

Title: Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study

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Background: Ivermectin is one among several potential drugs explored for its therapeutic and preventive role in COVID-19 infection. The study was aimed to explore the association between ivermectin prophylaxis and development of COVID-19 infection among healthcare workers.

Methods: A hospital-based matched case-control study was conducted among healthcare workers of AIIMS Bhubaneswar, India, from September to October 2020. Profession, gender, age and date of diagnosis were matched for 186 case-control pairs. Cases and controls were healthcare workers who tested positive and negative, respectively, for COVID-19 by RT-PCR. Exposure was defined as the intake of ivermectin and/or hydroxychloroquine and/or vitamin-C and/or other prophylaxis for COVID-19. Data collection and entry was done in Epicollect5, and analysis was performed using STATA version 13. Conditional logistic regression models were used to describe the associated factors for COVID-19 infection.

Results: Ivermectin prophylaxis was taken by 77 controls and 38 cases. Two-dose ivermectin prophylaxis (0.27, 95% CI, 0.15-0.51) was associated with 73% reduction of COVID-19 infection among healthcare workers for the following one month, those who were involved in physical activity (3.06 95% CI, 1.18-7.93) for more than an hour/day were more likely to contract COVID-19 infection. Type of household, COVID duty, single-dose ivermectin prophylaxis, vitamin-C prophylaxis and hydroxychloroquine prophylaxis were not associated with COVID-19 infection.

Conclusion: Two-dose ivermectin prophylaxis at a dose of 300 µg/kg with a gap of 72 hours was associated 73% reduction of COVID-19 infection among healthcare workers for the following one-month. Further research is required before its large scale use.

Keywords: COVID-19, Ivermectin, Chemoprophylaxis, Healthcare workers, India

Introduction

The SARS-CoV-2 pandemic has claimed over 1,101,298 lives and affected over 39,196,259 persons worldwide. ¹ Meanwhile, the subcontinent of India has reported 7,83,311 active COVID-19 confirmed cases and 1,14,031 deaths related to the same virus by 17th October 2020.² Healthcare workers (HCWs) worldwide, have been exposed to the infection as frontline workers in a battle to save patients affected by COVID-19 infection, which has led to an increasing number of cases and deaths in this group.

A systematic review on infection and deaths in HCWs due to COVID-19 found that the number of infected HCWs workers ranged from 1,716 to 17,306 according to each country's data.³ Another report in September 2020 stated that COVID-19 had infected nearly 570,000 HCWs while as many as 2,500 had succumbed to the disease in the region.⁴ Organisations at international and national levels have shared advisories and guidelines with measures to ensure the safety of HCWs while they serve amidst the COVID-19 pandemic. Provision of PPEs while on duty, free-of-cost COVID-19 testing, timely payments, support helplines, online discussions, training, and capacity building for infection prevention and control are some of the measures taken to prevent the infection and spread of COVID-19 among HCWs.⁵⁻⁷

For high-risk persons such as HCWs, additional safety measures are necessary to prevent them from getting infected. The use of hydroxychloroquine (HCQ) as chemoprophylaxis was used in India under the recommendation of a few experts with little evidence and lack of scientific data.^{8,9} The WHO Solidarity trial's Executive Group and principal investigators decided to stop the hydroxychloroquine arm based on evidence from the Solidarity trial and UK's Recovery trial which showed that HCQ did not result in the reduction of mortality of hospitalised COVID-19 patients compared with standard of care.¹⁰

Ivermectin has been used as a therapeutic treatment of mild to moderate COVID-19 cases.¹¹ It has also been found to prevent symptoms of COVID-19 in post-exposure prophylaxis among HCWs.¹² When given to high-risk healthcare workers in contact with COVID-19 patients in a study from Egypt, it was found that compared to 7.4% of the intervention arm, 58.5% of participants from the control arm had symptoms suggesting of COVID-19 infection.¹² Few other studies have also shown favourable results with the use of ivermectin as prophylaxis and treatment.^{13,14}

All India Institute of Medical Sciences, Bhubaneswar, is a tertiary care, government-funded teaching hospital situated in Odisha which is in the Eastern part of India. From August 2020 onwards, large numbers of HCWs who were employees of the hospital were getting infected, which was affecting healthcare at the hospital. Considering the fact that ivermectin had been shown to have diverse mechanisms by which it successfully attacks the SARS-CoV-2 and the fact that ivermectin has a proven safety profile as a safe drug which has been used for many decades and the encouraging results of the study from Egypt prompted us to explore the role of ivermectin as prophylaxis for HCWs for the prevention of COVID-19.

Methods:

Study population and Sample Size

The present study is a hospital-based matched case-control study, conducted among HCWs of the All India Institute of Medical Sciences (AIIMS) in Bhubaneswar, Odisha, India, during September-October 2020. AIIMS, Bhubaneswar is a tertiary care hospital located in Eastern India. To calculate sample size, we assumed ivermectin in the control group to be 30% as there were no data available from prior studies. Considering, 80% power, 5% alpha, 1:1 matching of cases to controls, minimum discordant pairs to be detected was set to 68, with an expected odds

ratio of 0.5, the sample size was estimated to be 183 pairs, i.e. 366 individuals.¹⁵ Cases and controls were identified from the existing line list, which was prepared by the contact tracing team at AIIMS Bhubaneswar. This line list contains the list of the AIIMS Bhubaneswar HCWs' risk of exposure to COVID-19 assessment based on World Health Organization(WHO) risk assessment guidelines.¹⁶ This risk assessment helped in identifying similar risk population of cases and controls. Cases were HCWs who were diagnosed as positive for COVID-19 by Reverse Transcription Polymerase Chain Reaction (RT-PCR). Controls were defined as HCWs who were diagnosed as negative for COVID-19 by RT-PCR with a similar risk of exposure to COVID-19. For every enrolled case, a control was selected from the existing line list. Individual matching was done for their profession, gender and age, and also an attempt was made to match for the date of diagnosis. However, when the match was not possible for the same date, we selected the control from the nearest possible date of diagnosis. In the majority of cases, it was within a week. The average number of days for a difference in date of diagnosis was 3.8 days between cases and controls. Exposure was defined as the prophylaxis viz., ivermectin and or/ (HCQ) and or/ vitamin C and or/ other interventions taken for the prevention of COVID-19. HCWs of AIIMS Bhubaneswar were advised for HCQ prophylaxis as per ICMR guidelines from 11th April 2020 in addition to the appropriate Personal Protective Equipment (PPE) depending on the place they were posted.⁹ However, the uptake was not encouraging on account of known side-effect. Further, on 17th September 2020, a decision to provide all HCWs with ivermectin for prophylactic use was announced, based on a consensus statement that was released. **(Panel 1)**

Data collection and Statistical Analysis

After the selection of cases and controls, a phone call was made to each participant. The data related to COVID duty, family type, history of prophylaxis intake, history of hospital admission

and physical activity were collected. Data was entered in Epicollect5. Data cleaning and analysis was done using STATA version 13. The difference in characteristics of cases and controls were assessed using the chi-square test for categorical variables and t-test for continuous variables. Mean and standard deviation was used for continuous variables and proportion was reported for categorical variables, proportions were reported. Matched pair analysis was done using the McNemar chi-square test. Matched pair odds ratio was estimated for ivermectin, vitamin-C and HCQ prophylaxis. The potential confounders which could not be matched were adjusted during analysis with conditional logistic regression models. In model 1, we included the variables -COVID duty, family type and physical activity (a proxy for social contacts), which may be the risk factors for COVID-19. In model 2, we included the variables- ivermectin, vitamin-C and HCQ, which were practised as prophylaxis by HCWs for prevention of COVID-19.

The study protocol was approved by the Institutional Ethics Committee of AIIMS, Bhubaneswar via ref number: T/IM-NF/CM&FM/20/125. Verbal informed consent was obtained telephonically before participation in the study. This consent procedure was approved by the ethics committee.

Results:

There were a total of 904 staffs of AIIMS, Bhubaneswar who got tested for COVID-19 during last one month (20th September 2020-19th October 2020). Out of 904 persons who tested, 234 persons were tested positive, and 670 persons were tested negative for COVID-19. After matching with the profession, gender, age and date of diagnosis, we have 190 cases for which controls were available. Out of 190 cases, 4 cases did not give consent for the participation. Therefore, we finally included 186 matched pair or 372 participants in our study. Participants

had a mean (SD) age of 29 ± 6.83 years, and the mean difference in date of diagnosis between cases and control was 3.8 days. In one matched case-control pair, one intern was matched with a final year undergraduate student which was the closest possible match for the case, the remaining 185 case-control pairs' profession was perfectly matched. (Table 1) Out of 186 cases, 18 (9.7%) cases were admitted in a hospital while 168 (91.3%) cases opted for home isolation.

Majority of the participants (60.75%) were below 30 years of age. Nearly two-thirds of participants (67.2%) were male. More than half of the participants (57.26%) had their duties in COVID wards or COVID-19 screening OPD in last one month. Most participants (82.26%) were not doing any physical activity during the study period. Among the various modes of physical activity jogging and yoga were opted by 38 participants each (10.22%), gymnasium by 15 (4.03%), and sports by 11 (2.96%) participants. Among 372 participants, 128 (34.41%) were nursing officers, 104 (27.96%) were supporting staffs, 72 (19.35%) were resident doctors, 25 (6.72%) were interns, 25 (6.72%) were students and 18 (4.84%) were faculty members. Half of the participants (49.33%) were staying in an extended family, one-third participants (32.08%) were staying with friends, and others were either staying in a nuclear family (12.94%) or living alone (5.66%). (Table 1)

Out of 372 participants, 169 participants (102 from cases and 67 from controls) have taken any form of prophylaxis. Hundred fifteen (30.91%) participants had a history of ivermectin prophylaxis-77 from controls and 38 from cases, 67 (18.01%) participants had a history of vitamin-C prophylaxis-38 from controls and 29 from cases, 18 (5.11%) participants had a history of HCQ prophylaxis-12 from controls and seven from cases. (Table 2) There were 4 participants who were taking home-based remedies for prevention of COVID-19. Ninety-one

(24.46%) participants had a history of two-dose ivermectin prophylaxis (300 µg/kg at Day 1 and Day 4) however 17 (4.57%) participants took only one dose (300 µg/kg), and 9 (2.42%) participants continued the same dose for three or more days. Out of 67 participants, who took vitamin-C prophylaxis, 54 participants took at a dose of 500 mg once daily, and 13 participants took vitamin-c 500 mg twice daily. Majority of participants took vitamin-C for less than one month; however, 27 participants were continuing vitamin-C prophylaxis for more than one month. HCQ prophylaxis was practised 400 mg once a week. Out 19 participants, who took HCQ prophylaxis, ten participants took for three or more weeks, five participants took for two weeks, and four participants took for a week.

In the matched pair analysis, ivermectin prophylaxis (0.30, 95% CI, 0.16-0.53) was associated with the reduction of COVID-19 infection however vitamin-C prophylaxis (0.71, 95% CI, 0.40-1.26) and HCQ prophylaxis (0.58, 95% CI, 0.19-1.61) had no significant association with COVID-19 infection. (Table 3) In multivariate conditional logistic regression model 1, those who did any physical activity for more than one hour (2.86 95% CI, 1.19-6.87) compared to who did not do any physical activity had an increased odds of contracting COVID-19 infection. In the multivariate conditional logistic regression model 2, ivermectin prophylaxis (0.27, 95% CI, 0.15-0.51) was associated with a reduction of COVID-19 infection after adjusting for COVID duties, type of household, physical activity, vitamin-C prophylaxis and HCQ prophylaxis. However, physical activity for more than one hour was an independent risk factor (3.06 95% CI, 1.18-7.93) for COVID-19 infection. (Table 4)

Discussion

Our study has shown that two doses of ivermectin prophylaxis at a dose of 300 µg/kg given 72 hours apart was associated with a 73% reduction of COVID-19 infection among HCWs for the

following month. Our results are similar to the randomised trial conducted by Waheed Shouman from the Zagazig University of Egypt in which out of the 203 HCWs in the intervention arm, only 7.4% developed symptoms versus the 58.5% of the 101 HCWs in the control arm after 14 days of enrolment. The study also reported no mortality or serious adverse events due to ivermectin in the intervention arm.¹² Mostly, ivermectin prophylaxis will benefit the HCWs who are vulnerable to the infection because of their profession. Our study findings throw light in the same direction that ivermectin may play a vital role in the prevention strategy of COVID-19 infection.

Our study also documented that single-dose ivermectin prophylaxis at a dose of 300 µg/kg, HCQ prophylaxis, and vitamin-C prophylaxis is not associated with preventing COVID-19 infection. Engaging in physical activity for more than one hour daily, which is taken for lack of physical distancing was an independent risk factor for COVID-19 infection in our study. Study participants practised outdoor physical activity like walking or jogging, many also worked out at the gymnasium, and few were involved in playing sports. The possible explanations may be that physical activity poses a greater risk of exposure to infection due to increased chances of social contact, difficulty wearing masks, and sharing of gymnasium equipment by multiple persons, thereby rendering individuals vulnerable to infection. Various studies have emphasised the need and effectiveness of social or physical distancing as a preventive measure against COVID-19 while maintaining the importance of hygiene measures, use of face masks, and increase in testing facilities to prevent and reduce COVID-19 transmission.¹⁷⁻²¹

The study by Caly et al. on the effect of ivermectin acting in vitro on Vero-hsLAM cell infected with COVID-19 has been quoted widely for providing the basis of usage of Ivermectin in Covid-19.²² It was found that the Vero/hSLAM cells infected with SARS-CoV-2 isolate Australia/VIC01/2020 and treated with 5µM ivermectin showed a 93% reduction in the viral

RNA compared to the vehicle DMSO (Dimethyl sulfoxide) at the end of 24 hours duration as much as 5000-fold reduction of viral RNA was observed at the end of 48 hours duration in the ivermectin-treated samples compared to the control samples. This observation indicated that approximately all viral material was eradicated by ivermectin treatment in 48 hours duration. However, at 72 hour-duration, there was no further reduction observed in the viral RNA levels. The study also determined the IC50 (half maximal inhibitory concentration) of ivermectin treatment to be 2.5 μ M under the test conditions.²²

Our study also estimated that single-dose prophylaxis has no association with a reduction of COVID-19 and two-dose of ivermectin (300 μ g/kg) was associated with a reduction of COVID-19. Our study finding is supported by another study conducted by Chang et al., which found ivermectin to be useful as prophylaxis among healthcare personnel.¹³ Their study aimed to investigate specifically post-exposure prophylaxis in contacts who tested negative for SARS-CoV-2 with ivermectin dose of 0.2mg/kg body weight on day one with an additional second dose of ivermectin on day 2 or 3 for men aged more than 45 years.¹³ In contrast, our study investigated the healthcare workers who had tested for COVID-19 with positive cases and negative controls. We also matched the cases and controls according to age, gender, designation, and date of testing. Also, our sample size was larger than the former study.

A randomised controlled study conducted by Boulware et al. tested hydroxychloroquine as postexposure prophylaxis among high-risk contacts of confirmed COVID-19 cases. Similar to our study findings, their study reported no significant difference between the HCQ arm and the placebo arm. There were also more side effects reported with hydroxychloroquine in their study.²³

In literature, the proposed hypothesis is that vitamin C may have a role to prevent COVID-19 infection due to its strong antioxidant and immunomodulatory effects.²⁴⁻²⁶ However, no

research or hardcore evidence supports these findings. In our study, we did not find any association between vitamin-C prophylaxis and prevention of COVID-19 infection.

The strengths of our study are the adequate sample size, completeness of the data collection and verification from subjects. All the HCWs received ivermectin procured from a single manufacturer and belonged to the same batch for each strength. We adjusted for confounders by matching and multivariate analysis. Though recall bias is inherent in case-control studies, our data regarding the drug intake within the last one month is less likely to be forgotten by HCWs. Due to its observational nature, our study's findings need further confirmation using longitudinal studies or interventional studies to strengthen the evidence before its large-scale use among HCWs and the implementation of public health programs.

Conclusion

We conclude that two-dose ivermectin prophylaxis at a dose of 300 µg/kg body weight with a gap of 72 hours was associated with a 73% reduction of COVID-19 infection among HCWs in the following one month. This is an intervention worth replicating at other centres until a vaccine is available.

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Availability of data and materials: All data generated or analysed during this study are available with the corresponding author and can be shared on request.

Competing interests: None

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Panel 1: AIIMS Bhubaneswar consensus statement for ivermectin prophylaxis among healthcare workers

Based on the long history of clinical use, favourable safety profile, and the reportedly promising effect of ivermectin as a prophylactic agent in COVID-19, the expert committee group proposes the following consensus statement:

Suggested prophylaxis for doctors/nurses/staff/students of AIIMS Bhubaneswar with ivermectin*

First Dose:

Ivermectin 300 µg/kg body weight on Day 1 (Directly Observed) and 4 (72 hours apart).

For 40-60 kg:15mg, 60-80 kg:18 mg, > 80 kg:24 mg

Subsequent dose: once a month dose (as above/kg body weight) on every 30th day after the last dose.

Ivermectin should be taken on an empty stomach with water.

*The above schedule will be followed till further guideline/new evidence is available.

*Pregnant women will not be given this drug. Women of childbearing age will be warned not to conceive while on this drug, in case they decide to take the drug.

This consensus statement had been prepared by a team of faculty members from various specialities and discussed and approved in the COVID-19 Working Group meeting on 11th September 2020.

Table 1: Characteristics of study participants (n=372)

	Control (n= 186)	Case (n=186)	Total (n=372)	P-value
Mean age in years (Mean ± SD)	29.26 ± 6.61	29.25 ± 7.05	29.25 ± 6.83	0.99
Age groups				
<30 years	110 (59.1%)	116 (62.4%)	226 (60.8%)	0.73
30-39 years	59 (31.7%)	52 (28.0%)	111 (29.8%)	
40-49 years	15 (8.1%)	14 (7.5%)	29 (7.8%)	
≥50 years	2 (1.1%)	4 (2.1%)	6 (1.6%)	
Gender				
Male	125 (67.2%)	125 (67.2%)	250 (67.2%)	1.00
Female	61 (32.8%)	61 (32.8%)	122 (32.8%)	
Whether you had COVID-19 duties in the hospital?				
Yes	107 (57.5%)	106 (57.0%)	213 (57.3%)	0.92
No	79 (42.5%)	80 (43.0%)	159 (42.7%)	
Duration of physical activity				
No physical activity	159 (85.5%)	147 (79.0%)	306 (82.3%)	0.06
Less than 30 minutes	6 (3.2%)	8 (4.3%)	14 (3.7%)	
30-59 minutes	14 (7.5%)	11 (5.9%)	25 (6.7%)	
≥60 minutes	7 (3.8%)	20 (10.8%)	27 (7.3%)	
Profession				
Support staff	52 (28.0%)	52 (28.0%)	104 (28.0%)	1.00
Residents	36 (19.3%)	36 (19.4%)	72 (19.4%)	
Nursing Officer	64 (34.4%)	64 (34.4%)	128 (34.4%)	
Intern	12 (6.5%)	13 (7.0%)	25 (6.7%)	
Student	13 (7.0%)	12 (6.4%)	25 (6.7%)	
Faculty	9 (4.8%)	9 (4.8%)	18 (4.8%)	
Type of household				
Extended family	86 (46.2%)	98 (52.7%)	183 (49.5%)	0.26
Nuclear family	28 (15.1%)	20 (10.7%)	48 (12.9%)	
With friend or roommate	64 (34.4%)	55 (29.6%)	119 (32.0%)	
Living alone	8 (4.3%)	13 (7.0%)	21 (5.6%)	
Total	186 (100.0%)	186 (100.0%)	372 (100.0%)	

Table 2: Comparison of nature of prophylaxis between the cases (n=186) and controls (n=186)

Variable	Control N (%)	Case N (%)	Total N (%)
History of prophylaxis			
No	84 (45.2)	118 (63.8)	202 (54.5)
Yes	102 (54.8)	67 (36.2)	169 (45.5)
History of intake of ivermectin for COVID-19 prophylaxis			
No	109 (58.6)	148 (79.6)	257 (69.1)
Yes	77 (41.4)	38 (20.4)	115 (30.9)
History of intake of vitamin-C for COVID-19 prophylaxis			
No	148 (79.6)	157 (84.4)	305 (82.0)
Yes	38 (20.4)	29 (15.6)	67 (18.0)
History of intake of HCQ for COVID-19 prophylaxis			
No	174 (93.5)	179 (96.2)	353 (94.9)
Yes	12 (6.5)	7 (3.8)	19 (5.1)
Total	186 (100.00)	186 (100.00)	372 (100.00)

Table 3: Matched pair analysis of exposure/prophylaxis taken for COVID-19 (n=186)

Variables		Controls		Total	McNemar's Chi-square
		Ivermectin	No ivermectin		
Cases	Ivermectin	21 (27.3%)	17 (15.6%)	38 (20.4%)	$\chi^2 = 20.84$ P<0.001
	No ivermectin	56 (72.7%)	92 (84.4%)	148 (79.6%)	
	Total	77 (100.0%)	109 (100.0%)	186 (100.0%)	
	Matched pair OR	0.30 (95% CI, 0.16 to 0.53)			
		Vitamin-C	No vitamin-C		
	Vitamin-C	6 (15.8%)	23 (15.5%)	29 (15.6%)	$\chi^2 = 1.47$ P=0.22
	No vitamin-C	32 (84.2%)	125 (84.5%)	157 (84.4%)	
	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	0 (0.0%)	7 (4.0%)	7 (3.8%)	$\chi^2 = 1.32$ P=0.25
	No HCQ	12 (100.0%)	167 (96.0%)	179 (96.2%)	
	Total	12 (100.0%)	174 (100.0%)	186 (100.0%)	
	Matched pair OR	0.58 (95% CI, 0.19 to 1.61)			

Table 4: Conditional logistic regression models for associated factors of COVID-19 infection

Variable	Unadjusted Odds ratio (95% CI)	p-value	Model-1		Model-2	
			Adjusted Odds ratio (95% CI)	p-value	Adjusted Odds ratio (95% CI)	p-value
History of COVID-19 duty						
No	Reference		Reference			
Yes	0.96 (0.55 to 1.66)	0.89	0.93(0.51 to 1.67)	0.81	0.88 (0.45 to 1.68)	0.69
Household type						
Extended family	Reference		Reference			
Friend/roommate	0.68 (0.39 to 1.18)	0.18	0.69 (0.39 to 1.21)	0.19	0.80 (0.43 to 1.48)	0.48
Nuclear family	0.61(0.31 to 1.19)	0.15	0.64 (0.32 to 1.27)	0.20	0.66 (0.32 to 1.35)	0.25
Alone	1.51 (0.49 to 4.66)	0.47	3.25 (0.53 to 5.45)	0.37	1.43 (0.42 to 4.91)	0.57
Physical activity						
No physical activity	Reference		Reference			
Less than 30 minutes per day	1.33 (0.46 to 3.84)	0.59	1.34 (0.46 to 3.92)	0.60	1.14 (0.36 to 3.61)	0.82
30-59 minutes per day	0.80 (0.35 to 1.83)	0.60	0.76 (0.33 to 1.79)	0.53	0.61 (0.24 to 1.57)	0.31
≥60 minutes per day	2.83 (1.20 to 6.71)	0.02	2.86 (1.19 to 6.87)	0.02	3.06 (1.18 to 7.93)	0.02
Ivermectin prophylaxis						
No Ivermectin prophylaxis	Reference				Reference	
Single-dose Ivermectin prophylaxis	1.23 (0.43 to 3.50)	0.70			1.30 (0.44 to 3.85)	0.63
Two or more doses Ivermectin prophylaxis	0.27 (0.14 to 0.47)	0.00			0.27 (0.15 to 0.51)	0.00
Vitamin-C prophylaxis						
No	Reference				Reference	
Yes	0.72 (0.42 to 1.27)	0.23			0.82 (0.45 to 1.57)	0.58
HCQ prophylaxis						
No	Reference				Reference	
Yes	0.58 (0.23 to 1.48)	0.26			0.56 (0.19 to 1.63)	0.29