

Role of Ivermectin in Prophylaxis and Treatment of Covid-19 Patients: A Systematic Review

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Expert Review

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ABSTRACT

For a systematic review, the present study made an extensive review around the formulated question by identifying, selecting and critically appraising data based on a comprehensive and reproducible search strategy. It was found that there exists a significant literature which speaks positively about the role of Ivermectin in prophylaxis. The drug has been found statistically significant in mortality reduction, clinical recovery time and viral clearance. Contrary to what the WHO has claimed, Ivermectin prophylaxis was associated with a very low rate of disease progression.

INTRODUCTION

Despite the fact that Ivermectin inhibits the replication of SARS-CoV-2 *in vitro*, the world seems to be still cautious of its use. There are studies which argue about the doses and posology. In a recent study^[1]. Found no significant differences in detection of the SARS-CoV-2 RNA from nasopharyngeal swabs at days four and seven after treating with a single oral dose of 400 mcg/kg of Ivermectin. Also, the drug has not been studied enough for its chronic use. The people have raised concern about its 'unsafe' use if it leads to excess of confidence among the population, especially when the side-effects with Ivermectin have not been clearly laid out. The medical fraternity frequently talks about the neglect of biosecurity measures with its indiscriminate use, no pharmacovigilance and without medical prescription. It has been recommended that the drug must be administered in the recommended posology. So to speak, Ivermectin seem to be receiving all the criticism despite the major benefits it has to offer to the world. This leaves us with a very important question – Does Ivermectin has its role in prophylaxis and treatment of Covid-19 patients?

Research Methodology

For a systematic review, the present study would make an extensive review around the formulated question by identifying, selecting and critically appraising data based on a comprehensive and reproducible search strategy. A mix of qualitative and quantitative data would be assessed, based on a clear inclusion/exclusion criterion for preparing a balanced and unbiased

summary of the findings. Assessment would be made of the data which is both numerical and textual. The research article would therefore try to find the evidential support in order to establish the prophylactic uses of Ivermectin versus the fears around its mass use. Also, the news sources would be studied for what they say about the protocol and the recommendations made by the medical fraternity in this regard.

Findings

Evidential support for Ivermectin's prophylaxis use: One of the most noted observational studies on Ivermectin prophylaxis has been done by [2]. The study makes statistically significant findings about Ivermectin as Pre-exposure prophylaxis for Covid-19 among healthcare providers in a selected tertiary hospital in Dhaka. For the purpose of the study, 118 healthcare workers were purposively enrolled in a tertiary care hospital in Dhaka for a period between May 2020 and August 2020. Out of the two groups, the experimental group was given an oral monthly dose of Ivermectin 12 mg for a period of 4 months. Post exposure, the symptomatic subjects were evaluated based on HRCT of chest and RT-PCR test. The statistics showed it clearly that only 6.9% workers from the experimental group contracted the virus while 73.3% of the subjects in the control group were tested positive for Covid-19.

Even on the Indian scenario there are major studies which have talked positively about Ivermectin and its possibilities in prophylaxis use in Covid 19 patients. A matched case-control study in Bhubaneswar was conducted at AIIMS during September-October 2020 for evaluating the role of Ivermectin in the prevention of SARS-CoV-2 infection among the healthcare workers [3]. Apparently, the study found out that two-dose Ivermectin prophylaxis at a dose of 300 µg/kg with a gap of 72 hours brought down SARS-CoV-2 infection by 73%. Here, the investigation would go further in studying similar evidences from across the world based on epidemiological analyses, expert meta-analyses, manuscripts and peer-reviewed studies. On a brief study, it was found that a large section of studies which highlight the role of Ivermectin in prophylaxis. The drug has been found statistically significant in mortality reduction, clinical recovery time and viral clearance; comparisons too have been drawn with Vitamin-C and HCQ. A regular use of the drug has been found to also reduce the risk of contracting Covid-19. Most importantly, Ivermectin-distribution has been associated with mortality and morbidity reduction across all phases of Covid-19 for a population wide effect. Here, the matched pair analysis showed that SARS-CoV-2 infection was statistically significant with Ivermectin (OR 0.35, 95% CI, 0.20–0.60). However, the same figures with HCQ prophylaxis (OR 0.58, 95% CI, 0.19–1.61) and vitamin-C prophylaxis (OR 0.71, 95% CI, 0.40–1.26) showed no statistical relevance (Table 1).

Ivermectin has on most occasions been approved for its high activity against Covid-19. In this fight against Covid-19, the drug has slowly found its place in I+Mask+Protocol for prophylaxis and an early treatment of outpatients with Covid-19. What really prompts its inclusion in the protocol is the demonstrated efficacy of Ivermectin in containing the replication prior to and after exposure to Covid-19. It has shown significant results in the early symptomatic stages. In one such randomized controlled trials (RCTs) in Egypt, only 2% of the household and healthcare contacts of active Covid-10 patients, who received Ivermectin and PPE kits, tested positive. In contrast to this, it was 10% for contacts who were only given PPE Kits [4]. In one more of such studies, it was established that the rate of progression was significantly low in patients who received Ivermectin. Even in the sample of severely ill Covid-10 patients, the patients with Ivermectin showed a low mortality rate [5]. In fact, the findings have encouraged the research agencies to make recommendations about Ivermectin in prophylaxis to all major national and global health authorities such as CDC and NIH.

Apart from its prophylaxis profile, Ivermectin has also been found to be a multifaceted medication. While a lot of drugs are probable candidates for this war against Covid-19, this anti-parasitic drug has already its established efficacy and safety profile [6]. The drug is found to have a wide distribution, high lipid solubility and rapid oral absorption in the body [7]. Ivermectin is already an approved drug for medical use for over 40 years and in all these years the drug has been found to possess broad-spectrum broad spectrum endo/ecto-parasiticide effect together with anticancer, antibacterial and antiviral effects. What makes it further effective is its ability to cause immunomodulation in the host [8]. Still, a lot of critics are apprehensive of the antiviral response of the drug.

An investigation into the antiviral response of Ivermectin was therefore central to this assessment. Out of a wide assortment of studies, prominently studied the SARS-CoV2 more elaborately than the others [9]. The study claims that Ivermectin was able to treat Vero-h SLAM cells within 2 hours of SARS-CoV-2 contagion. An important revelation was the fact that Ivermectin could cause a ~5000-fold reduction of viral RNA in a period of just 48 hours. It is further mentioned that MPα/β1 binds to the corona virus protein in the cytoplasm and translocate it into the nucleus where the complex disintegrates, thus, freeing the virus off the complex and enabling it to reduce the host cell's antiviral response, leading to enhanced infection [10]. Here, Ivermectin stops Impα/β1 from binding to the viral protein by binding with Impα/β1 heterodimer and weakening it. The mechanism has been found to reveal the antiviral response of Ivermectin.

In all this development, the prophylaxis potential of Ivermectin becomes all the more critical because of the steady mutations which the virus is taking. The virus has shown tremendous capability to spread and especially because of the asymptomatic patients. Containing this novel virus therefore requires a more pronounced collective effort on a mass scale. Ivermectin can thus be seen as the most eligible of the available lot for treating not just the asymptomatic or mild Covid-19 patients, but to also contain the virus long before it can cause the infection. The drug therefore is more suitable for mass administration for not just its antiviral response, but also for its established safety profile.

To sum it up, studied Ivermectin for a more comprehensive data for its prophylactic administration. In order to establish Ivermectin, data was collected from countries who have routinely deployed various drugs for prophylactic chemotherapy (PCT) ^[11]. Medical data was categorized under 2 head: (1) PCT with Ivermectin and (2) PCT with other. The composite figures were then contrasted with a 3rd group i.e. countries with no PCT at all. It was found out that the difference between countries which deployed Ivermectin as PCT and the countries with do not was highly significant (adjusted significance $P < 0.01$). The statistics showed it clearly that PCT with Ivermectin had the lowest incidence compared to other PCT and no PCT (**Figure 1**).

What the Major Agencies Say about Ivermectin’s Prophylaxis Use....?

There is no doubt over the fact that Ivermectin has the potential to end Covid-19 pandemic as the medicine has been found to reduce significantly the risk of contracting the disease if used in prophylaxis. The campaigners and the doctors worldwide too are looking at the antiparasitic drug as the miracle drug to end the pandemic. Apparently, what they believe is not without reason. The American Journal of Therapeutics has assessed one of the most comprehensive data from real-world, *in vitro* and clinical studies. The team of medical and scientific experts and the people from Front Line Covid-19 Critical Care Alliance have equivocally said that Ivermectin is effective prophylaxis. Pierre Kory, MD, President and Chief Medical Officer of the FLCCC has therefore claimed it categorically, ‘we applied the gold standard to qualify the data reviewed before concluding that Ivermectin can end this pandemic’ ^[12]. There seems no reason to not believe what FLCCC personnel says as the conclusions have been drawn on the basis of 27 controlled trails in January 2021 and a wide assortment of epidemiological analyses, expert meta-analyses, manuscripts and published peer-reviewed studies. The verdict is clear as the drug has been found statistically significant in viral clearance in Covid-19 patients, recovery time and mortality reduction. Similar assessments have been made by Paul E Marik, Chief, Pulmonary and Critical Care, Eastern Virginia Medical School, ‘based on the totality of evidence, there is no doubt that Ivermectin is the treatment for Covid-19 as it is found highly effective as a safe prophylaxis’ ^[13]. Marik has stated categorically, ‘we are appealing to these national and global health authorities to please review the data and provide guidance to healthcare workers across the world so that they can prescribe this medication’. A call has thus been made to the medical professionals around the world and the regional public health authorities to include Ivermectin in their standard of care.

NDTV Corona Dashboard

In fact the recommendations on Ivermectin by FLCCC have come as a major boost for the drug’s use in India’s combat with the virus. One of the biggest states in India, Uttar Pradesh has adopted Ivermectin as a front line prophylaxis. In fact, the state with the highest population has been using Ivermectin for significant results. More recently, the All India Institute of Medical Sciences (AIIMS) and Indian Council of Medical Research (ICMR) have put the drug into its guidelines for treating mild outpatient illness ^[14]. In a similar wake, Goa too has announced that all the people above 18 years of age will be given Ivermectin irrespective of their status with corona virus (**Figure 2**). The objective is to bring mortality down to levels where mass contagion does not really show high numbers, especially critically ill. For the patients in the mild category, the patients are recommended to take 12 mg Ivermectin for a period of 5 days. The objective is to find statistically significant numbers with viral clearance, recovery time and mortality reduction.

FLCCC has recommended Ivermectin in early covid-19 out-patient at a dose of 0.2 mg/kg - 0.4 mg/kg and for later phase, hospital patients 0.4 mg/kg – 0.6 mg/kg. In fact, in cases of severe illness, a higher dose range should be used for five days and until

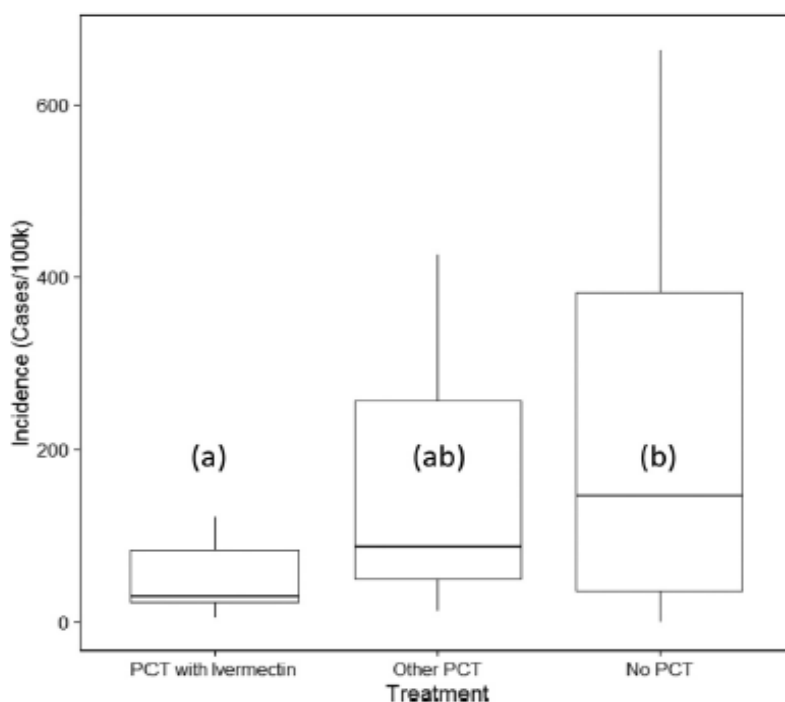


Figure 1. PCT with Ivermectin versus Other PCT and No PCT.



Figure 2. Goa: Is the worst over?

Table 1: Matched Pair Analysis for prophylaxis of Ivermectin, vitamin-c and HCQ.

Variables	Controls		Total	McNemar's Chi-Square
	Ivermectin	No Ivermectin		
Ivermectin	22(29.05%)	19(17.3%)	41(22.0%)	x ² =16.78
No Ivermectin	54(71.0%)	91(82.7%)	145(78.0%)	p<0.001
Total	76(100.0%)	110(100.0%)	186(100.0%)	
Matched Pair OR	0.35(95% CI, 0.20 to 0.60)			
	Vitamin-C	No Vitamin-C		
Vitamin-C	6(15.8%)	23(15.5%)	29(15.6%)	x ² =1.47
No Vitamin-C	32(84.2%)	125(84.5%)	157(84.4%)	p=0.22
Total	38(100.0%)	148(100.0%)	186(100.0%)	
Matched Pair OR	0.71(95%CI, 0.40 to 1.26)			
	HCQ	No HCQ		
HCQ ^b	0(0.0%)	7(4.0%)	7(3.8%)	x ² =1.32
No HCQ ^b	12(100.0%)	167(96.0%)	179(96.2%)	p=0.25
Total	12(100.0%)	174(100.0%)	186(100.0%)	
Matched Pair OR	0.58 (95%CI, 0.19 to 1.61)			

recovered. It has further been proposed that vitamin-D, in the form of Calciferol, should be given as adjunct. Uttar Pradesh was among the 1st of the Indian states to have placed Ivermectin as covid-19 prophylaxis for mass distribution in the dose of 0.2 mg/kg (12 mg for a 60 kg person) weekly preventing the mass spread of the disease [13].

CONCLUSION

Does Ivermectin have its role in prophylaxis and treatment of Covid-19 patients?

For a systematic review, the present study makes an extensive review around the formulated question by identifying, selecting and critically appraising data based on a comprehensive and reproducible search strategy. It was found that there exists a significant literature which speaks positively about the role of Ivermectin in prophylaxis. The drug has been found statistically significant in mortality reduction, clinical recovery time and viral clearance. Contrary to what the WHO has claimed, Ivermectin prophylaxis was associated with a very low rate of progression. Even in severely ill Covid-10 patients, the patients with Ivermectin showed a low mortality rate. In fact, the findings have encouraged the research agencies to make recommendations about Ivermectin in prophylaxis to all major national and global health authorities such as CDC and NIH. Apart from its prophylaxis profile, Ivermectin has also been found to be a multifaceted medication. While a lot of drugs are probable candidates for this war against Covid-19, this anti-parasitic already has its established efficacy and safety profile. The drug is found to have a wide distribution, high lipid solubility and rapid oral absorption in the body. What makes it further effective is its ability to cause immune-modulation in the host and which is of significant use in Covid-19 patients.

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