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ORIGINAL RESEARCH

Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19

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Background: Ivermectin is an FDA-approved broad-spectrum anti-parasitic agent that has been shown to inhibit SARS-CoV-2 replication *in vitro*.

Objective: We aimed to assess the therapeutic efficacy of ivermectin mucoadhesive nanosuspension intranasal spray in treatment of patients with mild COVID-19.

Methods: This clinical trial included 114 patients diagnosed as mild COVID-19. Patients were divided randomly into two age and sex-matched groups; group A comprising 57 patients received ivermectin nanosuspension nasal spray twice daily plus the Egyptian protocol of treatment for mild COVID-19 and group B comprising 57 patients received the Egyptian protocol for mild COVID-19 only. Evaluation of the patients was performed depending on improvement of presenting manifestations, negativity of two consecutive pharyngeal swabs for the COVID-19 nucleic acid via rRT-PCR and assessments of hematological and biochemical parameters in the form of complete blood counts, C-reactive protein, serum ferritin and d-dimer which were performed at presentation and 7 days later.

Results: Of the included patients confirmed with mild COVID-19, 82 were males (71.9%) and 32 females (28.1%) with mean age 45.1 ± 18.9. In group A, 54 patients (94.7%) achieved 2 consecutive negative PCR nasopharyngeal swabs in comparison to 43 patients (75.4%) in group B with P = 0.004. The durations of fever, cough, dyspnea and anosmia were significantly shorter in group A than group B, without significant difference regarding the duration of gastrointestinal symptoms. Duration taken for nasopharyngeal swab to be negative was significantly shorter in group A than in group B (8.3± 2.8 days versus 12.9 ± 4.3 days; P = 0.0001).

Conclusion: Local use of ivermectin mucoadhesive nanosuspension nasal spray is safe and effective in treatment of patients with mild COVID-19 with rapid viral clearance and shortening the anosmia duration.

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Keywords: ivermectin nanosuspension, nasal spray, COVID-19, biochemical and molecular

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Introduction

Coronaviruses (CoV) include a large number of viruses causing diseases ranging from mild common cold to severe Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Coronaviruses are zoonotic viruses; SARS-CoV was transmitted from civet cats to humans and MERS-CoV from dromedary camels to

humans.[1] The worldwide pandemic of Coronavirus Disease 2019 (COVID-19), is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), first discovered in Wuhan, China in 2019.[2–4]

Common manifestations of COVID-19 infection include respiratory symptoms, cough, fever, breathing difficulties and anosmia. Severe cases result in pneumonia, severe acute respiratory syndrome, kidney failure and even death. WHO recommendations to prevent infection spread include frequent hand washing, covering nose and mouth when sneezing and coughing, and avoiding close contact with anyone showing symptoms of respiratory symptoms such as coughing and sneezing.[1]

There is currently no specific drug therapy or vaccine available to treat COVID-19. Antimalarial drugs such as hydroxychloroquine and azithromycin, as well as antifilarial drugs such as ivermectin and antiviral drugs such as favipiravir, remdesivir, and umifenovir, have been studied. Many study groups around the world are looking into their potential effectiveness against COVID-19.[5] Additionally, SARS-CoV and other viral infections are believed to be inhibited by a variety of medicinal plants and natural products such as ilimaquinone (marine sponge metabolite), which have been shown to act on the ACE-2 receptor as well as other viral protein targets.[6,7] When compared with other cell-based therapies, which may experience challenges such as the cells sticking to the respiratory tract epithelia during administration, mesenchymal stem cells (MSCs) and their exosomes (MSCs-Exo) have shown promise in clinical trials as a therapeutic tool for severely affected COVID-19 patients.[8]

Ivermectin is an FDA-approved broad-spectrum antiparasitic agent that in recent years has shown to have antiviral activity against a broad range of viruses.[9,10] The mechanism of action of this drug against COVID-19 is unclear, though researchers suggest it works in the same way as it does against other viruses.[9] It is proved to inhibit integrase protein (IN) nuclear import and HIV-1 replication,[11] as it inhibits interaction between the importin (IMP) α/β1 heterodimer responsible for IN nuclear import and human immunodeficiency virus-1 (HIV-1) integrase protein.[11] Ivermectin is proved to limit infection caused by some Ribonucleic Acid (RNA) viruses such as West Nile viruses, influenza and dengue virus.[12] It is reported that ivermectin inhibits the replication of SARS-CoV-2 *in vitro*, and causes reduction about 5000-fold in SARS-CoV-2 viral RNA at 48 hours.[13] In addition, the binding of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane may be hindered by ivermectin docking.[14] Nanosuspension is a very fine dispersed drug particle in an aqueous vehicle for either topical and oral use or pulmonary and parenteral administration.[15] Nanosuspensions have high chemical stability, high drug loading capacity and low toxicity. Intranasal administration needs localization of drug in the nasal cavity for a prolonged time for absorption.[16] So, nanoparticles must be incorporated into mucoadhesive formulations that maintain the properties of nanosizing simultaneously with localization inside the nasal cavity.[17]

Because olfactory disturbances (anosmia/hyposmia) are frequently presenting manifestations of COVID-19,[18] and many patients could still have these disturbances for variable times (days to months) after complete cure from SARS-CoV-2, which can significantly affect their psychological status, we studied the local use of ivermectin as a mucoadhesive nanosuspension intranasal spray (where a large viral load is found at the early stages of the infection) to explore its possible effect in curing mild COVID-19 patients, with special concern on assessment of the possible efficacy in curing the olfactory manifestations based on clinical, biochemical and molecular data of the included patients, as previous clinical trials regarding local "nasal" use of ivermectin in humans are limited.

Patients and Methods

Study Design and Participants

This is a prospective clinical trial which included 114 patients diagnosed as mild COVID-19 who presented to the outpatients clinic, Qena University Hospital, Upper Egypt, during the period from February to March, 2021. Ethical approval from the Ethics Committee, Faculty of Medicine South Valley University was taken before starting the study (code: SVU 2021/1/120). Written informed consents were obtained from the included patients regarding the approval to use the drug and performing the required investigations and the study was conducted in accordance with the Declaration of Helsinki. The patients with mild COVID-19 were divided randomly into two groups; group A included 57 patients with mild COVID-19 who received ivermectin nanosuspension nasal spray twice daily plus the Egyptian protocol of treatment for COVID-19 and group B included 57 patients with mild COVID-19 who received the Egyptian protocol for COVID-19 only.

The diagnosis of COVID-19 was based on history of exposure, the presence of respiratory manifestation and/or fever, radiological signs suggestive of COVID-19: ground glass opacity "GGO", changes in total leucocytic count and lymphocytic count (normal or reduced).[19] All cases were confirmed by real-time PCR test positive for SARS-CoV-2 using upper respiratory tract swabs.

Regarding illness severity, severe or critical COVID-19 was diagnosed by the presence of one or more of the following; (1) respiratory rate 30 cycles per minute or more, (2) resting room air oxygen saturation of 93% or less, (3) PaO_2/FiO_2 is 300 mmHg or less, (4) respiratory failure requiring mechanical ventilation, shock, organ dysfunction syndrome and ICU admission. COVID-19 patients who did not meet these specifications yet had a positive COVID-19 nucleic acid test were considered to have a mild disease level.[20,21] A mild case of COVID-19 is defined as symptomatic case with lymphopenia or leucopenia with no radiological signs for pneumonia, according to the Egyptian management Protocol for COVID-19.[22]

All patients with severe COVID-19 or patients indicated to receive systemic ivermectin according to the Egyptian management protocol for COVID-19 patients,[22] were excluded from this study. Also chronic ENT disorders such as chronic sinusitis, nasal allergy, patients using nasal spray preparation, systemic or local use of steroids due to any cause, or allergic to ivermectin were excluded.

The Egyptian protocol for treatment of mild COVID-19 includes:

1. Paracetamol 500 mg intravenously every 6 hours.
2. Hydroxychloroquine 500 mg/12 h with close monitoring of liver and kidney functions.
3. Azithromycin 1 g first day, then 500 mg per day for 3 days or clarithromycin 500 mg every 12 hfor 7–14 days.
4. Oseltamivir 150 mg/12 h for 5 days.
5. Ascorbic acid 500 mg/12 h.
6. Cyanocobalamin IV once daily.

Data Collection

Demographic data were recorded for all patients including age, sex, BMI, comorbidities, and smoking, clinical manifestations including fever, cough, dyspnea, anosmia and gastrointestinal tract (GIT) symptoms such as diarrhea, vomiting and/or abdominal pain. Full laboratory investigations were done in all patients and chest CT performed.

Follow-up of all included patients until complete recovery from COVID-19 and the recovery durations of all symptoms for all included patients were recorded in days. Follow up of routine laboratory tests was conducted 7 days after starting ivermectin nanosuspension nasal spray. Group A patients were followed also for any side effects of the ivermectin nanosuspension nasal spray.

Hematological, Biochemical and Molecular Measurements

(A) 6 ml of venous blood was withdrawn from every included patient prior to therapy and was divided into 3 parts (2 ml were evacuated into EDTA tubes for CBCs; 2 ml were evacuated into serum gel separator tubes and allowed to be clotted at 37°C for 30 min and then centrifuged 3500 rpm for 10 minand the separated sera were used for C-reactive protein (CRP) and ferritin assays, while the remaining 2 ml were adjusted to be evacuated into citrate tubes and after centrifugation the separated citrated plasma was used for D- dimer assays) as follows:

1. CBC with differential: By using cell Dyne-Ruby (Abbott Diagnostics,Santa Clara, CA,USA), automated cell counter.
2. Determination of D-dimer: By automated blood coagulation analyzer CS-1600, Japan. The assay kit was supplied by Spectrum, Egyptian company of biotechnology, Cairo, Egypt, catalogue No. 585002. The assay is based upon reinforced immunoturbidimetry monoclonal anti D-dimer antibodies in the reagent react with the D-dimer antigen in the sample, forming antigen/antibody complexes that increase the work solution turbidity.
3. CRP (C-reactive protein): Assays were performed using the semi-quantitative latex agglutination test (AVITEX CRP kits; Catalog No. OD023; supplied by Omega Diagnostics, UK).
4. Serum ferritin assays were performed using commercially available ELISA assay kits (supplied by BIOCHECK Inc., Foster City, CA, USA, catalog number: BC-1025), by an ELISA multiskan EX microplate photometer, Thermo Scientific (STAT FAX-2100, USA) according to the manufacturer's protocol.

(B) PCR testing was performed on aliquots of Universal Transport Medium (UTM) used for

nasopharyngeal swabs collection (Huachenyang Technology, China). Aliquots were extracted on the QIA symphony platform (QIAGEN, USA) and tested with real-time reverse-transcription PCR (RT-qPCR) using the QIAamp ® DSP Virus Spin Kit (QIAGEN Hilden, Germany) on a Rotor-Gene Q (QIAGEN Hilden, Germany).[18] PCR was repeated at day 5 and every 48 h thereafter until 2 consecutive negative PCR were obtained.

Ivermectin Nanosuspension

Materials

Poloxamer 407 and Poloxamer 188 were obtained from Sigma Chemicals Co. (St. Louis, MO, USA). Sodium alginate was supplied by General Chemical and Pharmaceutical Co. Ltd, Sudbury, UK. Hydroxypropyl methylcellulose 15,000 (HPMC) was obtained from El-Gomhouria Co., Cairo, Egypt. Carbopol 974P (CP) was obtained from Lubrizol Co., Cleveland, OH, USA.

Preparation of Ivermectin Nanosuspension

Ivermectin nanosuspension was developed using a nanoprecipitation method followed by ultrasonication as reported in the literature.[23] A specified amount of ivermectin was dissolved in a small amount of acetone to form the solvent phase (120 mg/L). Poloxamer 407 and Poloxamer 188 as stabilizers were dissolved in distilled water at concentrations of 2 and 1% w/v, respectively to form antisolvent phase. The drug solution was then added dropwise to the aqueous stabilizer solution using a suitable syringe under continuous stirring on magnetic stirrer at 25° C (3000 rpm for 30 min). The resultant homogenous suspension was immediately subjected to ultrasonication using a probe-type sonicator (Cole-Parmer, Vernon Hills, IL, USA) for 10 min at 5 spauses and amplitude pressure 50% for further control of particle aggregation. After sonication, the nanosuspension was placed on a magnetic stirrer for 2 h to ensure the complete evaporation of solvent.

Preparation of Mucoadhesive Nasal Spray Containing Ivermectin Nanosuspension

For the preparation of the mucoadhesive nasal formulation of ivermectin nanosuspension, mucoadhesive polymer mixture (HPMC K15M (0.3% w/v), Carbopol 974P (0.1% w/v) and sodium alginate (0.2% w/v)) were added to the prepared nanosuspension with continuous stirring until an homogenous viscous dispersion was obtained. To this formulation other ingredients such as sodium benzoate (0.01%w/v) and glycerol (1.0%w/v) as preservatives were added and mixed well. Finally, the prepared formulation was filled into nasal spray containers. Concentration of ivermectin per puff was 70 µg/mL.

Therapeutic Efficacy Points

The judging points regarding the efficacy of Ivermectin nanosuspension nasal spray in improving patients with mild COVID-19 were as follows (Figure 1):

1. Clinical improvements of the presenting manifestations with recording the recovery duration for every manifestation.
2. Two consecutive pharyngeal swabs were negative for COVID-19 nucleic acid via rRT-PCR, and the time between them, up to 72 h.
3. Improvement of the abnormal routine laboratory parameters (CBCs with differential, CRP, ESR, ferritin, d-dimer) 7 days after starting treatment.

Statistical Analysis

Data entry and data analysis were done using SPSS version 26 (Statistical Package for Social Science). Data were presented as a number, percentage, the mean and standard deviation for parametric data, the median and inter-quartile range for non-parametric data. Chi-square test and Fisher exact test were used to compare qualitative variables. Mann–Whitney test was used to compare between two quantitative variables and Kruskal–Wallis test was used to compare between more than two quantitative variables for non-parametric data. Independent *t*-test was used to compare between two quantitative variables for parametric data. P-value was considered statistically significant when <0.05.

Results

Demographic Data of Study Groups

This prospective study included 114 patients with mild COVID-19; 82 males (71.9%) and 32 females (28.1%) with mean age 45.1 ± 18.9. All patients showed no signs suggestive of moderate or severe COVID-19 on CT chest. Co-morbidities were present in 47 patients of all patients (41.2%) in the form of chronic obstructive pulmonary disease [1 case (0.9%)], cerebrovascular stroke [4 cases (3.5%)], diabetes mellitus [14 cases (12.3%)], hypertension [20 cases (17.5%)], bronchial asthma and interstitial pulmonary fibrosis [3 cases for each, (2.7%)]. Both groups were age and sex matched. Group A (ivermectin

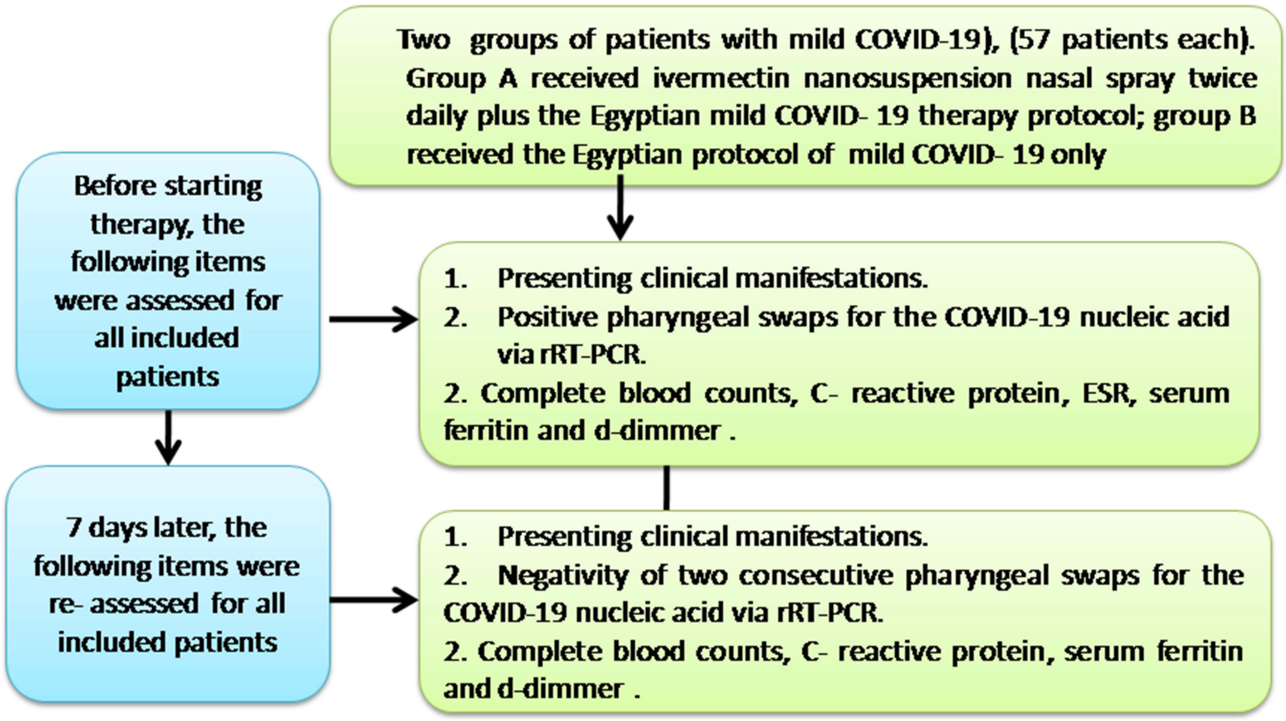

Figure 1 Flow chart of the study design.

nanosuspension nasal spray treated group) included 40 males (70.2%) and 17 females (29.8%) and group B included 42 males (73.7%) and 15 females (26.3%) with no significant difference (P = 0.7). The mean age (years) of group A is 44.8 ± 19.2 versus 45.5 ± 18.8 in group B, with no significant difference (P = 0.8). Neutrophil/lymphocyte ratio before treatment was 3.1 ± 1.3 in group A versus 3.1 ± 1.2 in group B with P = 0.9. Also the median values of CRP, D-dimer, and serum ferritin were not significantly different between the two study groups (P = 0.9, 0.5, and 0.7 respectively). There were no significant differences regarding the history of contact cases which was found in 30 patients of group A (52.6%) versus 28 patients of group B (49.1%) with P = 0 0.7. As regards the frequency of different blood groups, there were no statistically significant differences between both groups, P = 0.9 (Table 1). There was no statistical significant difference between both groups regarding frequency of cough, dyspnea, anosmia, and GIT symptoms, as shown in Table 1.

Response to Ivermectin Mucoadhesive Nanosuspension Nasal Spray

In the ivermectin-treated group (group A) 54 patients (94.7%) achieved 2 consecutive negative PCR nasopharyngeal swabs in comparison to 43 patients (75.4%) in the control group, P = 0.004, as shown in Table 2. Patients who progressed to more severe disease were only 3 (5.3%) cases in the ivermectin-treated group and 14 (24.6%) cases in group B. No side effects were recorded in the ivermectin nanosuspension nasal spray treated group.

The durations (days) of fever, cough, dyspnea, anosmia, and GIT manifestations were assessed in the improved patients in both groups. Ivermectin-treated group (group A) exhibited significantly shorter mean duration of fever, cough, dyspnea, and anosmia compared with group B: 5 ± 1.7 days versus 13.6 ± 2.7 days; 5 ± 1.9 days versus 14 ± 2.6; 4.4 ± 2.7 days versus 10.1 ± 3.4; 0.5 ±0.9 versus 1.6 ± 3.2, respectively with P = 0.0001 for all (Table 3). As regards gastrointestinal symptoms duration there was no significant difference between both groups, P = 0.884, as shown in Table 3. In this study no patients in both groups showed persistent anosmia or gastrointestinal manifestation, even those who failed to achieve negative PCR.

Mean duration taken for nasopharyngeal swab to be negative was significantly shorter in group A than in group B (8.3± 2.8 days versus 12.9 ± 4.3 days; P = 0.004) (Table 3).

All laboratory parameters [neutrophil/lymphocyte ratio, CRP (mg/dl), D-dimer (ng/mL), and ferritin (ng/

Table 1 Comparison Between Demographic Data of Both Study Groups

Variables		Ivermectin-Treated Group (n=57)	Control Group (n=57)	P-value
Age (years, mean±SD)		44.8 ± 19.2	45.5 ± 18.8	0.8
Sex (No., %)	Male Female	40(70.2%) 17(29.8%)	42(73.7%) 15(26.3%)	0.7
Body Mass Index (kg/m^2, mean±SD)		26.9 ± 3.5	28.1 ± 4.9	0.1
Smoking (No., %) •Yes •No		 19(33.3%) 38(66.7%)	 25(43.9%) 32(56.1%)	 0.2
Neutrophil/lymphocyte ratio before treatment (mean ± SD)		3.1 ± 1.3	3.1 ± 1.2	0.9
CRP (mg/dl, median and inter-quartile range)		14 (0.25–80)	15 (0.25–82)	0.9
D dimer (ng/mL, median and inter-quartile range)		320 (100–850)	300 (100–1000)	0.5
Ferritin (ng/mL, median and inter-quartile range)		689 (75–2009)	630 (75–2009)	0.7
Contact cases (No., %)	Yes No	30(52.6%) 27(47.4%)	28(49.1%) 29(50.9%)	0.7
Blood groups (No., %)	A AB B O	17(29.8%) 14(24.6%) 9(15.8%) 17(29.8%)	18(31.6%) 14(24.6%) 9(15.8%) 16(28.1%)	0.9
Cough (No., %)	Yes No	56(98.2%) 1(1.8%)	57(100%) 0(0%)	0.3
Dyspnea (No., %)	Yes No	50(87.7%) 7(12.5%)	54(94.7%) 3(5.3%)	0.2
Anosmia (No., %)	Yes No	13(22.8%) 44(77.2%)	14(24.6%) 43(75.4%)	0.8
GIT symptoms (No., %)	Yes No	23(40.4%) 34(59.6%)	22(38.6%) 35(61.4%)	0.8

mL)] of both groups showed reduction towards normality references 7 days after diagnosis with more significant reduction in group A compared with group B. The median values and inter-quartile ranges in group A versus group B were [1.5 (0.5–3.5) versus 1.9 (0.6–4.2); 6 (3–96) versus 15 (2–120); 250 (100–900) versus 310 (10–900); 199 (76–2020) versus 253 (75–2100) respectively] (Table 4).

Discussion

There is no definite drug therapy for COVID-19 up till now. Several drugs are under clinical trials for treatment of this serious disease, Ivermectin is one of these drugs.[10,24] Ivermectin previously has been used in treatment of lymphatic filariasis, and *Onchocerca volvulus*.[2] It is proved to have antiviral activity against a number of viruses in *in vitro* investigations'[3,25–27] and is also found to limit viral infections such as influenza, West Nile viruses, and dengue fever. An *in vitro* study reported that ivermectin inhibits SARS-CoV-2, with a single addition to Vero/hSLAM cells 2-h post infection and reduces viral RNA ~5000- at 48 h.[2,3,10,11,26,27] Recent studies that examined the efficacy of ivermectin have shown antiviral activity for many viral infections.[28]

Table 2 COVID-19 PCR Negative Conversion Achievement in Ivermectin and Control Group

PCR Negative Conversion	Ivermectin Treated Group (n=57)	Control Group (n=57)	P-value
Yes No	54(94.7%) 3(5.3%)	43(75.4%) 14(24.6%)	0.004*

Note: *Significant at $P < 0.05$.

Caly et al. found that a single dose of 5 μM ivermectin can inhibit SARS-CoV-2 *in vitro* with 99.98% reduction of viral RNA in 48 h.[10] The FDA-approved dose of ivermectin for other diseases is 150–200 mcg/kg. But Caly et al. used a single large dose 30 times greater than the FDA-approved one.[6] This study showed that mean age of mild COVID-19 patients is 45.1 ± 18.9 years, which is in agreement with Ghweil et al., who reported that severe COVID-19 was more frequent in older age groups, while mild to moderate infection was more frequent in younger age groups;[29] this is also reported by other investigators.[30–34]

In this study the most common comorbidities were diabetes mellitus and hypertension which is similar to results reported by Ghweil et al.[29] Astudy done by Marhl et al. reported that a higher risk for COVID-19 among diabetic patients may be due to associated dysregulation of angiotensin-converting enzyme 2 (ACE2), liver dysfunction, and chronic inflammation;[35] Singh et al. reported the same results.[36] In a randomized trial done by Shouman et al., ivermectin was used as a chemoprophylactic agent for contacts of COVID-19 patients and they found that ivermectin is a safe and effective chemoprophylactic agent in prevention of COVID-19.[37]

Table 3 Comparison Between Both Groups as Regards Duration of Fever, Cough, Dyspnea, Anosmia, GIT Symptoms and Duration to PCR Negative Conversion

Duration (Days)	Ivermectin-Treated Group (n = 57)	Control Group (n = 57)	P-value
Fever (mean ± SD)	5 ± 1.7	13.6 ± 2.7	0.0001*
Cough (mean ± SD)	5 ± 1.9	14 ± 2.6	0.0001*
Dyspnea (mean ± SD)	4.4 ± 2.7	10.1 ± 3.4	0.0001*
Anosmia (mean ± SD)	2 ±0.8	6.4 ± 3.3	0.0001*
GIT symptoms (median and inter-quartile range)	5 (1–9)	4 (1–9)	0.884
PCR negative conversion (mean ± SD)	8.3± 2.8	12.9 ± 4.3	0.0001*

Note: *Significant at $P < 0.05$.

A randomized, double-blind trial was done in Dhaka, Bangladesh in which oral ivermectin alone (12 mg once daily for 5 days) or in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline day-1 followed by 100 mg 12-hourly for next 4 days) was compared with placebo among patients with COVID-19 infection. Negative PCR was earlier in the 5-day ivermectin treatment group versus the placebo.[38] A recent study done in Florida, USA, reported that COVID-19 patients given ivermectin with other treatments (e.g., azithromycin and hydroxychloroquine) showed lower mortality rate than COVID-19 patients who did not receive ivermectin.[39]

Various studies have reported the nasal delivery of nanosuspensions. Saindane et al. incorporated a carvedilol-containing nanosuspension into *in situ* gel,[40] and Alshweiat et al. prepared a loratadine-based nasal nanosuspension to improve bioavailability.[12] SARS-CoV-2 invades the oropharynx and nasopharynx, from which it transmits even before any signs appear. The first symptoms (odynophagia, anosmia, dry cough, fever) and lung parenchyma colonization occur when the virus replicates in this region. The use of a nasal ivermectin spray to deposit the drug in the upper respiratory tract may be a useful method for exposing the SARS-CoV-2 virus (or the cells that contain the viral particles) to high ivermectin concentrations. As a result, early in the infection, the viral load is reduced, preventing extensive viral replication, transmission, and disease aggravation.[41]

No previous study has used ivermectin in a nanosuspension nasal spray. In this study we tried to decrease the viral load in the nose and nasopharynx in early COVID 19 patients by the direct action of an ivermectin nanosuspension nasal spray. Administration of nanosuspension by nasal spray provides uniform distribution of the drug through the nasal mucosa. Mucoadhesive polymers such as hydroxypropyl methylcellulose 15,000 (HPMC K15M), carbopol 974P and sodium alginate were used in a mixture to increase the residence time of formulation at site of action.[12,13]

In this study, COVID-19 patients treated with an ivermectin mucoadhesive nanosuspension nasal spray showed shorter duration of fever, dyspnea, cough, and anosmia but not GIT symptoms duration. Additionally, the findings of the current study revealed that patients with COVID-19 treated with ivermectin showed more

Table 4 Comparison Between Both Groups as Regard Laboratory Parameters Changes 7 Days After Diagnosis

Variables	Ivermectin Treated Group (n = 57)	Control Group (n = 57)	P-value
Neutrophil/lymphocyte ratio (median and inter-quartile range)	1.5 (0.5–3.5)	1.9 (0.6–4.2)	0.008*
CRP (mg/dl, median and inter-quartile range)	6 (3–96)	15 (2–120)	0.0001*
D dimer (ng/mL, median and inter-quartile range)	250 (100–900)	310 (10–900)	0.03*
Ferritin (ng/mL, median and inter-quartile range)	199 (76–2020)	253 (75–2100)	0.004*

Note: *Significant at P <0.05.

significant reduction in measured hematological and biochemical parameters towards normal values with rapid viral clearance as evidenced by conversion of nasopharyngeal swab to negative. Further studies should be done to assess the ivermectin nanosuspension nasal spray in prophylaxis of close contacts to COVID-19 patients.

Conclusion

Local use of ivermectin mucoadhesive nanosuspension nasal spray is safe and effective in treatment of mild COVID-19 patients, with rapid viral clearance and recovery of respiratory manifestations (anosmia, cough, and dyspnea). The result of efficacy of ivermectin in reducing patients' symptoms can promote the current protocols of COVID-19 treatment. Further studies should be done to assess the possible role of ivermectin mucoadhesive nanosuspension nasal spray as a prophylaxis against COVID-19 infection.

Study Limitations

The current study's main limitation was the lack of a multi-dose design of ivermectin to assess the potential dose-effect relationship, which could be designed in future studies.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

No potential conflicts of interest between authors to be declare.

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