

Therapeutic Efficacy of Ivermectin in Novel Coronavirus Disease-2019 Patient Admitted at the Ward of a Tertiary Care Hospital: A Retrospective Study

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Received on: 25 April 2022; Accepted on: 28 September 2022; Published on: 14 March 2023

ABSTRACT

Objective: An observational, retrospective, institution-based study to observe the pattern of ivermectin use related to patients' characteristics.

Methods: Patient data including short-term diagnosis, investigations done, and drug usage data were captured in a predesigned, structured case report form; and suspected adverse events were recorded in the standard suspected adverse drug reaction reporting form recommended by the "Central Drug Standard Control Organization," India. The study was for a period of 7 months from August 01, 2020, to February 28, 2021. A total of 4,552 patients were recruited in this study and followed up till their discharge or death. The comparison was made between not given and given of ivermectin among patients.

Results: Data were summarized by routine descriptive and statistical analysis. The mean age (years), length of stay (days) onset from hospitalization, pulse rate, systolic blood pressure (SBP), and temperature did not show significant change. However, respiratory rate was found to decrease significantly ($p < 0.001$), and oxygen saturation (SpO_2) was found to increase significantly ($p < 0.001$) in the ivermectin-treated group. It was also observed that a positive correlation with a highly significant value ($p < 0.000$) between age (years), length of stay (days) onset from, pulse rate, SBP, and temperature and ivermectin usage while a negative correlation with highly significant value ($p < 0.000$) between SpO_2 and ivermectin usage was obtained.

Conclusion: As per the studied parameters, a significant correlation was observed in combinations of the treated and untreated groups. Further research suggested the dose-dependent efficacy of ivermectin usage in the novel coronavirus disease-2019 patients.

Keywords: Infectious disease, Ivermectin therapy, novel coronavirus disease-2019, severe acute respiratory syndrome coronavirus-2

Indian Journal of Respiratory Care (2023); 10.5005/jp-journals-11010-1009

INTRODUCTION

"Novel coronavirus disease-2019" (n-COVID-19) or "severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2) caused by the virus and has become a pandemic situation worldwide and treatment is the highest priority described by "Johns Hopkins University of Medicine" in 2020.¹

The medicine ivermectin is a drug to treat parasitic infections, earlier approved by the US Food and Drug Administration (FDA) while it has been used to treat since 1980, and as per "International Centre for Diarrhoeal Disease Research" is previously recorded as "broad-spectrum antiviral activity *in vitro*."² Some alterations have been found for the nature and pattern of ivermectin usage with time as it was approved by the FDA as an anti-parasitic anthelmintic, which is an inhibitor of the causative virus of n-COVID-19 (SARS-CoV-2) and capable to decrease ~5000-fold viral RNA of Vero-hSLAM cells at 48 h.² In this context, ivermectin may warrant further study for a better outcome in humans.³

In a historical perspective, in 1975, a Japanese microbiologist, namely Professor Satoshi Omura and the Kitasato Institute in Japan, investigated an uncommon *Streptomyces* bacterium in the soil near a golf ground located at the southeast coast of Honshu in Japan.^{4,5} Furthermore, Prof. Omura and Campbell investigated a bacterial culture, in which it was observed to prevent host immune response when mice infected with the roundworm *Heligmosomoides polygyrus*. This drug was formerly launched for

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How to cite this article: Mishra K, Manna A, Roy RM, *et al*. Therapeutic Efficacy of Ivermectin in Novel Coronavirus Disease-2019 Patient Admitted at the Ward of a Tertiary Care Hospital: A Retrospective Study. *Indian J Respir Care* 2023;12(1):3–7.

Source of support: Nil

Conflict of interest: None

veterinary usage, which ultimately created a historic impact on human health, showing improvement on the nutritive factor, health status, and well-being of billions of human beings worldwide while subsequently, it was primarily used to treat onchocerciasis (river blindness) in humans during 1988.^{4,5} It has been proved suitable in many ways such as highly effective, broad-spectrum, safe, well-tolerated, and might be easily dispensed.⁴ Although it was used for the treatment of a variety of internal nematode infections and is well known as the essential mainstay of "two global diseases elimination campaigns."⁴ Furthermore, the impacts of ivermectin are to control the onchocerciasis and lymphatic filariasis diseases and it also kills the external parasites also.⁵

Table 1: Distribution of patient's characteristics between groups (mean±standard deviation)

Ivermectin	Age (years)	Length of stay (days)	Onset from (days)	Pulse rate (bpm)	Respiratory rate (per min)	SpO ₂ (%)	SBP (mm Hg)	Temperature (°F)
NG (n=1090)	56.50 ± 16.91	8.88 ± 6.62	11.05 ± 7.21	88.04 ± 16.10	20.07 ± 4.01	94.88 ± 7.60	126.42 ± 19.86	98.37 ± 0.62
Given (n=3462)	55.71 ± 16.10	8.65 ± 6.19	11.05 ± 7.59	87.24 ± 14.01	19.18 ± 3.22*	96.57 ± 4.33*	125.99 ± 17.40	98.39 ± 0.49

*P<0.001. NG, Not given; SBP, systolic blood pressure; SpO₂, oxygen saturation

Table 2: Correlations between ivermectin usage and patients' characteristics

	Spearman's rho	Score	p
Ivermectin usage			
Age (years)	CC	0.551	0.000
Length of stay (days)	CC	0.082	0.000
Onset from	CC	0.124	0.000
Pulse rate	CC	0.223	0.000
Respiratory rate	CC	0.472	0.000
SpO ₂	CC	-0.349	0.000
SBP	CC	0.060	0.000
Temperature	CC	0.100	0.000

CC, correlation coefficient; SBP, systolic blood pressure; SpO₂, oxygen saturation

There are several preclinical studies carried out by many investigators. Since 2012, many studies at the cellular level have revealed that ivermectin has antiviral properties against an increasing number of RNA viruses, namely, influenza, Zika, HIV, dengue, and ultimately, SARS-CoV-2.⁶⁻¹⁴ A study emphasized that the mechanisms of action of ivermectin are based on the entry and replication of SARS-CoV-2 within human cells.⁵ In 2020, Caly et al.³ reported in the first time regarding the usage of ivermectin and found significantly inhibited multiplication of SARS-CoV-2 in a cell culture model, which observed the decaying of viral material 48 h after exposure to ivermectin.² However, some questions arose whether this antiviral activity is generalizable clinically given incapable to accomplish the same tissue concentrations that were used in their test model using standard or even enormous doses of ivermectin.^{15,16}

An observational, retrospective, and institution-based study was conducted on the survey among indoor patients admitted in the ward of IDBG and Hospital, Kolkata, to observe the pattern of ivermectin use and any adverse drug reaction related to their use. Other drugs used in n-COVID-19 are also assessed simultaneously.

METHODS

Study Design

The present study was an observational, retrospective, and institution-based study.

Study Setting and Timelines

The study was carried out in the indoor patients admitted to the COVID ward at IDBG and Hospital, Kolkata. Microbiology laboratory help is taken as needed. Data compilation and analysis was done at the Department of Medicine.

All the data of patients were taken between August 01, 2020, and February 28, 2021, and evaluated everyday round data along with disease severity, medication received, followed by therapeutic

outcome of all patients (n = 4552) were recorded. The sample size calculation was not performed because all the data were collected from hospital records. In this study, it was aimed to gather the patient profile and therapeutic outcome of patients who admitted with n-COVID-19 infection. The comparison was made between not given and given of ivermectin among patients.

Place of Study

The study was conducted at IDBG and Hospital, departments included—the Department of Medicine as well as the Department of Microbiology.

Period of Study

The study is intended to be completed within a period of 7 months included follow-up.

Study Population

The data bank of patients and patients were screened and recruited if they satisfy the proposed criteria.

Sample Size

During the study period of 7 months, we proposed to analyze the cases (4,552 patients) that were admitted during the study period as per inclusion/exclusion criteria. As such no control groups are necessary for this study. Each patient's data were evaluated during the study period to know the therapeutic outcome.

Inclusion Criteria

- Patients of either sex aged >18 years
- Patient or legally acceptable representative give consent for study
- Positive reverse transcriptase–polymerase chain reaction.

Exclusion Criteria

- Patients who were seriously ill
- Hypersensitive to ivermectin
- Patients not willing to take part of any ongoing clinical trial
- Pregnant and lactating mothers and critical cases such as the occurrence of respiratory failure requiring mechanical ventilation; the presence of shock; and other organ failures that required monitoring and therapy in the ICU.

Study Parameters

All patients presenting for n-COVID-19-related symptoms had a physical examination and respective clinical profiles data, namely pulse rate (beats per minute), respiratory rate (per min), oxygen saturation (SpO₂ as %), systolic blood pressure (SBP as mm Hg), and temperature (°F) along with age (years), onset from hospitalization (days), and length of stay (days), were recorded.

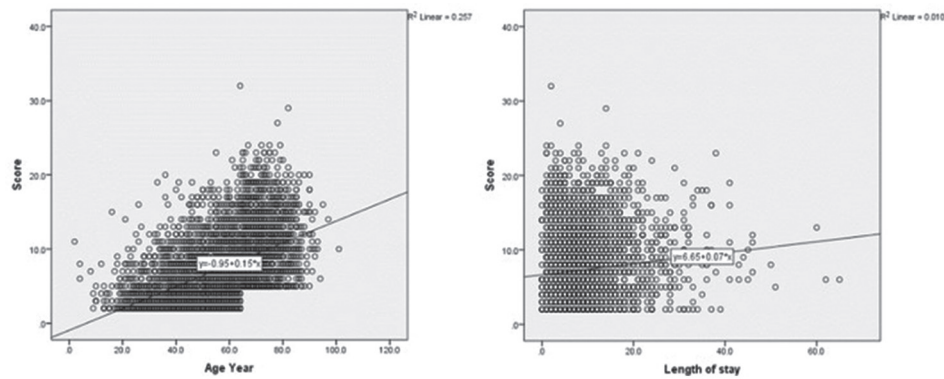


Fig. 1: Scattered dot plot representing for each variable (Age and length of stay).

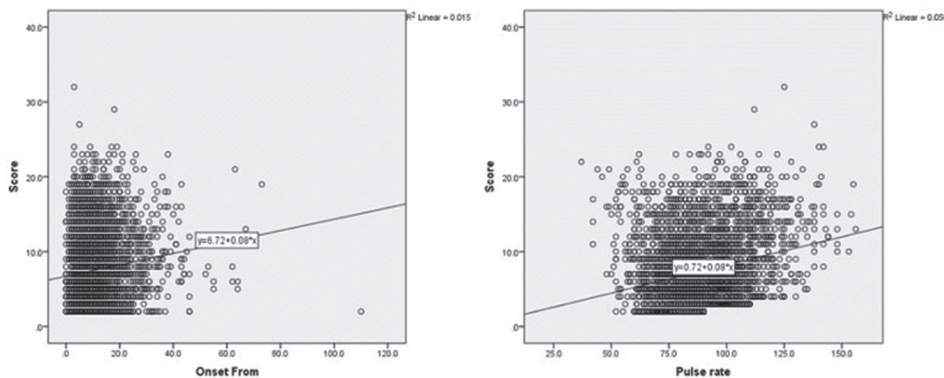


Fig. 2: Scattered dot plot representing for each variable (Onset from and pulse rate)

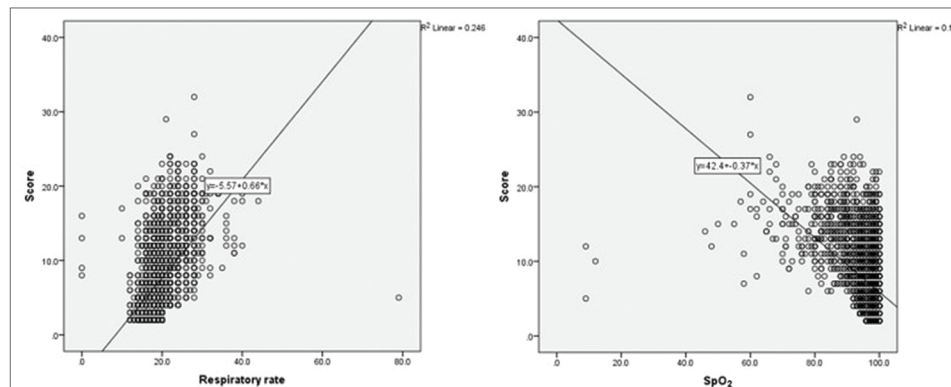


Fig. 3: Scattered dot plot representing for each variable (Respiratory rate and SpO₂). SpO₂, oxygen saturation

Ethical Approval

The study was conducted with prior approval from the Institutional Ethical Committee of IDBG and H, Kolkata, with Memo No.IDBGH/Ethics/4145 dated July 26, 2021. Data were also taken from the record section as part of retrospective study.

Statistical Analysis

Statistical analysis was performed using the SPSS tool for Windows (version 20.0). Continuous variables were taken as mean \pm standard deviation (SD) and the data were compared between ivermectin-treated (given) and without treated (not given) groups using the Student's t-test. Spearman's rank correlation coefficient was used to study the strength of association between the two ranked variables between patients' characteristics and

ivermectin-treated and without treated patients. The level of significance was considered $P < 0.05$.

RESULTS

Table 1 describes a comparative analysis (mean \pm SD) of patients' characteristics between the group of ivermectin not given and given groups. The mean age (years), length of stay (days) onset from, pulse rate, SBP, and temperature did not show significant change. However, the respiratory rate was significantly ($p < 0.001$) decreased and SpO₂ was significantly ($p < 0.001$) increased in the ivermectin-treated group when compared to the untreated group.

Table 2 evaluates Spearman rank correlation analysis between the group of ivermectin not given as well as given groups and different patients' characteristics to know better efficacy of the

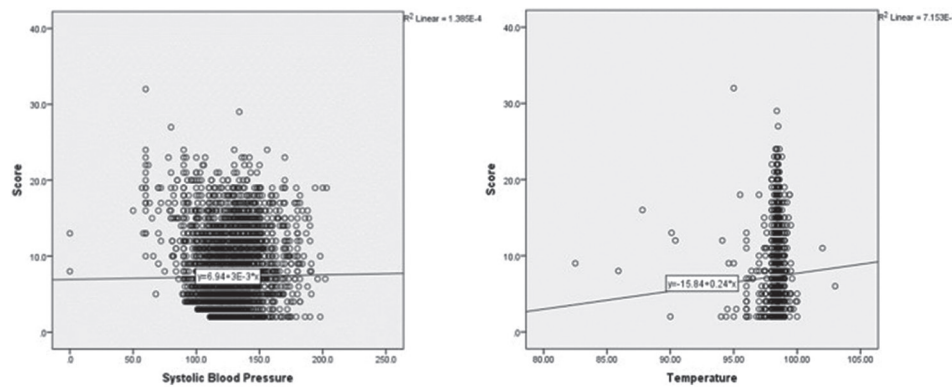


Fig. 4: Scattered dot plot representing for each variable (Systolic blood pressure and temperature)

drug. It was demonstrated that a positive correlation with a highly significant value ($p < 0.000$) between age (years), length of stay (days) onset from, pulse rate, SBP, and temperature and ivermectin usage while a negative correlation with highly significant value ($p < 0.000$) between SpO_2 and ivermectin usage was obtained.

Figs 1 to 4 exhibit a scatter dot plot for each variable of the patient and the ivermectin usage, which observed a moderate positive correlation for all parameters except SpO_2 as a moderate negative correlation.

DISCUSSION

This present retrospective observational study attempted to detect the antiviral activity of ivermectin against n-COVID-19 or SARS-CoV-2 in adult patients who were received treatment in our tertiary care hospital, Kolkata, the eastern part of India.

However, an earlier study indicated a dose-dependent antiviral activity of ivermectin in SARS-CoV-2-infected adult patients treated within 5 days of symptoms commencement. The investigator also observed a significant difference with an association between plasma concentrations of ivermectin and the primary outcome.¹⁷

In the present study, a significant change of respiratory rate, which was decreased, and SpO_2 value was increased in the ivermectin given group when compared to not given group, which is supported by other researchers regarding the efficacy of ivermectin therapy among the patient of n-COVID-19.¹⁸ A respiratory rate of 20 ± 4 and 19 ± 3 per min have not much clinical significance. Similarly, the saturation difference does not seem to be clinically significant.

On the other hand, previous reliable results observed by Vallejos et al. regarding the IVERCOR-COVID-19 trial,¹⁹ which observed less hospital stay who received ivermectin while the present study observed reduced length of hospital stay without significant change when compared between given group and not given group. Interestingly, the past study indicated the rate of the requirement of mechanical ventilation was reduced significantly ($p = 0.019$) in the ivermectin group when compared to the placebo group.¹⁹ It was evidenced that the significantly increased SpO_2 level among ivermectin-treated patients.²⁰ The results seem to be not of clinical significance, although statistically significant. However, few studies suggested that the dose-dependent ivermectin treatment found better efficacy.^{21,22}

CONCLUSION

In conclusion, this is a first-time endeavor to know the therapeutic efficacy of ivermectin among adult patients of eastern India. As

per the studied parameters, positive correlation with a significant value for age (years), length of stay (days) onset from, pulse rate, SBP, and temperature while a negative correlation with a significant value for SpO_2 due to ivermectin usage. Further research suggested the dose-dependent efficacy of ivermectin usage in n-COVID-19 patients.

ACKNOWLEDGMENTS

The authors convey thanks to the head of the institution for the necessary permission for this study and staff members of the institution for patient coordination.

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