**Original Research Article**

# Utility of Ivermectin and Doxycycline combination for the treatment of SARS-CoV-2

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## Abstract

**Background:** On March 11, 2020, the World Health Organization (WHO) officially declared coronavirus disease 2019 a global pandemic. Ivermectin and Doxycycline against SARSCoV-2 under in-vitro conditions showed beneficial results. However, large population studies with this combination are not elaborately studied, which was the aim of our study.
**Materials and Methods:** A total of 122 patients admitted in a tertiary care centre, who tested positive for Reverse-transcriptase-polymerase-chain-reaction (RT-PCR) for SARS-CoV2 were included in the study and a total sample size of 100 patients was obtained after exclusion. 50 patients of the treatment group were treated with Ivermectin-Doxycycline combination.
**Results:** The results had shown a significant reduction not only in mean duration of hospital (3.70 ± 2.27 days vs 4.69 ± 2.3 days), but also in complete resolution of symptoms stay (6.67 ± 2.01 days vs 4.69 ± 2.3 days). In a small subset of 10 patients RT-PCR for COVID was tested on 10th day after the symptom onset in both the groups and there was no difference to be found. There was no significant difference in the side effect profile of either groups.
**Conclusion:** Our study supports the benefits of utilization of combination of Doxycycline and Ivermectin in mild to moderate COVID-19 infection in terms of early recovery based on the time for symptom resolution and the mean duration of hospital stay.

## Key words

COVID19, SARS-CoV2, Ivermectin-Doxycycline, RT-PCR.

## Introduction

After the origin of novel coronavirus (2019-nCoV) in December 2019 at Wuhan, On March 11, 2020, the World Health Organization (WHO) officially declared coronavirus disease 2019 a global pandemic, the prevalence of this virus had shown an exponential growth throughout the world [1].

Though Hydroxychloroquine was initially tried and multiple small trials showed marginal benefit, a recent meta-analysis showed that Hydroxychloroquine does not appear to offer significant benefits in terms of reducing the viral load, resolution of radiological findings, or progression of the COVID-19 and Hydroxychloroquine might be associated with increased all-cause mortality [2].

Recent study on Ivermectin against SARSCoV-2 under in-vitro conditions revealed that it can inhibit viral replication. The single treatment of this drug was able to reduce the SARS-CoV-2 virus up to 5000-fold in Vero-hSLAM cells bathed with Ivermectin within 48 hours. However, no further reduction was reported with further increase in time period i.e. up to 72 hours. Moreover, no toxicity was seen with the drug at any point of time [3]. Doxycycline acts on Zinc as part of their MMP complex, chelates it and also acts via reduction in pro-inflammatory IL-6 levels, hence may reduce the viral load [4].

Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate COVID19 disease [5].

## Materials and methods

A total of 100 patients admitted in a tertiary care centre, which tested positive for RT-PCR for SARS-CoV2 were included in the study.

Patients were seen at baseline for enrollment, initial data collection and treatment at day-0, and again for daily follow-up. Each day, patients received a standardized clinical examination and all clinical data were collected using standardized questionnaire.

Study variables collected on each patient included the following; patient demographics: age, gender; clinical characteristics: admission date, discharge date, length of stay (LOS), day of symptom resolution; comorbidities including: chronic lung disease, hypertension, asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus, immunodeficiency, and cancer (defined as active or past/ resolved). Additionally, intensive care unit (ICU) status and ventilator use at any point during admission, minimum O2 saturation level collected on day of admission in the emergency department. The duration and dosages of all therapies for COVID-19 were collected.

This prospective study was aimed to establish the efficacy of combination of Ivermectin and Doxycycline in the treatment of mild to moderate Covid-19 in India.

To study the outcome of the above mentioned drugs in at least 50 patients of covid-19 in comparison with the patients of covid-19 administered with placebos (Vitamin B6).

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**Inclusion criteria**

- All patients diagnosed with Covid-19 by RT-PCR, with mild to moderate symptoms.
- Respiratory Rate < 24/min and SpO2 > 93% on room air.
- Absence of Oxygen support on admission.
- Duration of symptoms prior to admission ≤ 7 days.

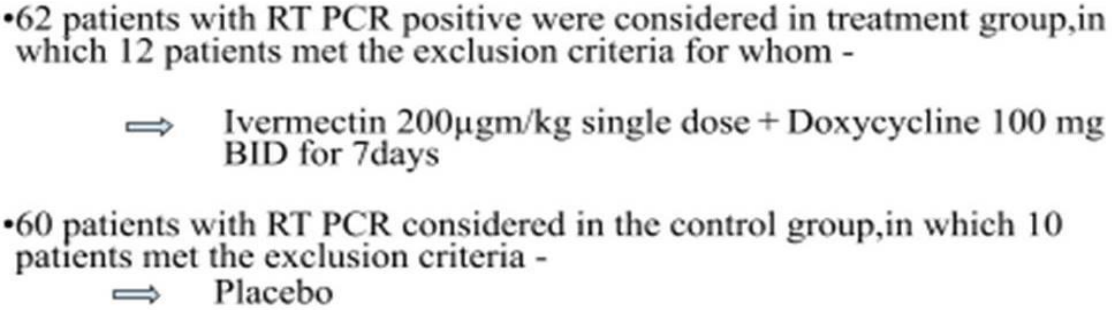
**Exclusion criteria**

- Patients with a history of allergy to Ivermectin or Doxycycline
- Pregnant or lactating women.

- Patients with a history of chronic liver disease (SGPT > 3 times of normal value).
- Patients with a history of chronic kidney disease (eGFR <60 ml/min/1.73 $m^2$).
- Patients with a history of chronic heart disease.

This study was done on 122 patients taken as a study population (**Figure – 1**) and Ethical committee clearance was obtained.

**Figure – 1:** Group distribution.




**Statistical analysis**

The quantitative data were described as the mean ± standard deviation, or as the median (min − max). The qualitative data were described by number of cases (proportion, %). Patient characteristics were compared using the $\chi^2$ test or Fisher's exact test for categorical data, and the Wilcoxon rank-sum test or Student's *t* test for continuous data. Potential influencing factors of viral clearance were analyzed by univariate and multivariate Cox regression models. A p value lower than 0.05 was required for statistical significance. All of the analysis was performed using SPSS Version 22.0.

## Results

Out of 62 patients in the treatment group, 6 patients had a history of chronic kidney disease, out of which 3 were on Hemodialysis and all the patients had e GFR < 30 ml/kg/min/$m^2$, 2 antenatal patients along with 1 lactating patient, 2 had congestive heart failure and 1 had decompensated chronic liver disease with severe transaminitis.

Out of 100 patients, male population was slightly higher than the female population in both the groups, diabetics were slightly more in the placebo than in the treatment group. Very small number of patients had pulmonary issues, which were almost equal in both the groups (**Table – 1**).

The mean duration of hospital stay was 6.67 ± 2.01 days in treatment Group and 7.89 ±2.35 days and the entities were compared using unpaired t-test, which attained statistically significant (P = 0.01) as per **Figure – 2** and **Table - 2**.

**Table – 1:** Baseline characteristics of patients.

| Patient baseline characteristics | Treatment group | Placebo group |
|---|---|---|
| Age (Median ± SD) | 50.95 +_13.64 | 48.72+_13.42 |
| Males | 26 (52%) | 28(56%) |
| Females | 24(48%) | 22(44%) |
| Diabetics | 6 | 7 |
| Hypertensive | 5 | 4 |
| Old pulmonary tb | 1 | 1 |
| Chronic obstructive lung disease | 2 | 2 |

**Figure – 2:** Hospital stay and symptoms duration.

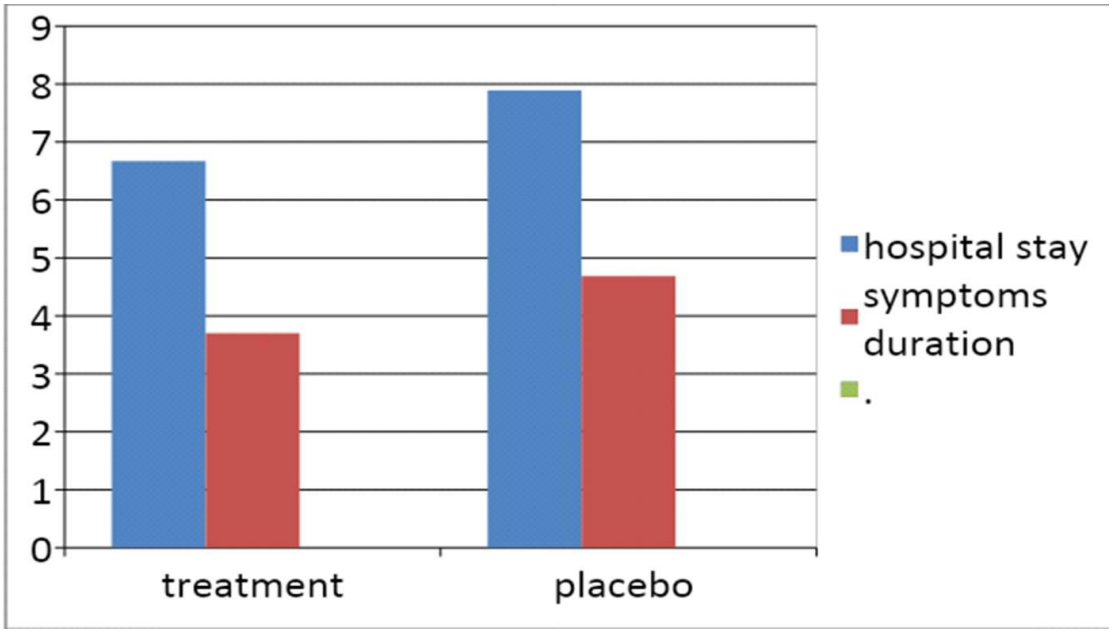



**Table – 2:** Hospital stay and symptoms duration.

| | **Mean +_SD** | **Mean +_SD** | **P value** |
|---|---|---|---|
| Mean duration of hospital stay (days) | 6.67 ± 2.01 | 7.89 ±2.35 | 0.01 |
| Time for symptom resolution (days) | 3.70 ±2.27 | 4.69 ±2.3 | 0.03 |

**Table – 3:** Side effects.

| **Side effects** | **Treatment group** | **Placebo group** |
|---|---|---|
| Diarrhea | 4 | 2 |
| Vomiting | 3 | 2 |
| Pruritus | 1 | 0 |

The duration for complete resolution of symptoms was 3.7 ± 2.27 days in the treatment Group and 4.69±2.3 days and a similar comparison between the either groups obtained statistically significant (P = 0.03). Comparison of side effects in both groups was as per **Table – 3**.

## Discussion

Our findings are consistent with the benefits of utilization of combination of Doxycycline and Ivermectin in mild to moderate COVID-19 infection. The results have shown a significant reduction not only in mean duration of hospital (3.70 ± 2.27 days vs 4.69 ±2.3 days), but also in complete resolution of symptoms stay (6.67 ± 2.01 days vs 4.69 ± 2.3 days). These results were consistent with another study done at Bangladesh, where mean resolution of symptoms were around 5.93 days [6].

Compared to the prior studies, the cohort of our patients was elderly, with slight male predominance. The previous studies done similarly had a slightly younger age group of population.

In a small subset of 10 patients RT-PCR for COVID was tested on 10$^{th}$ day after the symptom onset in both the groups, there was no difference, with RT PCR being positive in 2 members of either groups on day 7 or positive in a single individual of each group on day 10. A recent multi-centric study compared to 1,918 conventionally treated patients, a survival benefit for Ivermectin mortality rate was observed. In the same study, the mean duration of symptom

resolution was reduced by 7.1 ± 2.1 days compared to those without Ivermectin. However, this study also included patients with respiratory failure [7].

Tetracyclines may be effective agents in the treatment of Covid-19 due to their ability to chelate Zinc compounds on matrix metalloproteinases (MMP) on which coronaviruses rely heavily for survival, cell infiltration, cell to cell adhesion and replication, many of which has Zinc as part of their MMP complex [3]. Ivermectin destabilizes the Impα/β1 heterodimer, via which the host cell antiviral response is reduced [8, 9].

In our study, the side effects of these drugs were reviewed and the common side effects included GI disturbances seen in 4 patients, however with the administration of proton pump inhibitors and regularizing the timing of the antibiotic after food intake, these side effects reduced after 2 days .1 patient had pruritus relieved with antihistamines .One patient in the treatment group expired after deteriorating on 5$^{th}$ day after he developed coagulopathy.

Our study had a few limitations, first the size of our sample was smaller, consisting of 100 patients only. Second all the patients could not be tested for RT PCR on the 10$^{th}$ day of symptoms, as most of them were discharged after symptomatic relief i.e., after around 7 days of admission.

Third, we could not consider patients with atypical covid symptoms such as diarrhea, acute gastritis [10] as we could not categorize them based on severity.

## Conclusion

Our study supports the benefits of utilization of combination of Doxycycline and Ivermectin in mild to moderate COVID-19 infection in terms of early recovery based on the time for symptom resolution and the mean duration of hospital stay.

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