Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic

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EDITORIAL NOTE:

Research Square withdrew this preprint on 14 July, 2021 due to an expression of concern communicated directly to our staff. These concerns are now under formal investigation.
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Abstract

Background: Up-to-date, there is no recognized effective treatment or vaccine for the treatment of COVID-19 that emphasize urgency around distinctive effective therapies. This study aims to evaluate the anti-parasitic medication efficacy "Ivermectin" plus standard care in the treatment of mild/moderate and severely ill cases with COVID 19 infection, as well as prophylaxis of health care and/ or household contacts.

Subject and methods: 600 subjects; 400 symptomatic confirmed COVID-19 patients and 200 health care and household contacts distributed over 6 groups; *Group I:* 100 patients with mild/moderate COVID-19 infection received a 4-days course of Ivermectin plus standard of care; *Group II:* 100 patients with mild/moderate COVID-19 infection received hydroxychloroquine plus standard care; *Group III:* 100 patients with severe COVID-19 infection received Ivermectin plus standar care; *Group IV:* 100 patients with Severe COVID-19 infection received hydroxychloroquine plus standard care. Routine laboratory investigations and rT-PCR, were reported before and after initiation of treatment. *Group V stick to personal protective measures (PPM) plus Ivermectin o.4mg / kg on empty stomach to be repeated after one week, and group VI stick to PPM only .Both groups V&VI were followed for two weeks ..*

Results: Patients received ivermectin early reported substantial recovery of laboratory investigations; and significant reduction in rT-PCR conversion days. A substantial improvement and reduction in mortality rate in Ivermectin treated groups; group I (99% & 0.0%, respectively) and group III (94% & 2.0% respectively) versus hydroxychloroquine plus standard care treated groups; group II (74% and 4%, respectively) and group IV (50% and 20%, respectively). Ivermectin had significantly reduced the incidence of infection in health care and household contacts up to 2% compared to 10% in non ivermectin group when used as a prophylaxis.

Conclusion: *Early addition of Ivermectin to standard care is very effective drug for treatment of COVID-19 patients with significant reduction in mortality,rt-PCR conversion days , recovery time hospital stay compared to Hydroxychloroquine plus standard care.* Early use of Ivermectin is very useful for controlling COVID 19 infections; prophylaxis and improving cytokines storm

Introduction

Coronavirus has been a recognized pathogen in animals in early 1960s that caused gastrointestinal side effects and additionally respiratory manifestations. In late 2019, the coronavirus advanced to contaminate the human respiration system (SARS-CoV-2) as visible inside the outbreak in Wuhan, China. Later, the World Health Organization (WHO) named the SARS-CoV-2 pandemic COVID-19 [1].

This novel virus infection has incapacitated the world's medical services framework as well as the political and financial relations [2]. As another section in human life opens up [3], the world is by all accounts divided into two sections pre-and post-COVID-19 time.

The median incubation period, is approximately 4 to 5 days, from exposure to onset of manifestation, about 97.5% of ongoing to have manifestations will have symptoms within 11 days after infection [4]. Assessment and management of Covid-19 are guided by the severity of the illness. As indicated by initial data from China, 81% of individuals with Covid-19 had the mild or moderate disease (including individuals without pneumonia and individuals with mild pneumonia), 14% had severe illness, and 5% had critical serious disease [5]. Cutaneous manifestations of COVID 19 are erythematous exanthema, dengue-like rash, cutaneous vasculitis, acute urticaria, and chickenpox like blisters [6].

Albeit a couple of medications have gotten crisis use approval for COVID-19 treatment, no demonstrated treatment has been found up till now. An ongoing in vitro study indicated that Ivermectin was dynamic against COVID-19-infected cell [7]. Ivermectin proposes numerous possibilities impacts to treat a scope of illnesses, with its antimicrobial, antiviral, and anti-cancer properties as a marvel drug. It is profoundly successful against numerous microorganisms including some infections. It was discovered in the late 1970s and approved for animal use in 1981. A couple of years later approved for human use. In this manner, William C. Campbell and Satoshi Ōmura who found and built up this drug got the 2015 Nobel Prize in Physiology and Medicine [8-9].

Studies uncovered that Ivermectin is broad-spectrum drug with high lipid solubility that has a various consequences for parasites, nematodes, arthropods, flavivirus, mycobacteria, and mammals through a variety of mechanisms [8-9]. Not only having antiparasitic and antiviral impacts, this medication likewise causes immunomodulation in the host. Studies have demonstrated its impact on repressing the multiplication of malignancy cells, just as directing glucose and cholesterol in animals. Regardless of the different impacts of this medication, a significant number of its hidden mechanisms are not yet known [10]. Although, Cytokines are naturally fraction of immunological response to infection, however their abrupt delivery in huge amounts in a storm pattern (*cytokine storm*) can cause multi-organ failure and death, which has motivated the utilization of powerful immunomodulatory therapies including ivermectin in clinical trials [11].

Ivermectin end up being a more of a 'Wonder drug' in human wellbeing, improving the nourishment, general wellbeing, and prosperity of billions of individuals overall since the time it was first used to treat Onchocerciasis in humans in quite a while in 1988. It demonstrated ideal from multiple points of view, being exceptionally effective and broad-spectrum, well-tolerated, safe and could be handily regulated (a single, yearly oral dose). It is utilized to treat a wide range of nematode infestations, including Onchocerciasis, Strongyloidiasis, Ascariasis, cutaneous larva migrans, filariasis, Gnathostomiasis, and Trichuriasis, just as for oral treatment of ectoparasitic diseases, for example, Pediculosis (lice infestations) and scabies (mite invasion) [12]. In contrast to the limited therapeutic index for hydroxychloroquine and chloroquine; ivermectin has a more safety margin [7]. The higher doses of ivermectin have been assessed in a phase III study, where $200-400$ μg/kg dosages were evaluated in patients with Dengue fever and were safe, even higher dosages (up to 10× higher than approved dosage) were assessed in a small phase I preliminary trial [13]. This trial demonstrated that ivermectin given orally in the fasting state was tolerated both after a single 120 mg dosage (10× higher than approved dosage) and after 60 mg three times weekly (every 3 days). The most widely recognized side effects were headache, nausea, dizziness, and rash [14].

The reported incidence and type of adverse events were generally comparable between ivermectin (24%) and placebo (35%) and didn't increase with dose. All dosing regimens had a mydriatic impact (the essential wellbeing endpoint dependent on results from toxicology studies) that was like placebo treatment [14].

Caly et al. [7] revealed that ivermectin hindered extreme intense respiratory syndrome-coronavirus 2 (SARS-CoV-2) in vitro for as long as 48 hours utilizing ivermectin at 5 µM. The concentration resulting in 50% inhibition (IC50; 2 µM) was > 35× higher than the most maximum plasma concentration (Cmax) after oral approved dose of ivermectin when given fasting.

The causative agent of the current COVID-19 pandemic, SARS-CoV- 2, is a single-stranded positive-sense RNA virus that is firmly identified with severe acute respiratory syndrome coronavirus (SARS-CoV). Studies on SARS-CoV proteins have uncovered a potential role for IMPα / β1 during infection in the signal-dependent nucleocytoplasmic closing of the SARS-CoV Nucleocapsid protein (15) that may affect cell division of the host. Additionally, the SARS-CoV accessory protein ORF6 has been appeared to offend the antiviral action of the STAT1 transcription factor by sequestering IMPα / β1 on the rough ER/Golgi membrane (16). Taken together, these reports proposed that ivermectin's nuclear transport inhibitory action might be powerful against SARS-CoV-2. The authors noted a 93–99.8% decrease in viral RNA for ivermectin versus control at 24h in the supernatant (released virions) and cell-associated viral RNA (total virus) respectively. They likewise reported by 48 hours a >5000-fold decrease of viral RNA and maintenance of effect at 72 hours. Additional investigations were directed with sequential dilutions of ivermectin to build up the concentration-response profile, and the authors described ivermectin as a powerful inhibitor effect of SARS-CoV-2, with an IC50 determined to be approximately 2 µM [17]. Physicians all over the world were utilizing Ivermectin off—label, As soon as the in vitro results were published.

Patients And Methods

I-Technical design:

Study design: A multicenter double blind randomized controlled clinical trial (RCCT) study design was carried out on 600 subjects; 400 symptomatic patients and 200 health care and household contacts at Benha and Kafrelshaikh University Hospitals. A block randomization method was used to randomize the study participants into two groups that result in equal sample size. This method was used to ensure a balance in sample size across groups over the time and keep the number of participants in each group similar at all times.

Study setting: Benha and Kafrelsheikh University (COVID-19 Isolation Hospitals).

Study period: The study was carried out from 8th June to 15th September 2020.

Study population (Sampling Design and Sample Size):

The study was conducted on 600 subjects; 400 patients and 200 health care and household contacts that were divided into 6 groups:

- **Group I:** 100 patients with Mild/Moderate COVID-19 infection received a 4-days course of Ivermectin 0.4mg/kg body weight maximum 4 tablets (6mg / tablet) once daily dose [13] before breakfast plus standard care as issued by Egyptian protocol of COVID-19 treatment (Azithromycin 500mg OD for 6 days, Paracetamol 500mg PRN, vitamin C 1gm OD, Zinc 50 mg OD, Lactoferrin 100mg sachets BID , Acetylcystein 200mg t.d.s & prophylactic or therapeutic anticoagulation if D-dimer > 1000), (MOH version 30 May 2020), [18].
- **Group II**: 100 patients with mild/moderate COVID-19 infection as a control group received hydroxychloroquine (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days) plus standard care (Azithromycin 500mg OD for 6 days, Paracetamol 500mg PRN, vitamin C 1gm OD, Zinc 50 mg OD, Lactoferrin 100mg sachets BID & Acetylcystein 200mg sachets t.d.s & prophylactic or therapeutic anticoagulation if D-dimer > 1000) as issued by Egyptian protocol of COVID-19 treatment [18].
- **Group III**: 100 patients with severe COVID-19 infection received a 4 days course of Ivermectin 0.4mg/kg body weight maximum 4 tablets (6mg / tablet) once daily dose [13] before breakfast plus standard care (Azithromycin 500mg OD for 6 days, Paracetamol 500mg PRN, vitamin C 1gm OD, Zinc 50 mg OD, Lactoferrin 100mg sachets BID , Acetylcystein 200mg sachets t.d.s , prophylactic or therapeutic anticoagulation if D-dimer > 1000 and systemic steroids) as issued by Egyptian protocol of COVID-19 treatment for severe patients [18].
- **Group IV**: 100 patients with severe COVID-19 infection as a control group received hydroxychloroquine (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 9days) plus standard care (Azithromycin 500mg OD for 6 days, Paracetamol 500mg PRN, vitamin C 1gm OD, Zinc 50 mg OD, Lactoferrin 100mg sachets BID , Acetylcystein 200mg sachets t.d.s , prophylactic or therapeutic anticoagulation if D-dimer > 1000 and systemic steroids) as issued by Egyptian protocol of COVID-19 treatment for severe ill patients [18].
- **Group V**: 100 health care (pre exposure) and / or household (post exposure) patients' contacts received a prophylactic dose of ivermectin 0.4mg/kg single oral dose before breakfast to be repeated after one week in addition to personal protective measures (PPM), (hand hygiene, social distance measures, avoiding touching the eyes, nose, and, face masks, gloves, respiratory etiquette and self-isolation) [19].
- **Group VI**: 100 health care and or household patients' contacts stick to personal protective measures only as a control group . (19).

Exclusion criteria: pregnancy, lactation, and critical cases defined as: occurrence of respiratory failure requiring mechanical ventilation; Presence of shock; other organ failure that requires monitoring and treatment in the ICU, [20].

Inclusion criteria:

1. Patients who have been diagnosed with COVID-19 infection with at least one positive rt-PCR result from nasopharyngeal/oropharyngeal swab.
2. Mild cases: Patients have mild symptoms such as anosmia, loss of taste, fever or respiratory tract symptoms, gastrointestinal symptoms, etc. and free chest imaging.
3. Moderate Cases: Patients have symptoms such as fever, respiratory tract symptoms, gastrointestinal symptoms, etc. and pneumonia manifestations can be seen in chest imaging.
4. Severe COVID-19 confirmed cases, fulfilling any of the following criteria:

   a. Respiratory rate more than 30/min.
   b. Blood oxygen saturation of less than 93%.
   c. PaO2/FiO2 ratio of less than 200
   d. Lung infiltrates >50% of the lung fields or rapid progression within 24-48 hours.
   e. Patients need respiratory support e.g. high flow oxygen noninvasive or invasive mechanical

Eligibility Criteria

All participants were from 18 years up to 80 years old. Patients agreed to sign an informed consent to participate in the current study and they are not participating in other clinical trials within 30 days from administration of the study drugs. Patients with hydroxychloroquine contra-indications: QTc > 500 m/sec, myasthenia gravis, porphyria, retinal pathology, epilepsy, G6PD deficiency, allergy to 4-aminoquinolone, chronic heart, kidney or liver disease, and arrhythmias. - Any patient demonstrates worsening of symptoms; radiological progression with virologically persistence within at least 7 days of the therapeutic evaluation period of the study after exclusion of cytokine storm was considered as a clinical failure and was shifted to the other management protocol. - Treatment was terminated at any time by a multidisciplinary team if a serious side effect occurred, which was attributed to the medications used ,e.g. cardiac arrhythmia, deteriorated liver or kidney function or unfortunately patient died.

Study methods and Tools:

All patients were subjected to:

- Full history and clinical examination taking, and laboratory assessment including liver function tests, kidney function tests, full blood count, serum Ferritin level. CRP, D-dimer, real-time PCR for COVID-19 and, radiological assessments including CT chest.
- Follow up: Patients were followed up daily clinically and by laboratory assessment for two weeks but radiological assessment after two weeks or until one of the endpoints is reached. Follow up the duration of treatment, swab conversion, hospital stay, the clinical and radiological improvement was recorded.

Endpoints:

The primary endpoint: clinical, laboratory investigations improvement and/or 2 consecutive negative PCR tests taken at least 48 hours apart.

Secondary endpoint: Patients presenting with adverse events requiring stoppage of treatment and management of any side effects accordingly.

Benefits: Ivermectin help in reduction of virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19.

Risks: The reported infrequent side effects are insomnia & nausea

Measures to prevent risks: Most side-effects are mostly resolved within 24 hours after drug initiation. If these adverse effects continue the drugs will be stopped.

II -Ethical design:

- An approval from the Research Ethics Committee at Faculty of Medicine, Benha

University (REC-FOMBU) was obtained, and the study had an approval number;

 (Re 96.2020).

- Informed written consent was obtained from all participants before participation; it was included data about the aim of the work, study design, site, time, subject and measures, confidentiality.

Statistical analysis:

The statistical analysis was carried out utilizing the Software, Statistical Package for Social Science, (SPSS Inc, Released 2009- PASW Statistics for Windows Version 21.0. Chicago: SPSS Inc.)The gathered information was summed up regarding mean± Standard Deviation (SD) and range for quantitative information and frequency and percentage for qualitative information. Correlations between the different study groups were completed utilizing the Chi-square test (χ^2) to

compare proportions as appropriate; the One-Way Analysis of Variance (ANOVA, F) test was utilized to distinguish the difference between parametric quantitative data for more than two groups. The Independent t-test was utilized to recognize the difference between parametric quantitative data in two independent groups. The pre-intervention and post-intervention comparison for the same groups was tested utilizing paired t-test, for the numerical variables when appropriate.

After the calculation of each of the test statistics, the corresponding distribution tables were counseled to get the "P" (probability value). Statistical significance was acknowledged at P value <0.05 (SS). A P value <0.001 was considered highly significant (HS) while a P-value >0.05 was considered non-significant (NS).

Results

The mean age in Group I was 56.7 ±18.4; included 72 % males and 28 % females. The mean age in Group II was 53.8 ±21.3; included 67 % males and 33 % females. The mean age in Group III was 58.2 ±20.9; included 68 % males and 32 % females. The mean age in Group IV was 59.6 ±18.2; included 74 % males and 26% females. The mean age in Group V was 57.6 ±18.4; included 75 % males and 25% females. The mean age in Group VI was 56.8±18.2; included 72 % males and 28% females. There was no statistical significance variation between groups regarding mean age or sex distribution (p-value >0.05).

Co morbid conditions distributed between different studied groups showed that DM was present in 15% of Group I patients, 14 % of Group II patients, 18% of Group III patients, 21% of Group IV patients 15% of group V and 19 % of group VI. HTN presented in 11% of Group I patients, 12 % of Group II patients, 14% of Group III patients, 18% of Group IV patients ,15 % of group V patients and 14%of group VI patients . 2% of Group I patients had IHD versus 6% in Group II, 5% in group III; 12% in group IV;1% in group V and 3 % in group VI respectively with statistically significant prevalence of ischemic heart disease as severity increase (p-value < 0.03).. Bronchial asthma presented in 5% of Group I patients, 6 % of Group II patients, and 14% of Group III patients, in 12% of Group IV patients; 5% of group V and 4% of group VI patients.

Clinically there was a highly statistically significant difference between groups of diseased patients regarding fatigue, dyspnea, and respiratory failure (p-value <0.001), as most of group III & IV, showed fatigue and dyspnea (86% and 88%, respectively), compared to (36%, 38% ; 54% and 52%, respectively), in group I & II. Respiratory failure had been detected in 38% and 40% in group III& IV respectively while no patients in group I& II developed respiratory failure. No skin manifestation had been detected in any group.

In this study hemoglobin and Lymphocyte significantly decreased with increased severity of the disease however, inflammatory markers; (TLC, CRP, serum ferritin, D- dimer) significantly increased with increase severity of the disease (p-value was < 0.001), **Table (1)**.

Patients received standard care plus ivermectin reported substantial improvement in laboratory and severity parameters; TLC, lymphocyte (%), CRP, ferritin D-dimer, and RT-PCR conversion days (6.4±2.1, 32.4 ± 6.8, 4.8 ± 2.1, 94.8 ± 48.6, 0.54 ± 0.06 and, 5 ±1, respectively) compared to Group II treated by standard care plus hydroxychloroquine (7.1±2.3, 28.2 ± 3.9, 8.3 ± 3.6, 98.4 ± 54.8, 0.68 ± 0.21 and, 10 ± 4, respectively) one week after starting treatment (P<0.001, **Table (2)**. Likewise sever patients with standard care plus Ivermectin (Group III patients) reported a significant improvement in Hg%, TLC, lymphocyte (%), CRP, serum ferritin, D dimer, and RT-PCR conversion days (13.8 ± 1.2, 8.9±2.4, 34 ± 6.7, 28.6 ± 9.4, 104 ± 19.6, 0.72 ± 0.12 and 6 ± 1, respectively) compared to Severe patients with standard care plus hydroxychloroquine (Group IV), (12.6 ± 1.9, 14.2±3.8, 24.6 ± 5.8, 58.6 ± 24.4, 294 ± 78.6, 1.86 ± 0.6 and 12 ± 4, respectively), one week after starting treatment (P<0.001), **Table (3)**.

The prognosis of the disease reported a significant improvement in groups received Ivermectin plus standard care & (groups I & III), (99% & 94% respectively) compared to those received *Hydroxychloroquine* plus standard care only (Group III&IV), (74% & 50% respectively), (p-value <0.001). The mortality rate significantly reduced in Ivermectin treated patients groups I& III (0.0% & 2%, respectively) versus *Hydroxychloroquine treated* groups II & IV (4% & 20%, respectively), **Table (4 &6)& figure (1)**

In this study Ivermectin is very effective in preventing corona virus infection in health care or household contacts of COVID 19 patients group V (2%) compared to non Ivermectin group VI (10%), Table (5).

Discussion

This study is one of more than 40 such clinical trials that research the medication repurposing of an FDA approved an antiparasitic drug called Ivermectin. In view of the seriousness of the COVID-19 pandemic, some low-income nations for example, Egypt are surveying possible reuse of medications that may help lessen the pandemic severity.

Lymphopenia, neutrophilia, raised serum ALT and AST levels, raised LDH, CRP, and ferritin levels have been related with more prominent infection seriousness [21, 22] and hospital admission [23] in COVID-19 patients. Patients with extreme and lethal infection have altogether elevated white blood cells count (WBC), and diminished lymphocyte and platelet counts contrasted with those with non-serious infection and survivors [24, 25]. In this study, hemoglobin and Lymphocyte significantly decreased with increased severity of the disease however, inflammatory markers; (TLC, CRP, serum ferritin, D- dimer) significantly increased with increase severity of the disease (p-value was < 0.001).

In this study, patients received ivermectin reported substantial improvement in TLC, lymphocyte (%), CRP, D-dimer, and RT-PCR conversion days compared to Group II treated by *Hydroxychloroquine* one week after starting treatment (P<0.001). Similarly, Ivermectin did in sever COVID-19 infection patients with significant Hg elevation compared to severe patients given *Hydroxychloroquine* (Group IV), (P<0.001). Although, no studies found elevating role of Ivermectin in severe cases, however, its results in this study is encouraging its use in severe case. Moreover, *Yan et al.,* [26] and *Zhang et al.* [27] reported that Ivermectin reduce the inflammatory process by decreasing the production of multiple cytokines, such as TNF-α, IL-1ss, IL-6, IL-4, IL-13 and IL5. So, ivermectin could

suppress a diversity of the inflammatory cytokines which had an important role in the intiation of the "cytokines storm". The documentation in the literature therefore indicates that ivermectin might be useful in the management of COVID-19 [28].

In this study, Ivermectin treated groups (I&III) showed significant reduction in recovery time and hospital stay days (5±1 and 6±1, respectively) compared to hydroxchloroquine treated groups (II&IV), (15±8 and 18±8, respectively), (P <0.001) that helps in reduction of resources consumption. *Chowdhury et al.,* [29] compare mild / moderate COVID-19 patient group A which received Ivermectin 0.2 mg/kg single dose plus Doxy 100mg BID for 10 days, versus group B (56 patients) which received; Hydroxychloroquine (HCQ) 400 mg1st day, then 200mg BID for 9 days plus Azithromycin 500mg daily for 5 Days. Group A versus Group-B: Recovery rate was 100% versus 96.36%, mean symptomatic recovery duration was 5.93 days' versus 6.99 days and negative PCR was achieved on 8.93 days versus 9.33 days, and by 5th day, 55.10% versus 23.8% respectively. In *Dominican Republic's clinical trial* [30], A 1,300 mild/moderate COVID-19 patients started Ivermectin with standard dosage of 0.1– 0.2 mg/kg and have titrated up to 0.4mg/kg and found that 99% of the patients reported cure with significant reduction of recovery time from 21 days to 10 days plus virus inhibited by ivermectin within a couple days in humans

The substantial improvement with significant reduction in mortality rate in Ivermectin treated groups; group I (mild/moderate cases), (99%, and 0.0%, respectively) and group III (severe cases), (94%, and 2.0% respectively) versus *Hydroxychloroquine* treated groups; group II (mild/moderate cases), (74% and 4%, respectively) and group IV (severe cases) (50% and 20%, respectively) highlighted the strong recommendation of its use in COVID -19 management . *Rajter et al.* [31] studied 280 patients with COVID-19; 173 patients received ivermectin and 107 with usual care and announced lower mortality in the ivermectin group (15.0 % versus 25.2% with P< 0.03) especially among patients with severe pulmonary disease who required higher inspired oxygen or ventilator support treated with ivermectin (38.8% versus 80.7%)

In this study Ivermectin is very effective in preventing corona virus infection in health care or household contacts of COVID 19 patients group V (2%) compared to non Ivermectin group VI (10%). Physicians have directed the usage of ivermectin in a few synchronous trials in many countries [32], and announced that patients' viral loads started declining very quickly after Ivermectin administration. We noticed that it has surprised physicians in clinical trials in many countries. Physicians' noticed that just single dosage of Ivermectin could improve patient's condition; however, some of them received a booster dose one week later. *Rajter et al.*[31] at the Broward Health Medical Center in Fort Lauderdale, Florida, submitted a dramatic, statistically significant improvement in mortality in 250 coronavirus patients involved in the Broward trial treated with Ivermectin medication.

Conclusion

Addition of Ivermectin to standard care is very effective drug for treatment of COVID-19 patients with significant reduction in mortality,recovery time and hospital stay days compared to Hydroxychloroquine plus standard treatment only. Early use of Ivermectin is very useful for controlling COVID 19 infections; improving cytokines storm and prophylaxis of frontline health care as well as house hold contacts.

Declarations

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Tables

Table (1): Initial Laboratory data of the studied patients before starting treatment:

Variable		Group I (n =100)	Group II (n =100)	Group III (n = 100)	Group IV (n =100)	Test
Hgb (gm/dl)	Mean ±SD	12.6 ± 1.8	12.9 ± 2.1	11.2 ± 1.9	10.9 ± 1.2	ANOVA-test F = 69.1 P <0.001
	Range	10 -14	9 – 15	9 -12	10 -13	
TLC (X 103/ mL)	Mean ±SD	5.8± 1.2	6.2± 1.8	7.3± 1.4	6.9± 2.1	ANOVA-test F=11.71 P <0.001
	Range	4-9	4.3-10.2	4.8-11.2	5.1-13.7	
Lymphocyte (%)	Mean ±SD	18 ± 2.3	17 ± 3.1	16 ± 2.8	17 ± 1.9	ANOVA-test F=430 P<0.001
	Range	14 – 20	15 – 18	13 - 19	9 – 18	
CRP (mg/l)	Mean ±SD	48.4 ± 14.6	50.6 ± 18.3	64.8 ± 16.4	68.2 ± 18.6	ANOVA-test F=280 P <0.001
	Range	10 – 69	12 – 89	18 - 64	24 – 82	
Serum ferritin (ng/ml)	Mean ±SD	168.4±12.6	172±18.6	420±72.8	334±108.6	ANOVA-test F=523 P <0.001
	Range	154-186	158-194	188-472	192-630	
D dimer (mg/l)	Mean ±SD	4.8±1.8	5.4±2.1	9.6±1.2	10.2±2.8	ANOVA-test F=478 P <0.001
	Range	4.3-5.6	3.2-6.2	8.2-10.4	8.6-11.2	

Table (1) showed that hemoglobin and Lymphocyte significantly decreased with increased severity of the disease however, inflammatory markers; (TLC, CRP, serum ferritin, D- dimer) significantly increased with increase severity of the disease (p-value < 0.001),

Normal levels [Hgb 12-15.5 gm/dl, TLC 4-11 X 10^3/ mL, CRP 0-6 mg /L, serum ferritin 30-220 ng / mL in males 30-150 mg / mL in females and serum D-diamer less than 0.5 mg / L]

Table (2): Comparison of Laboratory data of Group I& Group II patients one week after starting treatment

Group / Variable	Group I after one week of treatment Mean ±SD	Group II after one week of treatment Mean ±SD	Independent t-test	P-value
Hgb(gm/Dl	14.2 ± 1.8	14.8 ± 2.7	1.85	0.07
TLC (X 103/ mL)	6.4±2.1	7.1±2.3	2.25	<0.05
Lymphocyte (%)	32.4 ± 6.8	28.2 ± 3.9	5.36	<0.001
CRP (mg/l)	4.8 ± 2.1	8.3 ± 3.6	8.4	<0.001
Serum ferritin (ng/ml)	94.8 ± 4	98.4 ± 54.8	0.49	0.62
D dimer (mg/l)	0.54 ± 0.06	0.68 ± 0.21	6.41	<0.001
RT-PCR(days)	5 ±1	10 ± 4	12.13	<0.001

Table (2) shows that there was a highly statistically significant improvement in TLC, lymphocyte (%), CRP, D dimer, and RT-PCR conversion days of Group I patients (Ivermectin+ standard care) compared to Group II (Hydroxychloroquine + standard care) after one week of starting treatment (P<0.001).

Table (3): Comparison of Laboratory data of Group III & Group IV patients one week after starting treatment

Group Variable	Group III after one week of treatment Mean ±SD	Group IV after one week of treatment Mean ±SD	Independent t-test	P-value
Hgb (gm/dl)	13.8 ± 1.2	12.6 ± 1.9	5.34	<0.001
TLC (X 103/ mL)	8.9±2.4	14.2±3.8	12.9	<0.001
Lymphocyte (%)	34 ± 6.7	24.6 ± 5.8	10.61	<0.001
CRP (mg/l)	28.6 ± 9.4	58.6 ± 24.4	11.47	<0.001
Serum ferritin (ng/ml)	104 ± 19.6	294 ± 78.6	23.45	<0.001
D dimer (mg/l)	0.72 ± 0.12	1.86 ± 0.6	18.63	<0.001
RT-PCR(days)	6 ± 1	12 ± 4	14.56	<0.001

Table (3) shows that there was a highly statistically significant difference improvement in Hgb, TLC, lymphocyte (%), CRP, serum ferritin, D dimer, and RT-PCR conversion days of Group III patients (Ivermectin+ standard care) compared to Group IV (Hydroxychloroquine+ standard care)   after one week of starting treatment (P<0.001).

Table (4): Distribution of the studied groups as regard Prognosis:

Variable		Group I (n =100)	Group II (control) (n =100)	Group III (n = 100)	Group IV (control) (n =100)	Chi-square test
		No. (%)	No. (%)	No. (%)	No. (%)	
Prognosis	Improved	99	74	94	50	χ2=98.7 P<0.001
	Progressed	1	22	4	30	
	Died	0	4	2	20	
Recovery time &Hospital stay (days)	Range	4 -6	6 – 31	4 – 7	9 – 25	
	Mean ±SD	5 ± 1	15± 8	6 ± 1	18 ±8	χ2=87.6 P<0.001

Table (4) shows that there was a highly statistically significant improvement associated with significant reduction in mortality, recovery time, and hospital stay days in groups received Ivermectin (I & III) compared to those received Hydroxychloroquine (II & IV) (p-value <0.001).

Table (5): comparison between Group V stick to PPE plus ivermectin prophylaxis versus Group VI stick to PPE only as a control group:

	Group V (100 contacts)	Group VI (100 contacts)	Test	P- value
Confirmed infected subjects by RT-PCR	2 (2%)	10 (10%)	X^2=5.6738	< 0.05

Table (6) Summary of outcomes after 4 days treatment with ivermectin

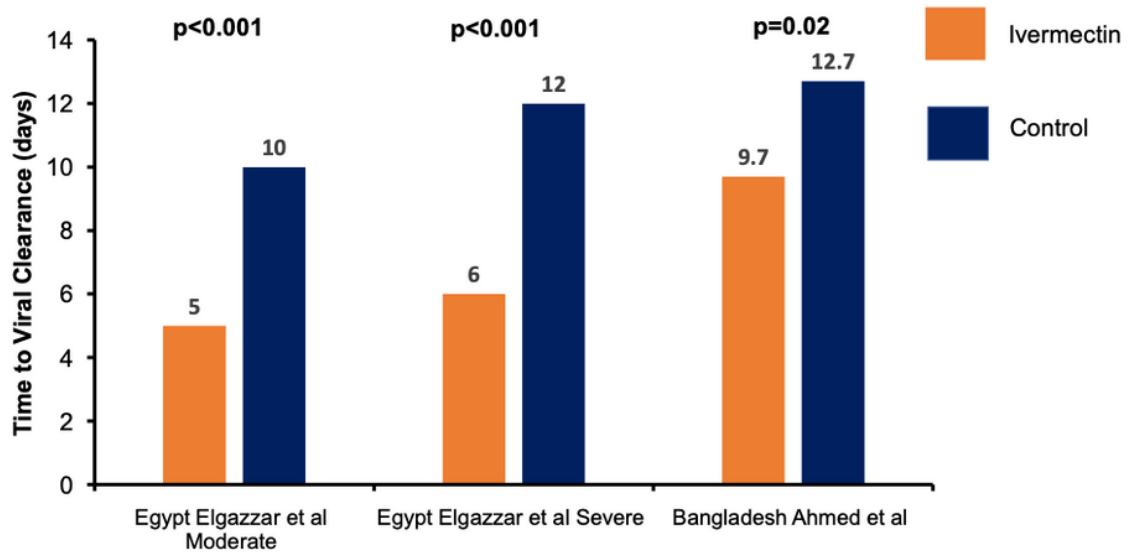|	Ivermectin	control	Ivermectin	control	P value
	Mild / moderate		severe		
Prognosis No. (%) Improved Progressed Died	99(99%) 1 (1%) 0 (0 %)	74(74%) 22 (22%) 4 (4%)	94 (94 %) 4 (4%) 2 (2%)	50 (50 %) 30 (30 %) 20 (20 %)	< 0.001
Hospital stay (days) mean±SD	5±1	15±8	6±8	18±8	< 0.001
RT- PCR (days) mean±S.D	5± 1	10 ± 4	6± 1	12±4	< 0.001

Figures

Figure 1

As regarding faster viral clearance, our results were better than Ahmed et al [33] in Bangladesh, they found viral clearance time in ivermectin treated group (9.7 days)in comparison to control group (12.7) days ,this can be explained the lower dose 0.2 mg / kg but we used 0.4 mg / kg in this study.