

Comparison of Artesunate and Ivermectin on the Treatment of Mild COVID -19 Infection in Kaduna State, Nigeria

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ABSTRACT

Background: At the outbreak, there was no specific therapeutic agent for the management of the novel Corona Virus Disease 2019 (COVID-19). Several agents have been tried in different countries with varying outcomes. Ivermectin an anti-parasitic agent was found to be effective in the management of mild COVID-19 infections. Artesunate, being a semisynthetic derivative of artemisinin, an antimalarial drug is suggested to be effective in the treatment of COVID-19. The study was carried out to compare the effect of Artesunate and Ivermectin in the treatment of mild COVID-19 cases in Kaduna state. **Methodology:** It was a comparative cross sectional study conducted among 40 mild COVID-19 cases enrolled for the study in the 3 isolation centers between 15/09/2020 to 14/12/2020. The outcome variables viral clearance and resolution of symptoms from the onset at the commencement of the treatment regimens. Data were collected from patients' folders using a questionnaire and was analyzed using SPSS 26 and level of significance at $P < 0.05$. **Results:** A total of 40 patients were enrolled in this study. 16 patients managed on Artesunate with a mean age of 40.37 ± 3.79 (95%CI= 32.79-47.95) while 24 on Ivermectin 33.58 ± 2.39 (95%CI= 28.8-38.36. There were 7 males (43.8) and 9 females (56.2) on Artesunate. There were statistically significant difference between respondents' ethnicity, religion and occupation and the type of regimen. Fifteen (93.8%) on Artesunate have symptoms comparable to twenty-two (91.7%) on Ivermectin and there was no significant statistical difference. Symptoms ranged from fever, anosmia, and cough. At Day 7 of commencement of therapy, 14 (87.5%) patients on Artesunate tested negative to COVID-19 PCR compared to 20 (83.3%) of the Ivermectin group. Bivariate analysis revealed no significant difference in symptom resolution and viral clearance between the two groups. However, patients on Artesunate reported side effects on the first and second day of treatment, ranging from dizziness and nausea while none among the Ivermectin group. **Conclusion:** Artesunate plus standard care in the management of COVID-19 was not found to have any difference from the use of Ivermectin plus standard care. It was however noticed to present more side effects.

Keywords: Ivermectin, Artesunate, Mild, COVID-19, Comparison, Treatment

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INTRODUCTION

The global pandemic of the novel coronavirus disease 2019 (COVID-19) was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a Beta coronavirus^[1]. SARS-CoV-2 is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)^[2]. There have been speculations that the likely origin of the virus, based on its genetic proximity is bat-derived coronaviruses through an unknown intermediate mammal host to humans^[3]. To enable diagnostic testing, epidemiologic tracking, and development of preventive and therapeutic strategies, the viral genome of SARS-CoV-2 was rapidly sequenced^[1, 4]. The development of new medications require a long period of time. A study by Derek *et al*, 2015 revealed an average of 77.2 months. Thus necessitating the need to identify existing drugs with an established safety profile and therapeutic potential against COVID-19 to suppress or even end the SARS-CoV-2 pandemic^[5]. The use of existing medications for this purpose is critical due to the long duration required to achieve reasonable global vaccination especially in low and middle income countries^[6]. The evidence of treatments documented to decrease the burden of morbidity and mortality due to COVID-19 are limited. Although mortality has been decreased using corticosteroids in severe cases, there is paucity of data on interventions that may prevent the disease, and decrease hospitalizations and the numbers of people progressing to critical disease and death^[6]. Artesunate, being a semisynthetic derivative of artemisinin, an antimalarial drug is suggested to be effective in the treatment of COVID-19 due to its anti-inflammatory activity, NF- κ B (nuclear Factor kappa B)-coronavirus effect and chloroquine-like endocytosis inhibition mechanism⁷. Hence, it is postulated that early administration of artemisinin and its derivative Artesunate during the infection may prevent the worsening of the health condition of patients with mild-moderate COVID-19^[7]. Ivermectin, a widely available anti-parasitic drug, is reported to

demonstrate strong therapeutic efficacy against COVID-19, however, there is paucity of data for its recommendation either for or against the treatment of COVID-19 due to the inadequacy in research. The inhibitory effects of Ivermectin against SARS-CoV-2 were demonstrated in an *in vitro* study^[8]. In Kaduna state it was found that Ivermectin reduced length of hospital stay and had fewer side effects compared to lopinavir/ritonavir being used initially, and was one of the recommended treatment options being utilized in the state at the time of this study^[9]. Since Artesunate was proposed to have likely therapeutic value in the management of COVID-19 infection from several studies^[6, 7], thus the therapeutic potential of Artesunate compared to Ivermectin in the management of mild COVID-19 infection was investigated among the study population.

METHODOLOGY

The study was conducted at the Infectious Disease Control Centre (IDCC) in Kaduna, Nigeria. The IDCC runs two isolation centres in Kaduna city as at the time of this survey; the Kakuri IDCC and the Hamdala Alternative Isolation. Other isolation center in the state was located in Zaria. The state had a total of 180 beds in the three Isolation centres and managed more than 10,000 COVID 19 cases.

Study design: This was a comparative cross-sectional study that involved a retrospective review of the clinical records of confirmed COVID-19 patients managed with Ivermectin or Artesunate regimen from 15/09/2020 to 14/12/2020. Ethical clearance(MOH/ADM/744/VOL.I/1129;NHREC/17/03/2018) was obtained.

Study Population: They consisted of patients aged between 18 and 65 years with reverse transcriptase–polymerase chain reaction (RT-PCR) test–confirmed or antigen test–confirmed COVID-19 who presented with mild illness (WHO clinical progression scale 2-4)^[10] defined as SPO₂ > 93%, respiratory rate \leq 24 cycles/minute and at least one of the following: contactless infrared

forehead thermometer temperature of ≥ 37.8 , cough, sputum production, nasal discharge, myalgia, headache or fatigue on admission. Patients who satisfied the criteria, signed written informed consent and agreed to comply with the study protocols and who were admitted into one of the three isolation Centers were included. Patients with known hypersensitivity to Artesunate (as reported by the patient), known hepatic or renal insufficiency (as previously being diagnosed or through an abnormal laboratory findings of liver and kidney function tests from the baseline blood sample taken), pregnant (from HCG pregnancy test) or lactating women were excluded. We identified a cohort of patients who were treated with Ivermectin for mild cases of COVID-19. Relevant information was collected from the patients' hospital records using a proforma. For the Artesunate group, the patients were recruited consecutively as they were placed on treatment and information collected from their hospital records using a proforma until the end of the study period of 14/12/2020. Any patient that completed the duration of treatment was discharged and followed up. Dosage of Artesunate (100 mg twice daily for 7 days) plus standard of care (Zinc 20mg bd, multivitamin I bd and Vitamin C 200mg tds) or Ivermectin (0.4 mg/kg body weight daily for 7 days) plus standard of care. The standard care was part of the protocol employed by the state Rapid Response Team to be administered to all COVID-19 patients irrespective of severity or clinical classification. The clinical features (fever, anosmia and cough) as reported by the patients were recorded before commencement of treatment and were re-assessed on the 7th day of treatment, with a repeat of either RT-PCR/Antigen testing. All outcome assessments were followed up by study investigators. The storage, dispensary, and administration of the medications were handled by trained study investigators, pharmacists, and nurses.

Statistical Analyses

Data analysis was done using IBM SPSS version

26 and Stata 12. Data was summarized using frequencies and percentages for categorical variables, mean and standard deviation for continuous variables, and bivariate analysis to compare clinical characteristics and outcome among the two groups of the dependent variables at level of significance $p < 0.05$.

RESULTS

A total of 40 patients were enrolled in this study. Sixteen patients were managed on Artesunate with a mean age of 40.37 ± 3.79 (95%CI= 32.79-47.95) while 24 on Ivermectin 33.58 ± 2.39 (95%CI= 28.8-38.36 with no statistical significance. There were 7 males (43.8) and 9 females (56.2) on Artesunate and 10 males (58.8), 14 females (60.9) on Ivermectin with no statistical significance. There were statistically significant difference in respondents' ethnicity ($X^2 = 18.195$ $P = <0.001$), religion ($X^2 = 11.11$ $P = 0.001$) and occupation ($X^2 = 4.83$ $P = 0.024$) and the type of treatment received Table 1. This is to ascertain the scientific distribution of the respondents among the different study groups. Fifteen (93.8%) on Artesunate had symptoms at commencement of the intervention compared with twenty-two (91.7%) on Ivermectin and there was no significant statistical difference between the two groups. Symptoms ranged from fever, anosmia, and cough. More patients with fever and anosmia were managed on Ivermectin while more with cough were managed on Artesunate with no statistical significance Table 2. At Day 7 of commencement of therapy, 14 (87.5%) patients on Artesunate tested negative compared to 20 (83.3%) of the Ivermectin group Table 3. Bivariate analysis revealed no significant difference in symptom resolution ($X^2 = 0.175$, $P = 0.675$) and viral clearance ($X^2 = 0.131$, $P = 0.718$) between the Artesunate and Ivermectin groups. However, patients on Artesunate reported some side effects on the first and second day of treatment; ranging from dizziness and nausea, while none among the Ivermectin group reported any side effect and that was statistically significant.

Table 1: Socio-demographic characteristics of respondents evaluated for the efficacy of artesunate and ivermectin in the management of COVID-19

Characteristic	Artesunate (%) n= 16	Ivermectin (%) n= 24	Test statistic	P
Mean age ± (SE)	40.37±3.79 (95%CI= 32.79 -47.95)	33.58±2.39 (95%CI= 28.8 -38.36)	t= 1.6	0.119
Sex				
Male	7 (43.8)	10 (58.8)	0.017	0.896
Female	9 (56.2)	14 (60.9)		
Ethnicity				
Hausa	15 (71.4)	6(28.8)	18.195	0.0001
Others*	1 (5.3)	18 (94.7)		
Religion				
Islam	15 (60.0)	10 (40)	11.11	0.001
Christianity	1 (6.7)	14 (93.3)		
Occupation				
Employed	11 (57.9)	8 (42.1)	4.828	0.024
Unemployed	5 (23.8)	16 (76.2)		
Education				
Secondary	3 (60.0)	2(40.0)	0.952	0.329
Tertiary	13 (37.1)	22 (62.9)		
Marital status				
married	9 (52.9)	8 (47.1)	2.063	0.095
Not married	7 (30.4)	16 (69.6)		

*Igbo, Yoruba, Bajju, Kadara

Table 2: Clinical characteristics of COVID-19 patients involved in the study.

Characteristic	Artesunate (%) n= 16	Ivermectin (%) n=24	Chi- square	p value
Presence of symptoms				
Yes	15 (93.8)	22 (91.7)	0.601	0.447
No	1 (6.2)	2 (8.3)		
Presence of fever				
Yes	13 (86.7)	16 (72.7)	1.023	0.203
No	2 (13.3)	6 (26.3)		
Presence of anosmia				
Yes	7 (46.7)	8 (36.4)	0.393	0.220
No	8 (53.3)	14 (63.6)		
Presence of cough				
Yes	8 (53.3)	6 (31.8)	0.060	0.806
No	7 (46.7)	16 (68.2)		

Table 3: Clinical characteristics and viral clearance of the respondents on the 7th day of commencement of therapy.

Characteristic	Artesunate (%) n= 16	Ivermectin (%) n=24	Chi square	p-value
Presence of symptoms				
Yes	5 (93.7)	7 (91.7)	0.175	0.675
No	11 (6.3)	17 (8.3)		
Presence of fever				
Yes	3 (86.7)	4 (72.7)	0.029	0.865
No	13 (13.3)	20(26.3)		
Presence of anosmia				
Yes	1 (46.7)	1 (36.4)	0.088	0.767
No	15 (53.3)	23 (63.6)		
Presence of cough				
Yes	1 (53.3)	2 (31.8)	0.060	0.806
No	15 (46.7)	22 (68.2)		
Day 7 testing				
Positive	2 (12.5)	4 (16.7)	0.131	0.718
Negative	14 (87.5)	20 (83.3)		

DISCUSSION

This study was conducted on the comparison of Artesunate and Ivermectin in the management of mild COVID-19 cases in Kaduna state. Ivermectin has been in use in the state for the management of mild/moderate COVID-19 infection due to its effectiveness on the reduction of hospital stay and lesser side effect compared to lopinovir/ritonavir that was initially being used as reported by Oyefabi et al. in 2022 [9]. Our findings in this study showed improvement in symptomatology and viral clearance among COVID-19 patients treated with Artesunate, this was in keeping with the findings in a systematic review conducted on the use of Artesunate, Imatinib and infliximab in management of COVID-19 which revealed that Artesunate showed significant improvement in patients with COVID-19 compared to imatinib and infliximab [11]. However, the survey revealed no significance difference between the symptom's resolution and overall viral clearance among the Artesunate and the Ivermectin group. However, no known previous study that compared the Artesunate and Ivermectin in the management of COVID-19 infection for possible inference. More so, the group on Artesunate reported some side effects which were not found in the Ivermectin group, this was also what gave Ivermectin preference over lopinovir/ritonavir in the management of mild/moderate COVID-19 infection in Kaduna state as patients placed on it reported no side effect as opposed the lopinovir/ritonavir group [9]. A study conducted on the antiviral activity of artemisia and artemisia products in the management of COVID-19 proposed that understanding its safety and efficacy when administered either as a monotherapy or combination therapy, mechanism of action, formulation and active dosage for COVID-19 drug development is required because of its high toxicological profile [12]. The proposed effectiveness of Artesunate by Uckun *et al.* 2021 on likely prevention of worsening of symptoms on mild-moderate COVID-19 cases due to its anti-inflammatory effect could not be proven to be

better than Ivermectin in this study.

Limitations of study

Our study is not without its limitations. First, we recognize that our sample size was small. Second, the study did not enroll severely or critically ill patients, or patients at increased risk of poor outcome with many comorbidities and was conducted in only one center. Third, there was no treatment with artesunate alone, therefore it is add-on therapy, even though the comparable group of Ivermectin was also as an add-on therapy.

CONCLUSION

In conclusion, Artesunate in this study had not proven to be better than Ivermectin in the management of COVID-19 mild infection in the study population, rather had more side effects. Therefore, the need to continue the use of other proven medications for patients' management in the state.

Recommendations

Considering the economic crisis related to the COVID-19 pandemic, the use of *Artesunate* will particularly be beneficial for impoverished populations in resource limited settings. The inexpensive over the counter treatment regimen would be a valuable source to lower the burden on healthcare system while significantly dampening impact of the disease. The study will affect clinical practice and direct future research in the field of emerging infectious diseases. Nevertheless, these findings should be tested and replicated in further multi-national, larger clinical trials. A multinational study with a larger sample size is required to investigate potential variations in responses to the treatment in COVID-19 patients from different racial and ethnic origins. There is also the need to fully understand the safety and efficacy of Artesunate when administered either as a monotherapy or combination therapy, mechanism of action, formulation and active dosage for COVID-19 so as to prevent the possible side effects that might be associated with it.

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Conflict of interest

None

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. *New England journal of medicine*. 2020 Feb 20;382(8):727-33.
2. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nature Reviews Microbiology*. 2021 Mar;19(3):141-54.
3. Hansen ES, Moeller AL, Backer V, Andersen MP, Kober L, Kragholm K, Torp-Pedersen C. Severe outcomes of COVID-19 among patients with COPD and asthma. *ERJ Open Research*. 2021 Jan 1;7(1).
4. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging microbes & infections*. 2020 Jan 1;9(1):221-36.
5. Raimondi F, Novelli L, Ghirardi A, Russo FM, Pellegrini D, Biza R, Trapasso R, Giuliani L, Anelli M, Amoroso M, Allegri C. Covid-19 and gender: lower rate but same mortality of severe disease in women—an observational study. *BMC pulmonary medicine*. 2021 Dec;21(1):1-1.
6. Bryant A, Lawrie TA, Dowswell T, Fordham EJ, Mitchell S, Hill SR, Tham TC. Ivermectin for prevention and treatment of COVID-19 infection: a systematic review, meta-analysis,

- and trial sequential analysis to inform clinical guidelines. American journal of therapeutics. 2021 Jul;28(4):e434.
7. Uckun FM, Saund S, Windlass H, Trieu V. Repurposing anti-malaria phytomedicine artemisinin as a COVID-19 drug. *Frontiers in Pharmacology*. 2021 Mar 19;12:407.
 8. Mcgonagle D. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information. 2020.
 9. Oyefabi A, Musa S, Kambai H, Usman I, Gwamna J, Sheyin J, Ige O, Abdullahi M, Sunday J, Kera HN, Atiku A. Comparison of the Ivermectin and Lopinavir/Ritonavir Treatment Outcomes among COVID-19 Mild to Moderate Cases in Kaduna State. *West African Journal of Medicine*. 2022 Feb 1;39(2):140-6.
 10. Osibogun A, Balogun M, Abayomi A, Idris J, Kuyinu Y, Odukoya O, Wright O, Adeseun R, Mutiu B, Saka B, Osa N. Outcomes of COVID-19 patients with comorbidities in southwest Nigeria. *PloS one*. 2021 Mar 15;16(3):e0248281.
 11. Amani B, Zareei S, Amani B, Zareei M, Zareei N, Shabestan R, Akbarzadeh A. Artesunate, imatinib, and infliximab in COVID-19: A rapid review and meta-analysis of current evidence. *Immunity, inflammation and disease*. 2022 Jun;10(6):e628.
 12. Orege JI, Adeyemi SB, Tihamiyu BB, Akinyemi TO, Ibrahim YA, Orege OB. Artemisia and Artemisia-based products for COVID-19 management: current state and future perspective. *Advances in Traditional Medicine*. 2023 Mar;23(1):85-96.