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Original Research

Studies on the Effect of Ivermectin Addition on Patients with Comorbidities who Tested Positive for COVID-19 Infection in Delta State

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ABSTRACT: This study aimed to study the effect of ivermectin addition in the management of patients with comorbidities who tested positive for Covid-19 infection in Delta State. Patients who were hospitalized with a pre-diagnosis of severe comorbidity and thereafter diagnosis of Covid-19 were also confirmed microbiologically with Polymerase Chain Reaction (PCR) positivity in the respiratory tract sample were included in the study. Patients that met the following criteria were accepted with severe comorbidity and they were all randomized into the study and control groups respectively. The presence of tachypnea ≥25/min, peripheral capillary oxygen saturation (SpO2) level < 93% in room air, also partial pressure oxygen (PaO2)/(FiO2) < 310 in oxygen receiving patients. Acute organ dysfunction findings; patient with SOFA (sepsis-related organ failure assessment) score < 4. The reference treatment recommended by NDCC for Covid-19 (SARS CoV-2 Infection) was applied to both patients in the Study Group and Control Group respectively. Also, patients in the study group received Ivermectin treatment in the form of Tablet 12mg each for enteral use for 5 days. A total of 72 patients, were included in the study of which 40 were included in the study group and 32 in the control group, 12 patients were excluded from the study due to mutation which affects ivermectin metabolism. They were only given reference treatment. The demographic data and pre-treatment clinical and laboratory findings of the patients were compared no significant difference was found between the study group and the control group in any of the parameters. Baseline demographics and characteristics of patients were well-balanced between the study group and the control group. The majority had pulmonary diseases in both the study and the control group which is (89%), (89%) (and 86%) from the study group had hypertension while those in the control area (75%), zero persons had kidney failure in the study group while those in the control group are up to 20%, the number of cardiac arrests in the study group is 51% compared to 35% in the control group, the number of patients with diabetes mellitus is high in the control group with 46% having diabetes mellitus while those in the study group are 33%, 6% of the study group have Malignancy while none of the patients have it in the study group, 3% of the control group have immunodeficiency while none have it in the study group, none of the patients in both the study group and the control group, while 20% of patients in the study group have liver failure compared to 16% in the control group. The findings gotten from the use of Ivermectin in the treatment of patients with comorbidities who tested positive for Covid-19, it shows that the drug can provide an increase in clinical recovery and an improvement in prognostic laboratory parameters. There should be a consideration for the use of ivermectin as an alternative drug that can be used in the treatment of Covid-19 disease or it should be used as an additional drug to the existing protocols.

Keywords: SARS COV-2; COVID-19; ivermectin, comorbidity, treatment subject classification codes

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an illness caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV) (Oxford English Dictionary, 2020). The outbreak was initially reported to the World Health Organization (WHO) on December 31, 2019. By January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency (Moriarty, Plucinski, Marston, Kurbatova, Knust, Murray, & Richards, 2020).). The virus was first identified during an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China. It was initially reported to the World Health Organization (WHO) on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a

global health emergency (WHO,2020). On March 11, 2020, the WHO declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009 (Nussbaumer-Streit et al., 2020). The outbreak was initially reported to the World Health Organization (WHO) on December 31, 2019. By January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency (Moriarty, Plucinski, Marston, Kurbatova, Knust, Murray, & Richards, 2020). Illness caused by SARS-CoV-2 was termed COVID-19 by the WHO, the acronym derived from "coronavirus disease 2019. The name was chosen to avoid stigmatizing the virus's origins in terms of populations, geography, or animal associations by WHO, 2020 as cited in Pan et al. (2021).

Ivermectin is a broad-spectrum antiparasitic endectocide active against a wide range of internal and external parasites. It was originally introduced as a veterinary drug, predominantly in domestic livestock, but since 1987 has been widely used in human medicine. Ivermectin at a dose of 150 or 200 mcg/kg is the first-line treatment for *Onchocerca volvulus* (the cause of river blindness), *Wuchereriabancrofti* (the cause of lymphatic filariasis), and *Strongyloidesstercoralis* (roundworm, an intestinal helminth). Ivermectin at these doses is used as MDA in annual campaigns for the control of river blindness and lymphatic filariasis in endemic areas. More than 1.8 billion treatments have been distributed (González et al., 2012). The ivermectin MDA campaigns have been reported to have a secondary effect of reducing intestinal helminths in humans (Rodari et al., 2020), and on ectoparasites such as nuisance insects including head lice, mites, bedbugs, and scabies (Schmidt and Levit, 2012).

Ivermectin is a macrocyclic lactone 22,23-dihydro avermectin B obtained from a gram-positive bacterium named Streptomyces avermitilis belonging to the genus Streptomyces (Crump and Omuram 2011; Bray et al., 2020). Ivermectin is regarded as a miracle therapeutic drug in medicine because of its wider antiparasitic efficacy against ectoparasites and endoparasites. Ivermectin's active spectrum is growing yearly, labeling it as one the most effective pharmaceuticals ever developed. Also, Ivermectin has recently been used to reduce insect-borne diseases, including malaria (Crump and Omuram, 2011). The World Health Organization's Standard catalog of valuable drugs includes Ivermectin (Khan, 2020). Ivermectin was discovered in 1975 and commercially commercialized in 1981 for parasitic infection purposes in livestock before being authorized for clinical usage in 1987 for the treatment of Lyme disease and a variety of human parasitic infestations, including river filariasis, strongyloidiasis, and parasitic organisms that cause, rosacea, pediculosis, and scabies. Ivermectin has the unique property of being adapted pharmaco-dynamically by changing the kind of formulation Khan, Khan, Debnath, Nath, Mahatab and Nabeka (2020).The medium employed in Ivermectin drug formulations has critical control over its uptake from the site of injection and, as a result, bio-accessibility. According to Gokbulut et al. (2014), several findings have emerged since 2012, suggesting that Ivermectin has antimicrobial activity ((Tay et al. 2013; Varghese et al., 2016) against an increasing variety of RNA viruses, such as HIV-1, dengue virus, Zika virus, influenza, and more importantly COVID-19.11,56,57 Pseudorabies, polyoma, and adenoviruses are among the DNA viruses that are responsive to Ivermectin. Shixian et al., (2018) furthermore, asserted that Ivermectin has lately acquired popularity as a novel approach to preventing transmission of malaria. It focuses mostly on the zoophagic characteristic of the vector that transmits the disease, the Anopheles mosquito.3,15.

Moreover, Ivermectin therapy in animals has been proven to effectively prevent malaria transmission to humans from mosquitoes.3,15 Interestingly, the interaction with and blockage of the host importin (IMP) protein is the foundation of Ivermectin's broad-spectrum antimicrobial action. Shixian et al. (2018) argued that although Ivermectin is believed to facilitate the nuclear importation of several virus particles and critical host components, additional antimicrobial effects were postulated, notably when it comes to COVID-19.Ivermectin’s therapeutic efficacy against SARS-CoV-2 has been investigated by Uwishema et al. (2022).The researchers showed that a single dosage of Ivermectin reduced SARS-CoV-2 multiplication in Vero/hSLAM cells by about 5000-fold. This discovery has piqued the curiosity of scientists and healthcare professionals across the globe. Nevertheless, the findings should indeed be viewed with the utmost care (Formiga et al., 2020) and its usage, particularly in severely ill people, necessitates rigorous risk–benefit analysis. To start with, Ivermectin was only evaluated in vitro, which used a single line of monkey kidney cells that were modified to produce signaling lymphocytic activation molecule (SLAM) of humans, commonly referred to as CDw150 (a measles virus receptor). According to existing research, substantial levels of Ivermectin action towards SARS-CoV-2 will need drastic, perhaps lethal, increases in Ivermectin dosages in people. Not surprisingly, it has been suggested that before using Ivermectin to cure SARS-CoV-2, excellent research studies guided by rigorous pharmacokinetic designs must be investigated to confirm its effects (Chaccour et al., 2020). Nonetheless, findings using laboratory animals indicating up to about 3-fold increasing levels in the respiratory tract than in plasma 1 week after mouth dosage suggests that more study is needed, especially for treating certain types of viral infections. Since finding new treatments takes a long

time, discovering existing drugs that could be repurposed for COVID-19 and have proven safety and efficacy characteristics based on decades of usage might be important in reducing or perhaps eliminating the COVID-19 pandemic. This is particularly important as many of the global population, particularly amongst low- and middle-income countries (LMICs), may take months, if not years, to get vaccinated, and using repurposed drugs may be imperative (Bryant et al., 2021). Interestingly, the blocking of importin α/β mediated nuclear import of virus particles is postulated as the likely process behind Ivermectin's antivirus potential, given its ability to suppress viral multiplication. Because SARSCoV-2 is an RNA virus, it could have an identical potency (Kory et'al., 2021). Ivermectin is also being suggested to play an ionophore function. As the ionophore compound is being characterized as a possible antiviral therapeutic, Ivermectin might eventually cause an ionic disequilibrium, compromising both the structure and functioning of the SARSCoV-2 membrane (Heidary and Gharebaghi, 2020). Ivermectin is presently commercially accessible and cheap in several places across the World (Formiga et al., 2020). Banerjee et al., (2020) assert that as per a 2018 petition for Ivermectin usage against scabies, the expense of a hundred 12-mg pills is 2.90 USD. Hence, investigating Ivermectin's therapeutic role in SARS-CoV-2 might be very important for resource-constrained environments (Charccour et al., 2021). If proven successful as a COVID-19 therapy, its economic feasibility ought to be weighed based on the cost of available therapeutics and prophylaxes. This paper aims to study the effect of Ivermectin addition in the management of patients who tested positive for COVID-19 Infection in Delta State.

Safety of ivermectin in humans

Ivermectin's main mechanism of action in invertebrates is the opening of glutamate-gated chloride channels, resulting in flaccid paralysis and death. Glutamate-gated chloride channels do not exist in humans. Other weakly sensitive channels are found in the human central nervous system, but the blood-brain barrier curbs drug access to these channels. These features explain ivermectin's excellent safety profile. The standard dose of ivermectin in the control of onchocerciasis and lymphatic filariasis is 150 to 200 mcg/kg and was based on earlier dose-finding studies comparing 100, 150, and 200 mcg/kg which confirmed that a single dose of 150 micrograms of ivermectin/kg was equally as effective as 200mcg/kg for treatment of active onchocerciasis in patients with high microfilaria counts. Since 1987, 1.8 billion doses of 150-200 mcg/kg have been safely administered around the globe. The current standard dose for head lice is 400 mcg/kg, which is safe and well tolerated. Ivermectin is safely used in pregnancy. In a study in Liberia, 200 women treated with ivermectin 150 µg/kg were inadvertently found to be pregnant. In comparison with untreated mothers in the same population, no significant differences in birth defect rates, development status, or disease patterns could be found. These findings were later confirmed in hundreds of women in Cameroon, Mali, Ghana, and Uganda. As a result, since 1998, pregnant women in onchocerciasis-endemic areas are no longer excluded from ivermectin treatment. Four recent studies testing single doses of 800-2,000 mcg/kg showed all the tested doses to be safe and well tolerated.

MATERIALS AND METHODS

This prospective, controlled, randomized, single-blind clinical trial (conducted between, 2020-2023) assessed the effectiveness and safety of ivermectin use in treating patients without the mutation. Patients who were hospitalized with a pre-diagnosis of severe comorbidity and thereafter diagnosis with Covid-19 were also confirmed microbiologically with Polymerase Chain Reaction (PCR) positivity in the respiratory tract sample were included in the study. Patients that met the following criteria below were accepted with severe comorbidity and they were all randomized into the study and control groups respectively.

a. The presence of tachypnea ≥25/min, peripheral capillary oxygen saturation
(SpO2) level < 93% in room air, also partial pressure oxygen (PaO2)/(FiO2) < 310 in oxygen-receiving patients.
b. Presence of specific radiological findings for Covid-19 in the lung
tomography (bilateral lobular, peripherally located, diffused patchy ground glass opacities).
c. Acute organ dysfunction findings; patient with SOFA (sepsis-related organ
failure assessment) score < 4.
d. Mechanical ventilation requirement.

The exclusion of patients follows this criterion; Children below the Age of 18 years, pregnancy, active breastfeeding, concurrent autoimmune disease, kidney disease, chronic liver failure, immunosuppression, SNP mutation in MDR1/ABCB1, mutation of the CYP3A4 gene and or haplotypes.

Examination of genes

Patients included in the study group according to randomization, haplotypes, and mutation that cause the

function to lose its purpose were investigated by performing sequence analysis of the MDR-1/ABCB1 and the CYP3A4 genes with the Sanger method. Screening for mutation was done with the first dose of the research drug ivermectin given, the use of the drug was discontinued in patients with mutations, as a result of genetic examination and these patients were all excluded from the research and study.

Inclusion criteria

That was met by the patients they were grouped into two units the “Study Group” and “Control Group” by making use of a single-blind randomized method. Patients with Even Numbers are grouped into the Study Group while those with Odd numbers are grouped into the Control Group. All the Patients who took part in the study were provided with informed consent before the study enrolment and using the informed consent eligible patients went through a standardized symptom questionnaire and physical examination. Also complete blood count test, thoracic tomography, biochemical blood test, and first SARS CoV-2 PCR result were all recorded. The reference treatment recommended by NDCC for Covid-19 (SARS CoV-2 Infection) was applied to both patients in the Study Group and Control Group respectively. Also, patients in the study group received Ivermectin treatment in the form of a 12mg tablet each for 5 days use. Respiratory findings and laboratory parameters of the patient during the study were all recorded on the 1st, 3rd, and 5th days of the treatment respectively also on the 1st, 3rd, and 5th days after the treatment and during the follow-up period. All side effects during the treatment in all the patients were recorded as well. Efficacy and safety assessment for both the Primary and Secondary endpoints in the study were all determined as follows:

Primary endpoint

Both the Clinical response and the side effects of the drug obtained from the patients on the 5th day, at the end of Ivermectin treatment were all evaluated. Extubation in mechanically ventilated patients, respiratory rate <28, SpO2 level in the room air >93%, PaO2 / FiO2 >310 in patients receiving oxygen, At least two of the 2-point reduction criteria were present in SOFA (sequential Organ Failure Assessment) score were all evaluated as a ‘Clinical Response’.

Secondary endpoint

Drug side effects and clinical responses in patients on the 5th day after the end of using ivermectin treatment which total of the 10th day were all evaluated. For the clinical response, at least two of the following criteria present were sought: Respiration rate between 24 and 26, SpO2 level in room air >97%, absence of oxygen requirement, and need no intensive care. For us to evaluate the treatment response of patients: Blood Lymphocyte count, C-reactive protein (CRP), ferritin and D-dimer values, also changes in polymorphonuclear leukocyte (PNL/L) ratio. Also changes in SpO2 value and that of PaO2/FiO2 ratio were also α determined and compared between both groups at the primary and secondary endpoints. PCR negativity rates were evaluated in both groups at the end of the follow-up period. The study also monitored other effects on the body such as C-reactive protein (which is an indicator of the level of inflammation), and how the drug is changed in the body (pharmacokinetics). The study is paid for by Delta State Primary Health Care Agency.

RESULTS

A total of 72 patients, were included in the study of which 40 were included in the study group and 32 in the control group, 12 patients were excluded from the study due to mutation which affects ivermectin metabolism. They were only given reference treatment. The demographic data and pre-treatment clinical and laboratory findings of the patients were compared no significant difference was found between the study group and the control group in any of the parameters.

Statistical evaluation

The same size of the study with an α error of 0.07, a power of 0.97, and a medium size effect of 0.36 according to the standardized size effects was calculated for a 1:1 randomization in 30 patients in the study group i.e. the patients using the ivermectin and also 30 in the control group, so we could detect the differences between the two independents groups in the change in the mean viral load in nasopharyngeal swabs among the repeated measures. Baseline demographics and characteristics of patients were well balanced between the two groups (Tables 1, 2, 3) across the three senatorial districts. Both groups consisted of a patient from each of the senatorial districts so they could balance the study. Their age and gender and body mass were put into consideration as part of the study criteria, which helped in the study of using ivermectin on both males and females. Comorbidity of patients Baseline demographics and characteristics of patients were well-balanced between the study group and the control group (Table 4 and Figure 1). The majority had pulmonary diseases in both the study and the control group which is (89%), (89%) (and 86%) from the study group had hypertension while those in the control area (75%), zero persons had

Table 1: Baseline demographic and clinical characteristics of patients in Delta North.

Characteristics		Study Group	Control Group
Gender	Male	6 (60%)	7 (70%)
	Female	4 (40%)	3 (30%)
	Total	10	10
Age		≥27	≥30
		≥25	≥35
Body-Mass		≥50	≥50
Index (kg)		≥50	≥50

Table 2: Baseline Demographic and Clinical Characteristics of Patients in Delta South

Characteristics		Study Group	Control Group
Gender	Male	6 (60%)	7 (70%)
	Female	4 (40%)	3 (30%)
	Total	10	10
Age		≥27	≥30
		≥25	≥35
Body-Mass		≥50	≥50
Index (kg)		≥50	≥50

Table 3. Baseline Demographic and Clinical Characteristics of Patients in Delta Central.

Characteristics		Study Group	Control Group
Gender	Male	6 (60%)	7 (70%)
	Female	4 (40%)	3 (30%)
	Total	10	10
Age		≥27	≥30
		≥25	≥35
Body-Mass		≥50	≥50
Index (kg)		≥50	≥50

Table 4: Patients' Co-morbidity with COVID-19.

Co-morbidity	Study Group	Control Group	P
Hypertension	21(86%)	12(75%)	0.55
Diabetes Mellitus	8(33%)	11(46%)	0.76
Kidney Diseases	-	6 (20%)	0.23
Cardiac Arrest	16(51%)	9(35%)	0.44
Pulmonary Disease	7(30%)	5(13%)	0.33
Thyroid Disease	-	-	??
Malignancy	-	2(6%)	0.22
Immunodeficiency	-	1(3%)	0.15
Liver Failure	6(20%)	5(16%)	0.42

What does P stands for?

kidney failure in the study group while those in the control group are up to 20%, the number of cardiac arrests in the study group is 51% compared to 35% in the control group, the number of patients with diabetes mellitus is high in the control group with 46% having diabetes mellitus while those in the study group are 33%, 6% of the study group have Malignancy while none of the patients have it in the study group, 3% of the control group have immunodeficiency while none have it in the study group, none of the patients in both the study group and the control group, while 20% of patients in the study group have liver failure compared to 16% in the control group.

Post result after the use of Ivermectin

At the beginning of the treatment period, a decrease was seen in the PaO2/FiO2 ratios in the two groups, and it

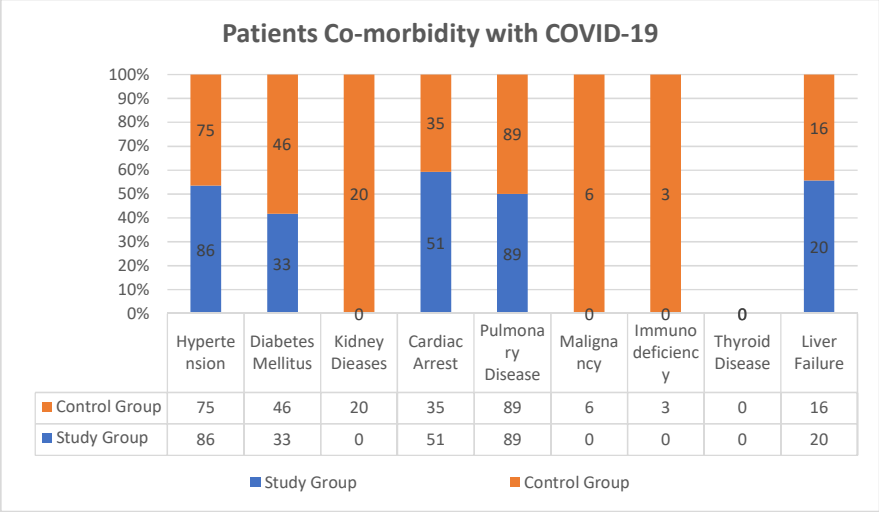

Figure 1: Patients' Co-morbidity with COVID-19

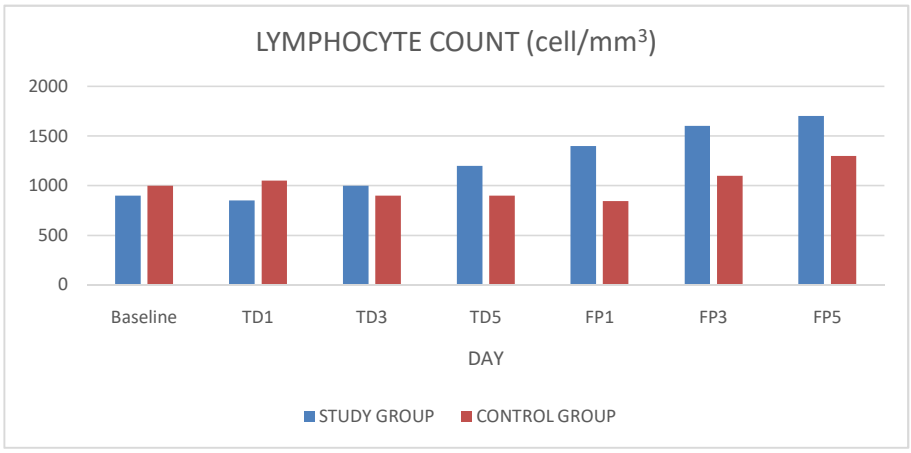

Figure 2: Lymphocyte Count (cell/mm^3).

was also observed that the PaO2/FiO2 ratios started to increase after the treatment. Despite the increase in the control group observed it was sufficient enough at the end of the treatment period and it remained slightly below the baseline. A significant increase was observed in the PaO2/FiO2 ratio in the study group. There was an increase in the PaO2/FiO2 ratios in both groups during the follow-up and also at the end of the follow-up period.

Laboratory parameter changes observed

There were significant changes in the laboratory parameters observed during the treatment and also during the follow-up period and after the follow-up period. These changes are explained below and well represented in the graph.

Blood lymphocyte counts (cell/mm^3)

At the end of the treatment period, the blood lymphocyte counts got increased in the study group and slightly decreased in the control group. The increase in the study group was statistically significant to the study (p=0.011). Also at the end of the follow-up period, there was an increase in both of the groups compared to the baseline values, the increase in both of the groups was statistically significant (p=0.009 and p=0.06). When both groups were both compared, there was no difference found (p=0.25) (Figure 2).

Serum C-reactive protein (CRP) values (mg/dl)

The Serum CRP values were gradually decreasing compared to the baseline value s in both of the groups

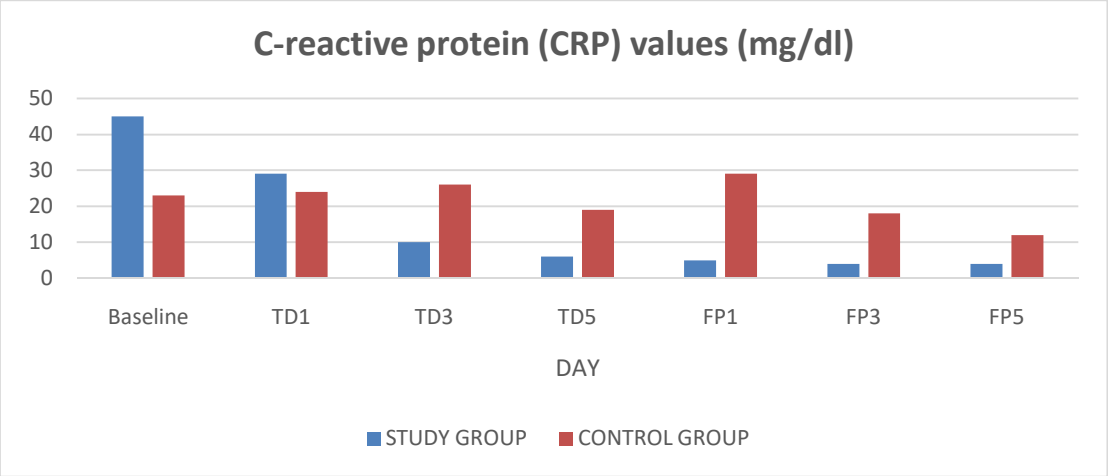

Figure 3: C-reactive protein (CRP) values (mg/dl).

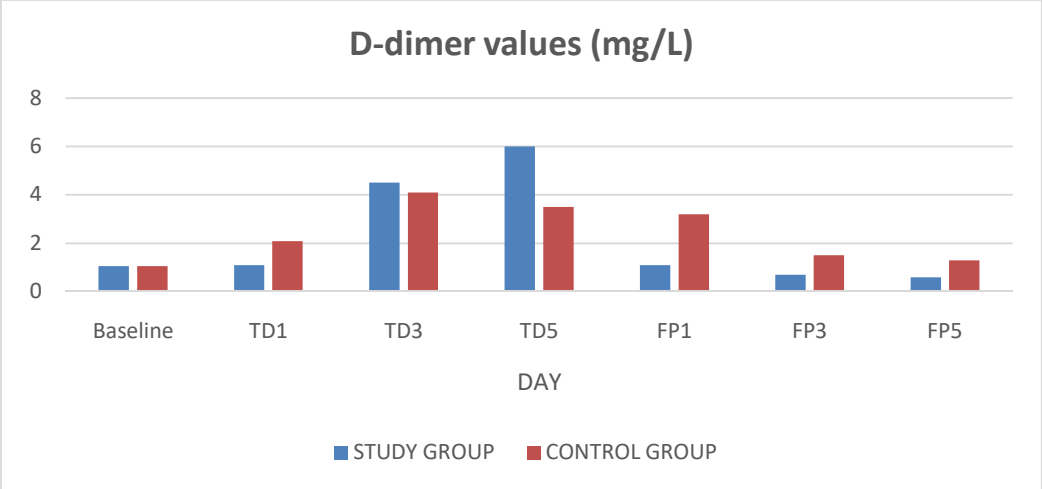

Figure 4: D-dimer values (mg/L)

during treatment and the follow-up period. The decrease found in the study group (p=0.04) is more significant than the decrease found in the control group (p=0.06). Additionally, CRP values found in the study group were significantly lower than those in the control group at the end of the follow-up period p=0.01 in figure 3 above.

Serum D-dimer values (mg/L)

During the treatment period, there was a significant increase in the D-dimer values in both of the groups (p=0.004 and p=0.003 for the study group and also the control group) compared to the initial values. In the follow-up period, D-dimer values started to decrease in both of the groups, and also at the end of the follow-up period, values in the study group reached a level that is significantly below the baseline values (p=0.05), the decrease in the control group was not sufficient enough (p=0.12) and was also higher than the baseline value. At the end of the follow-up period, the difference found between D-dimer levels of both groups was significant at p=0.04 in Figure 4 above.

Polymorphonuclear Leucocyte to Lymphocyte ratios (PNL/L)

During the treatment period, the PNL/L ratios were decreased in the study group and got increased in the control group (p>0.006 for both groups). Also during the follow-up period, the PNL/L ratios of both groups

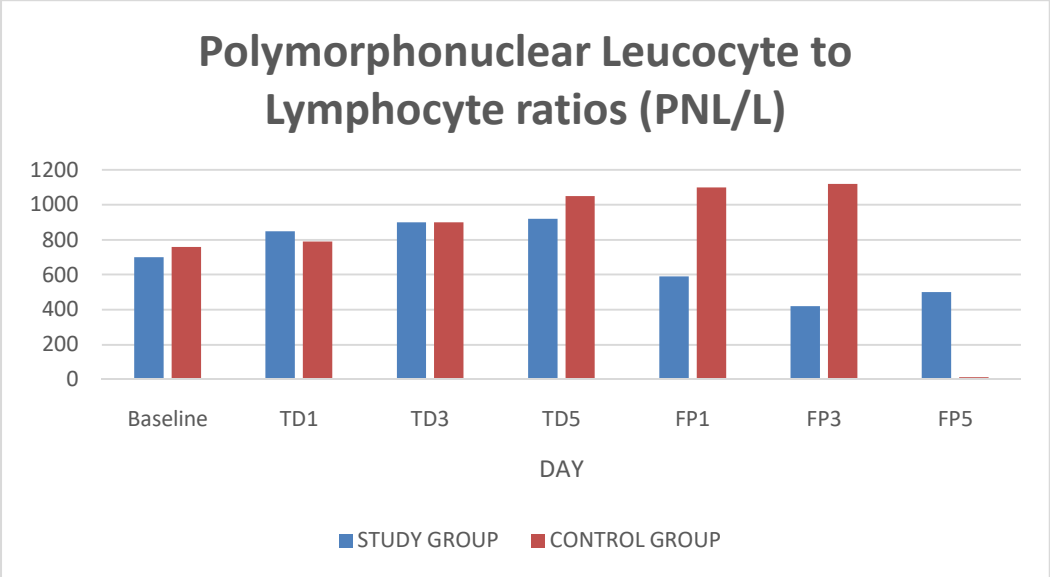

Figure 5: Polymorphonuclear Leucocyte to Lymphocyte ratios (PNL/L).

decreased and fell below the baseline values. This decline in both of the groups (p>0.06 for both groups) also the difference between both groups at the end of the follow-up period was not significant enough with p=0.65 in Figure 5 above.

Serum ferritin values (mg/dl)

The serum ferritin values increased compared to the baseline values in both of the groups during the treatment period (p=0.07 and p=0.05 for both the study group and the control group respectively). In the study group, ferritin values started to decrease during the follow-up period and also showed a significant decrease compared to the values of the baseline (p=0.05) at the end of the follow-up period, it was found that it continued to increase compared to the level of the baseline in the control group (p=0.02). When the Serum ferritin values of the two groups were compared at the end of the follow-up period, it was found to be significantly high in the control group showing p=0.005.

DISCUSSION

The study result outcome focused on ivermectin addition on patients with comorbidities on treatment only using primarily imminent randomized controlled trial examining the viability of ivermectin within the treatment of patients with extreme COVID-19. Within the study, there are many planned randomized controlled considers assessing the viability of hydroxychloroquine, lopinavir-ritonavir, redeliver, and favipiravir drugs, which are among the treatment alternatives for COVID-19 patients (Cao, Goreshnik, Coventry, Case, Miller, Kozodoy(2020) . When these considerations were inspected, it was detailed that remdesivir shortened the recuperation time compared to fake treatment, and favipiravir expanded viral clearance (Schmith, Zhou, and Lohmer, (2020).

In our study, we found that patients who included ivermectin in the HFA combination treatment (study group) had a better rate of clinical enhancement compared to patients who gotten as it were HFA combination treatment (control group). Additionally, after the follow-up period, mortality rates were found to be lower within the study group, compared to the control group accepting it was an HFA combination treatment. Even though clinical improvement and mortality contrast between the study and control groups were not factually noteworthy, these contrasts can be more clearly uncovered in a new study with bigger patient arrangements.

Considering that the patients included in our study have serious COVID-19, it can be thought that we have accomplished a higher clinical reaction with ivermectin treatment than the antiviral drugs examined so distant. In a review cohort examination conducted in Florida, it was detailed that mortality was decreased in COVID-19 patients with the use of a single dosage of ivermectin, supporting our result. However, our study about ivermectin recommends that ivermectin may be an elective or an extra choice to standard treatment conventions within the treatment of COVID-19 infection. SpO2 is underneath physiological levels in most patients who develop COVID-19 pneumonia and in all patients

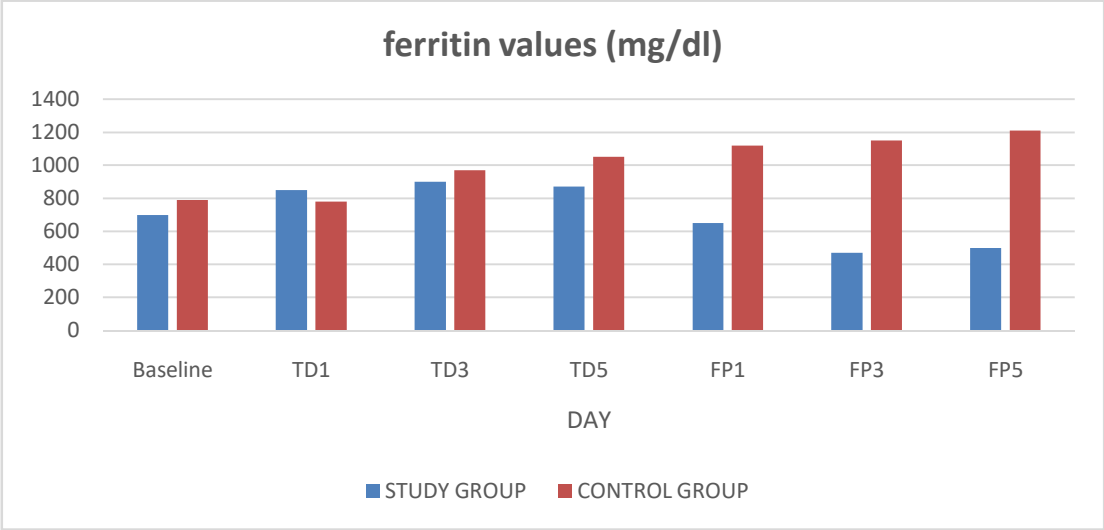

Figure 6. Ferritin values (mg/dl).

with extreme prognosis. An increase in SpO2 levels cannot reach ordinary limits most of the time despite oxygen support or other strong medicines in patients with serious prognoses. An increment in SpO2 level with treatment in patients could be a noteworthy pointer of clinical reaction to treatment (Liu et al., 2020; Capra et al., 2020). In our study, SpO2 levels expanded compared to the pattern levels in both groups amid the treatment and follow-up period, but come to the specified levels within the study group after the follow-up period (95.4%) and were found to be altogether higher than the control group. In like manner, it can be said that including ivermectin in the treatment includes a more positive impact on the treatment of Covid-19 pneumonia than the current treatment convention. As a matter of reality, in thinking about comparing the efficacy of single measurements ivermectin + doxycycline combination and azithromycin + hydroxychloroquine combination therapies in patients with diabetes mellitus to direct severity of COVID-19, it was detailed that symptomatic enhancement was accomplished in a shorter time with the combination containing ivermectin (Choudhary and Sharma, 2020).

The leading indicator of oxygenation within the blood is the PaO2/FiO2 ratio. Its typical range is 300–500 mmHg and being < 200 mmHg shows extreme hypoxemia. An increment in this rate shows clinical advancement in serious COVID-19 patients (Winch, Clough, Mant, Hamilton-Russell, Barker, Payne, S& Rothwell, 2020).We made the research universe from patients with serious COVID-19 at high mortality chance. Even though the starting PaO2/FiO2 proportions of the patients within the study group were lower than the control group and there was a slight diminish at the start of the treatment period, the truth is that they reached higher values after the treatment and follow-up period compared to the baseline and control group can be assessed as an indicator of the adequacy of adding ivermectin to the treatment. The truth that satisfactory reaction at PaO2/FiO2 proportions was gotten within the late periods of the study, proposes that more positive comes about can be gotten by beginning ivermectin treatment before serious pneumonia develops. The recommendation that ivermectin can be utilized in patients with mellow or moderate COVID-19 pneumonia ought to be upheld by further studies.

In COVID-19 infection, serum ferritin, CRP and D-dimer levels, blood lymphocyte number, and PNL/L proportion are laboratory parameters that have appeared to be related to prognosis. It is detailed that the prognosis is regrettable, particularly in patients whose lymphocyte check does not alter despite the medications given and whose ferritin and D-dimer values stay high. Hence, changes in these parameters are considered substantial indicators of clinical reactions in patients getting treatment (Zhang et al., 2020; Henry et al, 2020; Cheng et'al., 2020).

In our study, with the addition of ivermectin to the treatment, it was watched that a more articulated and prior increment in lymphocyte tallies was accomplished in patients within the study-group compared to the control group. Whereas the PNL/L proportion, one of the prognosis indicators, began to diminish early within the treatment period within the study group, it expanded within the control group. In the study group, this diminishes continued significantly within the follow-up

period. But within the control group, a diminish in the PNL/L ratio was watched as it was towards the center of the follow-up period. This result appears that ivermectin provides earlier treatment efficacy within the treatment of COVID-19 contamination compared to existing conventions.

Within the study, it has been detailed that the forecast will be destitute in patients > 27 a long time of age and with PNL/L > 2.13, and serious care follow-up is required (Fei et al., 2020). In this manner, the early diminish given by ivermectin in PNL/L proportions can contribute to shortening the serious care period and prognosis in COVID-19 contaminations. After the follow-up period, it was observed that PNL/L proportions were lower in both groups compared to the baseline values, the diminish within the study group was more pronounced than in the control group, but there was no critical contrast between both groups. Whereas the diminish within the PNL/L ratio proceeded essentially in the considered group until the 3rd day within the follow-up period, there was a slight increment on the 5th day. The reason for this may be leucocytosis due to secondary bacterial infections (unspecified data) that we recognized in patients.

The reality that serum CRP and D-dimer values diminished altogether prior and speedier within the study group, and serum ferritin values decreased significantly within the study group whereas kept on increment within the control group, can be considered as a pointer that including ivermectin increases the viability of the serious Covid-19 contamination treatment,Cochrane Database Syst Rev (2020)

When the result of those five laboratory parameters which are profitable within the follow-up of the prognosis of the illness (blood lymphocyte check, serum ferritin, CRP, D-dimer levels, and PNL/L proportion) were assessed; it was found that ivermectin was viable in the treatment of COVID-19, it appears to supply an prior treatment reaction and underpins the thought that ivermectin or including ivermectin to current treatment conventions may be an alternative for the treatment of COVID-19. In our study, no distinctive side effects were watched in patients getting ivermectin compared to patients receiving standard treatment. In any case, six of the 12 patients with MDR-1/ABCB1 or CYP3A4 gene mutation who received the first dose of ivermectin had mild (disturbance) and two had serious side impacts (disturbance, delirium-like behaviour, and aggressive behaviour and awareness changes).

The assurance of ABCB1 (NM_000927.4)1236 T > C/2677 T > G/3435 T > C genotypes is critical in deciding the hazard of side impacts in medicate utilization. ABCB1 (NM_000927.4) 1236 T > C/2677 T > G/3435 T > C genotype was identified in all 12 patients who were prohibited from the study. Subsequently, this haplotype counting in cases where it is heterozygous was considered as the most haplotype in terms of complication advancement, and after the think about it was decided that this forecast was for the most part rectify, Schmith, Zhou and Lohmer, (2020).

In one of these 12 patients, S400I (c.1199G > A), CM068130, and rs2229109 genotypes were found in expansion to ABCB1 quality. Even though it has been expressed in the study that the S400I change may modify film transport and cause drug resistance (PMID: 16917872), no side impacts related to ivermectin developed in these patients. ABCB1 (NM_001348945.1): c.210G >A(p.Gly70 =) genotype was additionally found in two of our 3 patients with mellow side effects. On the other hand, the discovery of the same genotype in 2 of 31 patients without side effects proposes that this genotype alteration has no effects on ivermectin metabolism.

In our patients, who developed the foremost severe and longest enduring side effects related to ivermectin, in addition to ABCB1 mutation, a alter in CYP3A4 quality was found to be c.1191C >T(p.T363M). It has been detailed within the think that the T363M alteration recognized within the CYP3A4 gene reduces the work of the enzyme, Jayasekera, Moseman , Carroll,(2007).

Hence, it has been prescribed in the study to reduce the medication measurements (HGMD: CM015322). After the first dose of ivermectin, disturbance, delirium-like symptoms, hostility, and changes in awareness was watched in these patients who were given remifentanil and dexmedetomidine for sedation and were avoided from the study. Midazolam administration was moreover required and it took approximately 2 weeks for symptoms to vanish in this patient. The reason for the longer and more severe clinical symptoms in this quiet compared to the patients with other sedate side effects was considered to be the coexistence of both ABCB1 and CYP3A4 changes. This finding recommends that the CYP3A4 quality is additionally viable and important in ivermectin metabolism, Abdul-Jabbar, et'al.(2013). In our study, in patients who developed side effects due to ivermectin, symptoms vanished totally within 2 weeks in 2 patients with serious side effects and 1–2 days in 3 patients with mild side effects. All these results propose that the medication can be utilized securely in patients who do not have a mutation that will influence ivermectin metabolism. In case it is chosen to utilize drugs at the community level or in huge groups, since sequence analysis isn't conceivable in practice due to time imperatives, patients ought to be followed up closely in terms of encephalopathy-like indications affecting the central nervous system, and symptoms can be controlled in these patients with fitting treatment and follow-up.

Our study is the primary randomized controlled planned study within the study in which MDR-1/ABCB1 and CYP3A4 gene variations which will cause changes in ivermectin measurements were explored in patients with COVID-19. There are notices within the study as the

study of (Jayasekera, Moseman and Carroll,2007) approximately the possible harmful impacts of Ivermectin that's a promising drug for the treatment of COVID-19 and the FDA too draws specific consideration to this issue (Wenjing, et,al 2022,). In any case, our result sheds light on the concerns in this respect.

One confinement of our study is that the intuition of the drugs utilized was not assessed. Be that as it may,we think that there are no adverse drugs interaction due to the nonappearance of any laboratory changes that cannot be clarified with the clinical conditions of the patients (Mishra et al., 2020).

The dosage regimens that produced favorable results against COVID-19 extended from 10- mg/kg single measurements to 12mg/kg/d for 5 days 29-32; a concentration subordinate antiviral impact was demonstrated by Krolewiecki et'al (2021). Pharmacokinetic studies have proposed that a single dose of up to 12 mg of ivermectin can be secure and well endured. Considering the top of SARS-CoV-2 viral load amid the primary week of ailment and its prolongation in serious disease the use of an ivermectin dose of 12mg/kg of body weight every day for 5 days. The eminently higher rate of AEs within the ivermectin group raises concerns about the use of these drugs outside of the trial settings and without restorative medical supervision, specific this regime was constantly not fulfilled by NAFDAC for the treatment of COVID-19.

Conclusion

This study uncovered that ivermectin may be an alternative drug that can be used within the treatment of COVID-19 illness or an extra choice to current treatment conventions. Indeed when used in serious COVID-19 patients, it can give an increment in clinical recovery, change in prognostic laboratory parameters, and a decrease in mortality rates. It is anticipated that ivermectin can be utilized securely without causing any genuine side effects in patients without MDR-1/ABCB1 and/or CYP3A4 gene mutation, and the emerging side effects can be eliminated with suitable treatment. All these come about suggest that ivermectin may be a trust within the treatment of COVID-19 malady and these results accomplished in this study should be backed with advanced studies, particularly with more cases counting early stages of COVID-19 patients. It is, therefore, concluded that Invertmetic when gradually administer to a patient enhances the recovery of a patient with COVID-19. To have better recovery for patients with Covid19, I will suggest that ivermectin 12mg should be used only with medical advice. Future research should enlarge the size of geographical tentacles by using four or more states that had cases of the covid19 to make more patients who tested positive for Covid-19. Also, the addition of ivermectin 12mg for the treatment of Covid-19 should be increased to 15mg for the treatment of the omicron Covid-19 variant to ascertain the level of recovery and responses of patients.

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Availability of data and materials

The dataset and materials used and also analyzed during the study are available from the author at a reasonable request.

Declaration

Ethics approval and consent to participate

This is a note. The style name is Footnotes, but it can also be applied to endnotes.

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