RESEARCH ARTICLE

Plasmodium falciparum resistance and malaria presentation in children at Dongola specialist hospital: A prospective cohort study

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Abstract

Objective: To provide evidence about the susceptibility of anti-malarial drugs, and to identify the clinical features of the disease in children.

Method: The prospective observational comparative study was conducted at the Dongola Specialist Hospital, Dunqulah, Sudan, from February 2016 to February 2017, and comprised children aged <16 years with bodyweight >5kg who had malaria. The subjects were enrolled into group 1, which received treatment based on physician's discretion, and group 2, which received treatment in accordance with the national guidelines. The follow-up was conducted on days 3, 7 and 14 to identify cases as early treatment failure, late treatment failure, or treatment success. Data were analysed in terms of frequencies and percentages using statistical analysis software R version 3.1.2.

Results: Of the 120 children, 60(50%) were in each of the two groups. Overall, 63(52.5%) were aged 1-6 years, 66(55%) were males, and 42(35%) were exposed to malaria for the first time. Post-treatment test was negative for all 120(100%) the subjects in both the groups. showing no inter-group difference.

Conclusion: Although resistance to combination therapy was not detected, it remains extremely important to remain vigilant for the emergence of resistance in the future.

Keywords: Child, Drug resistance, Malaria, Sudan. (JPMA 72: 649; 2022)

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Introduction

Despite decades of malaria eradication efforts, the disease still poses significant challenges.[1,2] It is widespread around the equator in the subtropical and tropical regions. Africa accounts for 92% of the disease burden, while Asia and Latin America account for 5% and 2%, respectively.[3] There are about 300 million clinical cases and about 450,000 deaths due to malaria globally.[3] Plasmodium (P.) falciparum is the most common malaria parasite, accounting for 99.7% cases in Africa.[4]

Malaria is both a cause and a consequence of poverty, which deserves more investment in housing improvement and agricultural development.[5] It has a significant impact on economic growth due to healthcare costs, loss of work, and effects on tourism.[5,6] The economic impact of malaria represents a burden of $332,286.24 every year in the district government of Mopeia in central Mozambique.[7] Many countries in Africa do not have successful malaria control programmes due to inadequate human and financial resources and insufficient health infrastructure.[6]

In Sudan, malaria is one of the leading causes of morbidity and mortality. Reported malaria cases account for 9.3% of outpatient clinic visits and approximately 8.7% of hospital admissions. Disease-proportional mortality is 2.6%, while the overall countrywide rate of reported cases against fatality is 0.64% and the annual reported malaria incidence is 357/10,000 population.[8,9] Based on the climatic model, it is estimated that 75% of people, about 24 million, are at risk of malaria, while entire populations are at risk of a malaria epidemic.[8,10]

The reduction of malaria-related mortality depends on an accurate early diagnosis and prompt effective treatment. The selection of an effective drug depends on the anti-malarial sensitivity profile of P. falciparum isolates in an area.[11] During the last 50 years, the development and spread of resistance to most frontline anti-malarial drugs used in the prevention and treatment of the most severe forms of human malaria have given reason for grave

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concern, which is considerably worsened by the reality that there are no available effective vaccines to date.[11] The resistance of P. falciparum to most anti-malarial drugs currently in use has been documented in almost all countries.[12] This may be due to drug pressure, overuse, or misuse; and Sudan is no exception.[12] Drug resistance happens when a malaria strain survives and multiplies despite administering an anti-malarial drug in a dosing regimen equal to or higher than those usually recommended.[12] The anti-malarial drug must access the parasite or the infected red blood cell (RBC) for the duration of the time necessary for its standard action within the tolerance dose.[12] Thus, a distinction between failure to clear malarial parasitaemia or resolving clinical disease following treatment with the anti-malarial drug and natural anti-malarial drug resistance must be made. While drug resistance can cause treatment failure, not all treatment failure is due to drug resistance.

The current study was planned to provide evidence about the susceptibility of anti-malarial drugs, and to identify the clinical features of the disease in children.

Patients and Methods

The prospective observational comparative study was conducted at the Dongola Specialist Hospital (DSH), Dunqulah, Sudan, from February 2016 to February 2017. Dongola is a city located in the north of Sudan on the west bank of the River Nile at an altitude of 227 metres above the sea level (Figure-1). DSH, as the main hospital of the northern state, receives patients from across the state with a capacity of 400 beds.

After approval from the Ministry of Health and permission from the DSH management, the sample was raised during the malaria transmission season. One hundred twenty subjects fulfilling inclusion criteria were enrolled in the study with non-probability sampling technique. Simple randomisation with a 1:1 allocation ratio was used to enroll the subjects into group 1, which received treatment based on physician's discretion, and group 2, which received treatment in accordance with the national guidelines.

Figure-1: Dongola Specialist Hospital in Sudan: The study site.

Those included were children aged <16 years with bodyweight >5kg who were positive for malaria on rapid diagnostic test (RDT) at DSH.

Patients with co-morbidities where the study drugs were contraindicated were excluded.

The treatment method, follow-up and outcome analysis were all based on World Health Organisation (WHO) guidelines.[13] After informed consent form the patients and their care-givers, complete medical history was obtained, and a comprehensive physical examination was performed.

Treatment was given according to the dose regimens and therapeutic ranges recommended for each drug by the WHO. Artemether-lumefantrine was given as 1, 2, 3, or 4 dispersible tablets (20/120mg strength) every 12 hours for three days for children with weight range 5-14kg, 15-24kg, 25-34kg, and >34kg, respectively. The dose of primaquine was 0.25mg/kg bodyweight for 14 days. Artesunate was given intravenously (IV) every 12 hours for three doses at 2.4mg/kg/dose for children with weight >20kg and 3mg/kg/dose for children with <20kg bodyweight. Sulfadoxine and pyrimethamine were given as quarter, half, three-quarter, one or one-and-a-half tablets (500/25mg strength) as a single dose for children with weight range 5-10kg, 11-20kg, 21-30kg, 31-45kg and >45kg, respectively. The tablets were crushed and dissolved in water for children who were not able to swallow them. The subjects were observed for vomiting for one hour. The total dose was repeated for those who vomited within 30 minutes, and half of the amount was repeated if the vomiting occurred between 30 and 60 minutes. The patients were requested to come on days 3, 7, 14 for follow-up, and they could access the facility any time they felt unwell.

Data was collected using a questionnaire having four sections. Section one included personal data, like age, gender and area, and the history of the disease, like last malaria diagnosis and the type of anti-malaria used, completing drug course, using anti-malarial drugs without medical prescription, using mosquito net or any anti-mosquito extract, and using any drug as prophylaxis

and prevention from malaria. Section two was related to clinical symptoms, like fever, shaking chills, headache, flu-like symptoms, diarrhoea, nausea, vomiting, sweating, abdominal pain, cough and fatigue, physical examination, including weight and temperature, signs, like wellness, respiratory rate, cyanosis, pale, jaundice, blood pressure (BP), pulse rate, splenomegaly and lower-limb oedema to detect severe malaria, and laboratory examination, like blood film (BF) thick and thin. The third section of the questionnaire related to the treatment, while the fourth related to the follow-up and BF thickness post-treatment.

Blood samples were collected, and laboratory methods, such as BF thick and thin, for malaria microscopy were prepared, stained with Giemsa for thick films and Leishman stain for thin films, as described by the WHO.[13] An immune chromatographic test was also done. All blood smears were independently double-checked, and in case of any discrepancy in species or parasite density, the average of the two most concordant readings was taken.

Data were analysed in terms of frequencies and percentages using statistical analysis software R version 3.1.2.

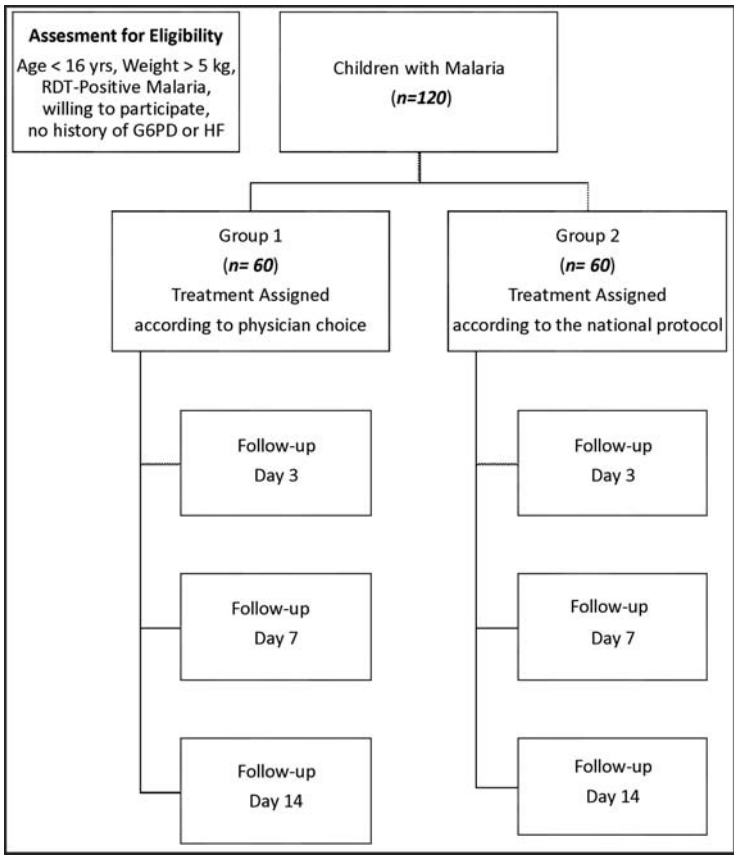

Figure-2: Study Flow-chart.

Results

Of the 120 children, 60(50%) were in each of the two groups (Figure-2). Overall, 63(52.5%) were aged 1-6 years, 66(55%) were males, 42(35%) were exposed to malaria for the first time, 54(45%) did not use mosquito protectors or mosquito nets, 6(5%) used medicines to protect themselves against malaria, Artesunate-plus-sulfadoxine-pyrimethamine was the most commonly used medication taken by 48(40%) in the last episode of malaria infection, followed by artemether injection 24 20%.

Most common symptoms in the sample were fever, shaking, chills, headache, flu-like symptoms, diarrhoea, nausea, vomiting, sweating, abdominal pain, cough and fatigue (Figure-3).

In group 1, 36(30%) subjects received artesunate-plus-sulfadoxine-pyrimethamine, 12(10%) got primaquine after artesunate-plus-sulfadoxine-pyrimethamine, and 6(5%) got primaquine after artemether-lumefantrine, while 42(35%) got artesunate, and 24(20%) received artemether-lumefantrine, while all group 2 subjects 60(100%) only received artemether-lumefantrine (Figure-4).

Post-treatment test was negative for all 120(100%)

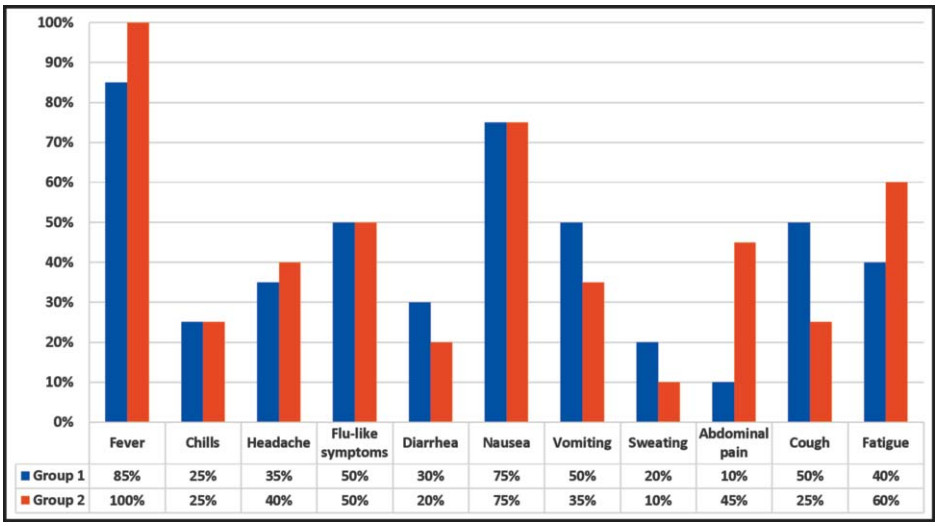

Figure-3: Clinical features of the subjects.

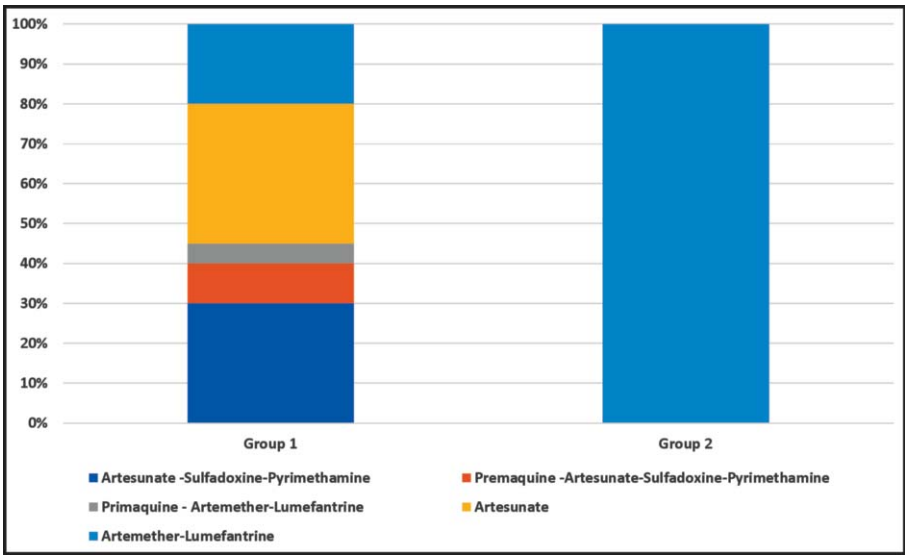

Figure-4: Anti-malaria drugs used.

subjects in the study regardless of the group, and had adequate clinical parasitological response.

Discussion

The prevalence of the disease in the study site was not as high as is generally preceived. The most affected age group 1-6 years can be attributed to the fact that children of this age are relatively difficult to be protected against mosquito bites with their frequent movement. Massive majority of people in Sudan do not use mosquito protectors and more social education effort is needed in this regard. Increasing mothers' education and improving their behaviour towards the use of insecticide-treated bed-nets may reduce the exposure of children to the disease.[14] The transmission of the disease can be reduced using the methods of prevention available in the region. The overall incidence of malaria in the area in a previous study was 65%.[15] Anti-malaria drugs are used extensively in Sudan which may indicate that they represented the first line of treatment in the old protocol.[16] This fact was confirmed by several studies in the Sudan, Uganda and Tanzania.[16-18]

Some symptoms showed higher rates in the current study and may be considered sensitive indicators of clinical malaria in the area. Such symptoms included fever, flu-like symptoms, nausea and fatigue. Other symptoms were comparatively less and included shaking, chills, headache, diarrhoea, vomiting, sweating, abdominal pain and cough. The result was similar to a study done in Kenya.[19] Variation in the appearance of symptoms may be due to many reasons and may appear in cycles. The current study made clear that malaria P. vivax was concentrated in specific areas, namely, the areas of the East Nile.

Many reports have confirmed the high cure rate of artemether-lumefantrine.[20-23] Also, some studies confirmed the high cure rate of both artemether-lumefantrine and artesunate-plus-sulfadoxine-pyrimethamine.[24,25] One study in eastern Sudan confirmed the high cure rate of artemether-lumefantrine, but said there was a decline in the efficacy of artesunate-plus-sulfadoxine-pyrimethamine against P. falciparum.[26] Also, some studies confirmed the high cure rate of artesunate-plus-sulfadoxine-pyrimethamine.[27]

This study focuses on the susceptibility of anti-malarial drugs, and the clinical features of the disease in children in this part of the world. Although these drug susceptibility and clinical features in association with malaria are not new to the subject, this data adds more detailed information to the limited body of knowledge. The limitation of this study was that these cases were not followed for relapse and recrudescence.

Conclusion

The social education of the prevention principle is necessary to protect against malaria in a low-economic endemic area. Nausea, fever, fatigue and flu-like symptoms can be malaria indicators. Although resistance to the combination therapy was not detected, it is extremely important to remain vigilant against the emergence of resistance in the future.

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Conflict of Interest: None.

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