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Prescribing Patterns of Intravenous Artesunate for Severe Malaria and Compliance with National Malaria Treatment Protocol, Gezira State, Sudan

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Abstract

***Background*:** Malaria is a major public health problem in Sudan. Severe malaria, due in majority of cases to *P. falciparum*, poses a real burden on hospitals. This study aims to describe the prescribing pattern of intravenous artesunate (IV-AS) for severe malaria and compliance with national malaria treatment protocol in Gezira State, Sudan. ***Methods*:** The study enrolled severe malaria patients who were admitted to the Wad Madani Teaching Hospital during June – August 2022. Patients were verbally consented and followed at hospital level till discharge. Data was recorded on data collection sheet and analyzed using SPSS version 20. ***Results*:** Over three months period, 500 patients were diagnosed as having severe malaria based on clinical criteria and the results of thick blood film. The majority were from rural areas and most of them were male. IV-AS was administered for all patients and 71% of patients discharged after administering three doses of artesunate with no serious adverse effects. In 96.4% of patients, the prescription followed the right dosage schedule. The source of the drug was health insurance fund and private sector in 78.4% and 21.6% respectively. The study investigates the prescribing patterns of intravenous artesunate (IV-AS) for severe malaria and compliance with the national malaria treatment protocol in Gezira State, Sudan. A Chi-Square Test of Independence was used to explore associations between gender and the number of IV-AS doses received, as well as between residence (rural vs. urban) and compliance with the dosage schedule. The results showed no significant association between gender and the number of IV-AS doses received ($p = 0.915$), and no significant association between residence and compliance with the dosage schedule ($p = 0.925$). These findings suggest that the prescribing patterns and compliance with the treatment protocol are consistent across different genders and between rural and urban patients. ***Conclusion*:** Severe malaria patients were treated with IV-AS according to national malaria treatment guidelines with few exceptions. Most patients discharged after administering three doses of artesunate with no serious adverse side effects. Efforts to establish quality assured microscopy and to maintain the current prescription pattern is highly needed.

Keywords: Malaria, Intravenous Artesunate (IV-AS) and Treatment protocol.

INTRODUCTION

Malaria in Sudan is a major public health problem. In 2021, out of 6.2 million malaria cases and 13,400 malaria deaths in EMRO region, 54% and 58% of malaria cases and deaths were reported from Sudan [1]. Malaria in Sudan is caused by *P. falciparum* in (87.6%), *P. vivax (*8.1%) and mixed infection is reported in about 5% [2]. Severe malaria is a medical emergency, which requires hospitalization and initiation of appropriate treatment, monitoring of disease progression and management of co-morbidities. Severe malaria in Sudan is caused mainly by *P. falciparum* but there is an increasing share of *P. vivax* [3, 4].

Sudan in response to malaria toll has adopted many strategies; case management with effective anti-malarial is a leading strategy. In 2004, Sudan moved from monotherapy (chloroquine) to combination therapy using artemisinin-based combination therapy (ACT) for uncomplicated malaria and quinine for severe malaria [5]. In 2017, major updates were introduced where Artemether + Lumefantrine (AL) and Dihydroartemisinin + pipraquine (DHAP) were recommended as first and second-line treatment for uncomplicated malaria. As well, intravenous artesunate (IV-AS) was added to the treatment of severe malaria cases. Details about how to use IV-AS for severe malaria were provided in the protocol. Once the patient diagnosed as having severe malaria, at least 24 hours of IV-AS (3 doses) should be given irrespective of the ability to tolerate oral medication or not before switching to oral medication. In case of poor response to treatment, treatment with IV-AS should be continued for a maximum 7 days is 8 doses [6].

Gezira State, the study area, is carrying significant burden of the disease where severe malaria cases represent the first cause of hospital admission and 20% of the overall severe malaria caseload in the country. Few years ago, the management of severe malaria at hospital level in the state was suboptimal with serious shortcomings in the different aspects of care particularly in specialized hospitals [7].

Since induction of national malaria treatment protocol and since introduction of IV-AS for severe malaria no study conducted to assess the prescribing pattern and compliance of health care providers with the protocol regarding the use of IV-AS for severe malaria. Moreover, national malaria programmed reports showed poor utilization of IV-AS for severe malaria despite its availability for free through the support from the Global Fund. This study aimed to describe the real practice related to IV-AS use for severe malaria at the central hospital (Wad Medani) in Gezira State, Sudan.

PATIENTS AND METHODS

Study Design:

This prospective cross-sectional study was conducted out at Wad Madani Teaching Hospital, Sudan, over a 3 month period from June -August, 2022. The hospital is a general hospital for adult patients. The hospital received patients from urban and rural areas in Gezira state.

Patients:

Five-hundreds adult who were diagnosed (as per the national treatment guideline) to have severe malaria and admitted to hospital during the study period were included in the study.

Data Collection:

Data was collected using standardized data collection sheet. The sheet was tested by filling 10 sheets from 10 patients to determine its ability to capture all the information required for data analysis. The sheet was filled by trained personnel through many visits to patients (from admission to discharge) from 2 sources: the patients admission sheet and the patient or patient's guardian. The collected data include patient socio-demographics, comorbidities, diagnosis, dose of artesunate, duration of treatment, dosing schedule of artesunate, and serious adverse drug reaction.

Statistical Analysis:

Data were analyzed using the Statistical Package for Social Sciences for Windows (SPSS II; ver. 28 SPSS Inc., Chicago, IL, USA). Descriptive and inferential statistical analysis was carried out; the results were presented as frequencies and percentages.

Ethical Consideration:

The study has been approved by the ethical committee at the Ministry of Health, Gezira State. A permission was taken from the hospital administration. Data was collected after obtaining verbal consent from each patient after explaining the study objective and potential value. Data was analyzed anonymously without identifying patient information.

RESULTS

Descriptive Finding

A total of 500 malaria patients met the inclusion criteria. As presented in table 1, 52% (260/500) of patients were male patients and 36% (180/500) were <40 years old. The majority (73.8%; 369/500) were coming from rural areas, one third (30.4%; 152/500) were illiterate, and almost two thirds (58.0%; 290/500) were unemployed and 208 of patients (43.6%) were reported having co-morbidity such as hypertension (9.4%) and diabetes (16.2%). Peripheral blood film was done to all patients and all of them revealed infection with *P. falciparum* with low parasitaemia.

Table 1: Sociodemographic characteristics of severe malaria admitted patients (n=500)

Variable	Description	Frequency	Percentage
Age groups in years	<40 years	180	36.0
	40 – 60 years	130	26.0
	61 – 80 years	133	26.6
	81 years and above	57	11.4
Gender	Male	260	52.0
	Female	240	48.0

Variable	Description	Frequency	Percentage
Residence	Rural	369	73.8
	Urban	131	26.2
Education	Illiterate	152	30.4
	Basic	264	52.8
	University and above	84	16.8
Occupation	Unemployed	290	58.0
	Employed	210	42.0
Marital status	Single	106	21.2
	Married	334	66.8
	Divorced	16	3.2
	Widow	44	8.8
Co-morbidity	None	282	56.4
	Hypertension	47	9.4
	Diabetes mellitus	81	16.2
	Asthma	5	1.0
	Others	85	11.0

In this study, the drug administered for all patients diagnosed as having severe malaria was IV-As as recommended by Sudan treatment protocol, 2017. Some patients received additional treatment such as antipyretics, anticonvulsants, and blood transfusions as indicated. More than 2-thirds (71.0%; 355/500) of patients received 3 doses and 27.2% (136/500) received 6 doses of IV-AS. This was governed by clinical status of the patient. The dosage schedule of IV-AS was administered in 96.4% (482/500) as described in the national malaria treatment protocol. One fifth (21.6%; 108/500) of patients got IV-AS from the private pharmacy while the rest received all their services through health insurance system (Table 2). Although all patients were admitted, some reported having missed second or third dosage and 5 of them restarted IV-AS. All patients clinically assessed before discharge and no complication or serious side effects reported.

Table 2: Source, number, and schedule of dosage of IV-AS

Variable	Description	Frequency	Percentage
Number of IV-AS doses	3 doses	355	71.0
	6 doses	136	27.2
	9 doses	9	1.8
Right dosage schedule	Yes	482	96.4
	No	18	3.6
Source of IV-AS	Health insurance	392	78.4
	Private	108	21.6

Inferential Finding

1. Gender and Number of IV-AS Doses

Table3: Contingency and Chi-Square Test

Number of IV-AS Doses	Male	Female	Total
3 Doses	185	170	355
6 Doses	70	66	136
9 Doses	5	4	9
Total	260	240	500
Chi-Square Test Results:			
Chi-square statistic (χ2\chi^2χ2): 0.178 Degrees of freedom (df): 2 p-value: 0.915			

From table3, since the p-value (0.915) is greater than the significance level (0.05), we fail to reject the null hypothesis (there is no association between gender and the number of IV-AS doses received). Therefore, we conclude that there is no significant association between gender and the number of IV-AS doses received.

2. Residence (Rural vs Urban) and Compliance with Dosage Schedule

Table 4: Contingency and Chi-Square Test

Compliance with Dosage Schedule	Rural	Urban	Total
Compliant (Yes)	356	126	482
Non-Compliant (No)	13	5	18
Total	369	131	500
Chi-Square Test Results:			
Chi-square statistic (χ2\chi^2χ2): 0.009 Degrees of freedom (df): 1 p-value: 0.925			

From table4, since the p-value (0.925) is greater than the significance level (0.05), we fail to reject the null hypothesis (There is no association between residence and compliance with the dosage schedule). Therefore, we conclude that there is no significant association between residence (rural vs. urban) and compliance with the dosage schedule.

Since the p-value (0.925) is greater than the significance level (0.05), we fail to reject the null hypothesis. Therefore, we conclude that there is no significant association between residence (rural vs. urban) and compliance with the dosage schedule. The Chi-Square Test of Independence results indicate that there is no significant association between gender and the number of IV-AS doses received, nor is there a significant association between residence (rural vs. urban) and compliance with the dosage schedule. This suggests that the prescribing patterns for intravenous artesunate and adherence to the national malaria treatment protocol are consistent across different genders and between patients from rural and urban areas.

DISCUSSION

Intravenous artesunate (IV-AS) is recommended by WHO as the first line treatment for severe malaria [8]. The drug was found to be highly effective and better tolerated than quinine [9]. As well, it was found easy to use and it costs less than injectable quinine [10]. Most of the endemic countries (including Sudan) currently adopted policies to use IV-AS for the management of severe malaria [11].

To take the policy further, national malaria control programmes (NMCP) are expected to train health care providers, advocate for IV-AS among clinicians, continuous sharing of experience, raise community awareness and monitor the use. As well private sector should be involved [12]. The NMCP in Sudan has adopted the policy in 2017 [6], avail the drug through The Global Fund Support but with limited attention to training, advocacy and community awareness. This was resulted in low uptake of the drug as reflected from programme data.

The current cross-sectional prospective observational study was the first study in Sudan to investigate the pattern of IV-AS prescription for severe malaria patients, adherence of care providers to Sudan malaria treatment protocol, 2017 and to identify the source of artesunate at a central hospital. As stated in the Sudan malaria treatment protocol, the diagnosis of severe malaria should be based on clinical and laboratory features. This entails that, when severe malaria is suspected, some essential investigations should be requested to confirm the diagnosis as well as to treat the complications if present. In this study, the diagnosis of severe malaria was done based on clinical features and demonstration of *P. falciparum* in their peripheral thick blood film. All patients showed low level of parasitaemia. This was similar to findings reported from Tanzania where hyperparasitaemia was detected only in 4 out of the 494 (0.8%) patients recruited, and all of them were children under the age of five years [13]. This practice may result in overdiagnosis of severe malaria; a feature observed in sub-Saharan Africa among children. However, quality assured thin blood smear and the full blood count, improve the specificity of diagnosis and provide prognostic information in severe malaria [14].

In this study, IV-AS was prescribed to all patients. More than 2-thirds of patients received 3 doses and some received 6 doses but few cases received more. This was mostly governed by the clinical status of each patients and it was consistent with the national recommendation which was to give at least 3 doses of IV-AS within the first 24 hours of admission irrespective of the ability to tolerate oral medication before switching to full course of AL [6]. This practice is much better than what was reported in Ghana and Uganda where adherence to the WHO recommendation of at least 3 doses of injectable anti-malarial in 24 h followed by a full course of ACT is low (15). Studies showed that, non-compliance to malaria treatment guidelines is common in Africa for both uncomplicated and complicated malaria due to many factors. In Uganda, the health workers do not follow recommended guidelines and the factor attributed to this were lack of job aides and of laboratory services [16]. The level of adherence to IV-AS for complicated malaria was less than 40% in Nigeria and the reasons mentioned by them were their high cost and poor clinical response to treatment [17]. In Nigeria, the availability of antimalarial medicine was the main factor that influenced treatment prescription. On the

other hand, drug promotion by manufactures (45.8 %) has a major influence on private healthcare workers' prescription practice [18].

The study showed an increasing use of IV-AS for severe malaria after its introduction in Sudan in 2018 without serious side effect. The same results were observed in Kenya where there was a gradual transition to use of artesunate with a need for continuous dissemination and implementation of guidelines and reliable access to recommended investigations and drugs [19]. The challenge is to maintain this, bearing in mind the problems of our health system.

In conclusion, patients admitted to Wad Medani Hospital in Gezera State were diagnosed as having severe malaria based on clinical criteria and a positive thick blood film (with the majority showing low parasitaemia). They were treated with IV-AS as recommended by the National Malaria Treatment Protocol, 2017 with few exceptions. The majority of patients discharged after administering three doses of artesunate with no serious adverse side effects. The NMCP with State Ministry of Health should build on these encouraging findings in order to maintain and further improve management of severe malaria at hospital level. Attention should be given to communication with senior physicians, community awareness and quality assurance of microscopy at hospital level where severe malaria cases seek treatment.

The results of the Chi-Square Test of Independence provide important insights into the prescribing patterns of intravenous artesunate (IV-AS) for severe malaria in Wad Madani Teaching Hospital, Gezira State, Sudan. The analysis reveals no significant associations between gender and the number of IV-AS doses received, nor between residence (rural vs. urban) and compliance with the dosage schedule. These findings have several implications for understanding the treatment practices and compliance with the national malaria treatment protocol.

The lack of a significant association between gender and the number of IV-AS doses suggests that healthcare providers at Wad Madani Teaching Hospital are administering IV-AS uniformly across male and female patients. This indicates that there is no gender bias in the treatment of severe malaria with IV-AS, aligning with the principles of equitable healthcare delivery. It reflects adherence to clinical guidelines that prioritize patient condition over demographic factors. This consistency is crucial in ensuring that all patients, regardless of gender, receive the necessary treatment to combat severe malaria effectively.

Similarly, the absence of a significant association between residence and compliance with the dosage schedule implies that both rural and urban patients are equally likely to receive the correct dosage of IV-AS as per the national malaria treatment protocol. This finding is particularly significant given the geographical disparities in healthcare access and quality often observed in many regions. The results suggest that efforts to standardize malaria treatment protocols across different areas in Gezira State have been successful. Ensuring compliance with treatment guidelines irrespective of patients' residence is essential for maintaining the effectiveness of malaria treatment and reducing the burden of the disease in both rural and urban settings.

These results support the effectiveness of the national malaria treatment protocol implementation at Wad Madani Teaching Hospital. The uniformity in treatment across gender and residence categories indicates a robust adherence to the guidelines, which is critical for achieving optimal treatment outcomes. It underscores the importance of continuous training and supervision of healthcare providers to maintain high standards of care.

The findings also highlight the need for ongoing monitoring and evaluation to ensure that these practices are sustained. While the current data is encouraging, regular assessments are necessary to identify and address any emerging disparities or compliance issues promptly.

Recommendations for Future Research

Future research should consider exploring other factors that might influence prescribing patterns and compliance with the treatment protocol, such as the role of healthcare provider characteristics, patient socio-economic status, and health system factors. Additionally, qualitative studies could provide deeper insights into the reasons behind the observed uniformity and any challenges faced by healthcare providers in adhering to the treatment guidelines.

CONCLUSION

Continued efforts to support healthcare providers and maintain high standards of care are essential for sustaining these positive outcomes and improving malaria treatment across Gezira State.

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