population subgroups (i.e. pregnant women, children and other high-risk groups).[2] Plasmodium falciparum is the main infecting species and its infection can be very fatal unless promptly treated. It is responsible for the majority of deaths due to malaria and the situation has been worsened by the development of resistance by this parasite to most antimalarial drugs.[3] Resistance to chloroquine for *Plasmodium falciparum* is most common and results due to mutation in putative chloroquine transporter, resistance to quinine and mefloquine is by increased expression of P-glycoprotein.[4] *P. falciparum* malaria should be treated with drug combinations and not with single drug in endemic areas. This combination strategy is based on simultaneous use of two or more drugs with different

modes of action. Artemisinin combination treatment (ACT) regimens are now recommended as first-line treatment for falciparum malaria throughout the malaria-affected world.[1] Mukhtar et al had reported that artesunate plus sulphadoxine/pyrimethamine is slightly more effective in malaria patients than artemether-lumefantrine in eastern Sudan.[5] The WHO now recommends the use of artemisinin-based combination therapies (ACTs) for the first-line treatment of *P. falciparum* in endemic areas. Artemisinin group of drugs are rapidly acting so they reduce the parasite load or burden because they are very potent drugs, and they are combined with longer acting drugs to eliminate the remaining parasites.[6]

Hence, this study was designed to compare the efficacy, safety and tolerability of three regimens of ACTs in malaria diagnosed patients of Kamineni institute of medical sciences hospital, Narketpally, Nalgonda (dist.), Telangana.

METHODS

After getting approval from institutional ethical committee of Kamineni Institute of Medical Sciences, Narketpally, (Ref no: IEC/KIMS/NKP/2013). Patients of either sex, of age 18 to 75 years admitted with clinical symptoms and signs of malaria and with positive malarial parasite smear/rapid diagnostic test for *P. falciparum* were included in the study. And patients who received any other anti-malarial drugs in the past 48 hours, pregnancy and lactating woman, subjects with complicated malaria where parenteral therapy required, mixed infections of plasmodia, those who refused to participate in the study were excluded from the study.

The study included a total of 109 subjects during December 2013 to November 2015. Out of 109 subjects, 5 subjects were excluded from the study who took other antimalarial drugs within 48 hours. Hence number of patients in all 3 regimens are 104. Out of 104 patients, 34 subjects received artesunate-sulphadoxine-pyrimethamine (AS/SP). 33 subjects received artesunate-lumefantrine (AL). 37 subjects received artesunate-doxycycline (AD) (Table 1). The demographic data of patients presenting with clinical signs and symptoms was collected. Blood sample was collected and sent for the malarial parasite smear. Subjects with smear/rapid diagnostic test positive for *P. falciparum* were included in the study. Informed written consent was taken from patients before collection of data. Randomization was done according to table of random numbers for allocating the patients into three groups for administering the three regimens.

Table 1: Division of 3 different ACT regimen groups (n=104).

	Group A (n=34)	Group B (n=33)	Group C (n=37)
Regimens	Artemisinin- sulphadoxine pyrimethamine	Artemisinin- lumefantrine	Artemisinin- doxycycline
Dosage	Artesunate :100 mg orally BD × 3 days Sulfadoxine 500 mg + Pyrimethamine 25 mg 3 tab × 1 day	Artemether : 80 mg orally BD×3 days Lumefantrine: 480 mg orally BD× 3 days	Artesunate: 100 mg orally BD × 7 days Doxycycline: 100 mg orally BD × 7 days

Parameters for assessing efficacy of 3 ACT regimens are 1) number of febrile days; 2) change in platelet count in thrombocytopenia observed patients. Body temperature of all patients was measured daily from day 1 to day 7. Period of febrile days in all patients with respect to each regimen were noted (normal oral temperature- 36.8±0.40 °C). Platelet count was measured on day 1 and day 7 i.e. before and after the completion of treatment for all patients. The values of day 7 are compared with the day 1 values. Safety and tolerability of the treatment regimen were assessed by checking RBC count, Hb%, WBC count, random blood sugar levels, blood urea and serum creatinine and observation of unwanted reactions from day 1 to day 7.

Statistical analysis was done by SPSS software version 19. Comparison between same group was done by student paired 't' test. Comparison between the groups was done by ANOVA. Chi-square test was for adverse drug reactions. $P<0.05$ was considered statistically significant.

RESULTS

The efficacy of the three regimens treatment was assessed by comparing the mean febrile days in each group. The safety and tolerability was assessed by doing RBC and WBC counts, Hb%, blood urea, serum creatinine on day 1 and day 7. Further all the ADR's from day 1 to day 7 in all the three regimen treatments were recorded.

The mean number of febrile days in artesunate-sulfadoxine pyrimethamine group (3.43±0.92) and artesunate-doxycycline group (3.51±0.74) were comparatively less than artemether-lumefantrine group (4.33±0.77) which is statistically significant ($p<0.001$) (Table 2).

Table 2: The mean number of febrile days in different groups (n=104).

Regimens	Number of febrile days (mean±SD)
Artesunate-sulfadoxine pyrimethamine (n=34)	3.43±0.92**
Artemether-lumefantrine (n=33)	4.33±0.77
Artesunate-doxycycline (n=37)	3.51±0.74**

**p<0.001.

Table 3: Hemoglobin (gm%) in study subjects before and after treatment (n=104).

Regimens	Day 1 (mean±SD)		Day 7 (mean±SD)	
	Males	Females	Males	Females
Artesunate-sulfadoxine pyrimethamine (n=34)	13.3±0.11	12.10±0.25	13.6±0.10	12.24±0.13
Artemether-lumefantrine (n=33)	13.5±0.25	12±0.18	13.7±0.16	12.2±0.14
Artesunate-doxycycline (n=37)	13.6±0.11	11.9±0.10	13.7±0.10	12.14±0.10

Table 4: RBC count (millions/cubic mm) in study subjects before and after treatment (n=104).

Regimens	Day 1 (mean±SD)		Day 7 (mean±SD)	
	Males	Females	Males	Females
Artesunate-sulfadoxine pyrimethamine (n=34)	4.3±0.11	4.10±0.25	4.6±0.10	4.34±0.13
Artemether-lumefantrine (n=33)	4.5±0.25	4±0.15	4.7±0.16	4.2±0.14
Artesunate-doxycycline (n=37)	4.6±0.31	4.2±0.30	4.67±0.10	4.24±0.10

Table 5: WBC count (per cubic mm) in study subjects before and after treatment (n=104).

Regimens	Day 1 (mean±SD)	Day 7 (mean±SD)
Artesunate-sulfadoxine pyrimethamine (n=34)	6373.52±1359.43	6600±1303.37
Artemether-lumefantrine (n=33)	7021.21±1166.39	7206.06±1164.56
Artesunate-doxycycline (n=37)	7206.06±1164.56	6674.32±1394.11

Table 6: Platelet count (per cubic mm) in study subjects before and after treatment (n=14).

Regimens	Day 1 (mean±SD)	Day 7 (mean±SD)
Artesunate-sulfadoxine pyrimethamine (n=5)	0.90±0.011	1.66±0.01**
Artemether-lumefantrine (n=3)	0.91±0.015	1.45±0.12**
Artesunate-doxycycline (n=6)	0.91±0.016	1.66±0.01**

**p<0.001.

Table 7: RBS (mg/dl) in study subjects before and after treatment (n=104).

Regimens	Day 1 (mean±SD)	Day 7 (mean±SD)
Artesunate-sulfadoxine pyrimethamine (n=34)	92.77±4.69	103±5.11*
Artemether-lumefantrine (n=33)	90.48±5.38	98±4.89*
Artesunate-doxycycline (n=37)	88.97±6.44	100±5.93*

*p<0.05.

The mean Hb%, RBC count, WBC counts were not significantly different on day 7 in comparison to day 1 in all the three regimens of treatment groups (Tables 3-5).

It was observed that 14 patients among the 104 total patients had mild thrombocytopenia which was significantly improved on day 7 (p<0.001) (Table 6). The random blood sugar (mg/dl) mean values in all the three regimens was significantly less on day 1 compared to day 7 (p<0.05) (Table 7). The mean blood urea (mg/dl) and serum creatinine (mg/dl) in all the three study groups were measured on both day 1 and day 7 an It was observed that there was no statistically significant difference between day 1 and day 7 values (Table 8).

The unwanted adverse effects in the patients of three ACT regimens were recorded from day 1 to day 7. The number of patients and the percentage of patients who developed

adverse effects were 15 (44.11%), 29 (87.87%) and 16 (43.24%) in artesunate-sulfoxadine-pyrimethamine, artemether-lume-fantrine and artesunate-doxycycline regimens respectively (Table 9).

Table 8: Blood urea (mg/dl) and serum creatinine (mg/dl) in study subjects before and after treatment (n=104).

Regimens	Blood urea		Serum creatinine	
	Day 1 (mean±SD)	Day 7 (mean±SD)	Day 1 (mean±SD)	Day 7 (mean±SD)
Artesunate-sulfadoxine pyrimethamine	21.02±3.45	23.05±3.64	0.78±0.11	0.81±0.12
Artemether-lumefantrine	20.66±2.33	22.81±2.04	0.77±0.14	0.83±0.13
Artesunate-doxycycline	21.40±2.76	23.16±2.43	0.82±0.13	0.86±0.14

Table 9: Distribution of adverse effects in different ACT regimens (n=104).

Adverse effects	Artesunate-sulfadoxine pyrimethamine (n=34)	Artemether-lumefantrine (n=33)	Artesunate-doxycycline (n=37)
	N (%)	N (%)	N (%)
Nausea	4 (11.7)	4 (12.12)	3 (8.10)
Vomiting	2 (5.88)	6 (18.18)	3 (8.10)
Dizziness	3 (8.82)	7 (21.21)	4 (10.81)
Headache	5 (14.70)	7 (21.21)	3 (8.10)
Abdominal pain	-	2 (6.06)	-
Pruritis	-	2 (6.06)	-
Myalgia	-	1 (10)	-
Others (diarrhoea, anorexia etc.)	1 (2.94)	-	3 (8.10)
Total	15 (44.11)	29 (87.87)	16 (43.24)

**p<0.001.

DISCUSSION

Malaria is a protozoan disease caused by plasmodium species and transmitted by bite of infected female anopheles mosquitoes.[1] It is present in 106 countries affecting about 3 billion people and causing approximately 2000 deaths each day. In India the deaths due to malaria from March 2013 to April 2014 were 379. About 92% of malaria cases and 97% of deaths due to malaria is reported from North-eastern states, Chhattisgarh, Jharkhand, Madhya Pradesh, Orissa, Andhra Pradesh, Maharashtra, Gujarat, Rajasthan, West Bengal and Karnataka.[7] As resistance to older anti-malarial drug chloroquine is more in many endemic areas, WHO recommended ACT consisting of following combinations for uncomplicated malaria cases including artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine, artesunate-sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine, artesunate-doxycycline.[4-6]

Among the available antimalarial drugs the only group of drugs which causes rapid clearance of the malarial parasite are artemisinins group of drugs. They are more potent and rapidly acting antimalarial drugs. And Artemisinins also have gametocytocidal activity, leading to a decrease in malarial parasite transmission.[8] Out of the above six regimens, artesunate-sulfadoxine-pyrimethamine, artemether-lumefantrine and artesunate-doxycycline regimens are being administered in patients of uncomplicated malaria admitted in general medicine wards of Kamineni Institute of Medical Sciences Hospital, who had shown positive response for malarial parasite by rapid diagnostic test/smear test. The data was recorded for 7 days from the day of admission. As fever is one of the important symptoms in malaria patient, the number of febrile days in each regimen had been taken as a parameter for assessing the efficacy. The febrile days was also considered as a parameter for studying the efficacy of anti-malarial drugs by previous workers. [9-11]

The mean febrile days in the present study groups were 3.43±0.92, 4.33±0.77, 3.51±0.74 in artesunate-sulfadoxine pyrimethamine, artemether - lumefantrine and artesunate-doxycycline regimens respectively. As the mean febrile days in artesunate-sulfadoxine pyri-methamine regimen and artesunate-doxycycline regimen is significantly lesser than artemether-lumefantrine regimen, so the artesunate-doxycycline and artesunate-sulfadoxine pyrimethamine regimens have more efficacy than artemether-lumefantrine regimen. Mukhtar et al 2007 in their study also reported more efficacy of artesunate-sulfadoxine pyrimethamine regimen than artemether-lumefantrine regimen by taking the parameter of parasite density.[5] In the present study, 14 patients had thrombocytopenia out of 104 patients at the time of admission. The platelet count returned to the normal level on day 7 in all the three regimens.

Serum creatinine and blood urea were in normal range in all the three regimen patients on day 1 and was not

significantly increased by day 7 suggesting no renal toxicity in all the three regimen patients within a period of 1 week. The subjective unwanted effects like nausea, vomiting, headache, dizziness, myalgia, pruritis, abdominal pain etc. were recorded in all the three groups of the patients in the 7 days observation period. These ADR's were significantly more in artemether-lumefantrine regimen 29/33 (87.87%) than artesunate-sulfadoxine pyrimethamine regimen 15/34 (44.11%) and artesunate-doxycycline regimen 16/37 (43.24%) respectively.

CONCLUSION

Statistically, ADR's appear significantly more in the artemether-lumefantrine regimen than artesunate-sulfadoxine pyrimethamine regimen or artesunate-doxycycline regimen.

Further studies are required to confirm the results of the present study by doing in more number of patients, parasite density parameter for studying the efficacy and monitoring adverse drug reactions beyond 7 days.

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REFERENCES

1. Kasper DL, Braunwalg E, Anthony S, Fauci, Stephen L, Hauser, editors. Harrison's Principles of Internal Medicine. 19th ed. The McGraw-Hill (New York); 2015: 1368-1371.
2. WHO. "World malaria report": A document of World Health Organization, Geneva. 2018.
3. Kimbi HK, Ntoko M, Ntonifor NN, Lum E, Njunda AL, Fon PN. Efficacy and Tolerability of Malartin and Sulphadoxine-Pyrimethamine Combination against Uncomplicated Falciparum Malaria in Dibanda, Southwest Cameroon. J Trop Med. 2012;372518:7.
4. Sharma HL, Sharma KK, Principles of pharmacology. 3rd ed. New Delhi: Paras Medical Publisher; 2017: 824-837.
5. Mukhtar EA, Gadalla NB, El-zaki SE, Mukhtar I, Mansour FA, Babiker A, et al. A comparative study on the efficacy of artesunate plus sulphadoxine/ pyrimethamine versus artemether-lumefantrine in eastern Sudan. Malar J. 2007;6:92.
6. WHO. Antimalarial drug combination therapy. Report of a WHO Technical Consultation," Report of a WHO Technical Consultation WHO/CDS/RBM/ 2001, WHO, Geneva, Switzerland, 2001.
7. Park K. Park's textbook of preventive and social medicine. 23rd ed. India: Bhanot Publishers; 2015: 256-260.
8. Brunton LL, Chabner BA, Knollaman BC. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2012: 1383-1399.
9. Elamin SB, Malik EM, Abdelgadir T, Khamiss AH, Mohammed MM, Ahmed ES, et al. Artesunate plus sulfadoxine-pyrimethamine for treatment of uncomplicated *Plasmodium falciparum* malaria in Sudan. Malar J. 2005;4:41.
10. Mockenhaupt FP, Ehrhardt S, Dzisi SY, Teun Bousema J, Wassilew N, Schreiber J, et al. A randomized, placebo-controlled, double-blind trial on sulfadoxine- pyrimethamine alone or combined with artesunate or amodiaquine in uncomplicated malaria. Trop Med Int Health. 2005;10(6):512-20.
11. Marquiño W, Ylquimiche L, Hermenegildo Y, Palacios AM, Falconí E, Cabezas C, et al. Efficacy and tolerability of artesunate plus sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine alone for the treatment of uncomplicated Plasmodium falciparum malaria in Peru. Am J Trop Med Hyg. 2005;72(5):568-72.

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