Ivermectin and Hydroxychloroquine for Chemo-Prophylaxis of COVID-19: A Questionnaire Survey of Perception and Prescribing Practice of Physicians vis-à-vis Outcomes

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**Abstract**

**Background:** Chemoprophylaxis (CP) along with masking and physical distancing seem an undeniable alternative. Considering the significant but uncertain role of CP for the current COVID-19 pandemic situation, we aimed to determine the various aspects of CP prescribing practices among physicians across India.

**Methods:** An online survey was conducted among prescribing physicians across India where physicians were assessed for their prescribing practices on COVID-19 CP. Responses to the questionnaire were obtained via telephone, email and WhatsApp messages. Responses were duly analyzed thereafter.

**Result:** Ivermectin was the preferred choice in 44% individuals followed by hydroxychloroquine in 34% individuals. Odds of COVID contact among those using HCQ and/or IVR prophylaxis was less than 1 of which IVR was found more protective. The present study also made a survey among 309 community dwellers, where odds of contacted COVID among those with any prophylaxis was 0.46 times than those without any prophylaxis.

**Conclusion:** The HCPs found IVR to have a greater risk reduction than with HCQ; while the combination showed the greatest reduction and lack of CP use was associated with a high risk of SARS-CoV-2 infection.

**Introduction**

Over the period of past 17 months, the world has witnessed more than 160 million cases of infection, as on date, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and nearly 2% (>35 lac) had fatal outcome.\(^1\) As we prepare this paper, several studies have reported inefficacy of different treatment interventions in terms of reduction in mortality in hospitalized patients, namely with remdesivir,\(^2\) hydroxychloroquine,\(^3\) lopinavir/ritonavir,\(^4\) interferon\(^5\) and convalescent plasma.\(^6\) The few therapeutic options in moderate to severely ill patients that have worked to a certain extent are the corticosteroids like dexamethasone.\(^7\) The risk for healthcare workers (HCW) is high due to prolonged exposure to infected patients which is even greater in those who provide endotracheal intubation or adorning insufficient personal protective equipment (PPE).\(^8\)

Unfortunately, the latest factor that has compounded the pandemic worry is the incidence of mucormycosis, which has been found in more than 76% patients treated with corticosteroids. Also, 80% of the patients diagnosed with mucormycosis are diabetics,\(^8\) and India is the home to alarming 8.9% diabetics of the total adult population.\(^10\)

Thus far, prevention of SARS-CoV-2 is a better alternative to contain the pandemic. Though the vaccines have been developed and are a ray of hope, there are many logistic and other challenges in vaccinating a meaningful proportion of the population at risk within a short time.\(^11\) Another threat are the Concerns about newer neutralization escape mutants are being reported from several parts of the world.\(^4\) Further, the prolonged Covid-19 pandemic has already shown its potential to shatter global fiscal and societal predicament.\(^14\)

Overall it appears that the disease is unlikely to vanish soon and therefore to resume the daily activities and live life amidst the various restrictions, a rational, multi-pronged strategy needs to be adopted. Chemoprophylaxis (CP) along with masking and physical distancing seem an undeniable alternative. CP seems a particularly useful strategy for the frontline HCWs, including healthcare professionals, the ones who need to be on site for earning their livelihood and the care-takers of infected family members. Two drugs ivermectin (IVR), which is an anti-parasitic drug with lower drug interaction potential and hydroxychloroquine (HCQ) have been used as chemoprophylactic agents. No less than eight RCTS and observational studies have demonstrated statistically significant decreases in the transmission of COVID-19 among human subjects with IVR.\(^15\) Based on available evidence and the guideline recommendation from the international BIRD conference, ivermectin has been proposed to be positioned in the prevention of COVID-19.\(^4\) However, when available published...
**Prophylaxis**

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In general population, from 60 prescribers nationwide who had reduced RR of infection compared to those who received HCQ. Among HCPs, who self-prescribed CP majority opted for IVR, followed by HCQ or combination; very few did not use either CP. Clearly, those who used CP had reduced RR of infection compared to those who did not. The HCPs found ivermectin to have a greater risk reduction than with HCQ; while the combination showed the greatest reduction and lack of CP use was associated with a high risk of SARS-CoV-2 infection.

**Table 2: Statistical association between use of any prophylaxis and contact with COVID among prescribers**

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Total Participants</th>
<th>Participants contacted COVID</th>
<th>Proportion of participants with COVID</th>
<th>Odds Ratio (95% CI)</th>
<th>Chi-square value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis</td>
<td>81</td>
<td>29</td>
<td>35.8</td>
<td>1 (Control)</td>
<td></td>
</tr>
<tr>
<td>HCQ prophylaxis</td>
<td>129</td>
<td>12</td>
<td>9.3</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>IVR Prophylaxis</td>
<td>164</td>
<td>12</td>
<td>7.3</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

On an average 10 patient were advised HCQ in a month, compared to 23.67 who were advised IVR instead. Majority of the prescribers believed that IVR or HCQ chemoprophylaxis should be given to all health care workers at higher risk of transmission, e.g., doctors, nurses, other health staff along with those with occupational or behavioral risk of (unknown) transmission, e.g., policemen etc. An interesting finding reflects that out of an average of 99 patients put on HCQ chemoprophylaxis, an average of 10 persons suffered from COVID-19. Of an average of 154 patients put on IVR chemoprophylaxis, an average of only 3.67 persons suffered from COVID-19. Noticeably despite being in self-chemoprophylaxis, 15% (n=9) prescribers still contacted COVID-19, though were mostly mild in severity grading. Odds of COVID contact among those using HCQ and / or IVR prophylaxis is less than 1 of which IVR was found more protective. Chi-square value for trend is statistically significant.

The present study also made a survey among 309 community dwellers. Out of 309 population 109 people were with any CP. Among them only 11 people contacted COVID. Out of 200 people without any CP, 39 people contacted COVID. Odds of contacted COVID among those with any prophylaxis is 0.46 times than those without any prophylaxis. Association between use of prophylaxis against COVID and getting infected with COVID is statistically significant and as the value is less than 1, so use of any prophylaxis is protective among community dwellers (Table 2).

Most prescribers added to their prophylactic therapy advised personal protection measures like mask, hand hygiene, physical distancing etc. Some noted adverse reactions to HCQ/IVR therapy were gastrointestinal complications (nausea, vomiting, abdominal discomfort etc.) and cardiac complaints (palpitations, arrhythmia, tachycardia etc.).

**Discussion**

Considering the crucial need of CP, HCQ was recommended by the COVID-19 National Task Force of India for all HCW, other frontline workers involved in COVID-19 activities, and asymptomatic household contacts of RT-PCR-confirmed cases. 

Cohort and retrospective studies have demonstrated that HCQ CP by HCW at high risk, significantly reduced the rate of RT-PCR positivity compared to no-CP. However, a later meta-analysis concluded that the use of HCQ did not reduce the risks of developing COVID-19, hospitalization, or mortality. Besides, the analysis also revealed that HCQ increased the risk of adverse events. On the contrary, results of meta-analyses of 4 RCTs and 5 observational studies of IVR have found significantly reduced risks of contracting COVID-19 with the regular use of ivermectin.

In the current study, we found that IVR was preferred by physicians for self-chemoprophylaxis and for general population along with HCW at risk of developing the infection. Similar to the recently published meta-analysis, we found a reduced risk of contracting SARS-CoV-2 infection in subjects who received IVR prophylaxis compared to those who received HCQ. Among HCPs, who self-prescribed CP majority opted for IVR, followed by HCQ or combination; very few did not use either CP. Clearly, those who used CP had reduced RR of infection compared to those who did not. The HCPs found IVR to have a greater risk reduction than with HCQ; while the combination showed the greatest reduction and lack of CP use was associated with a high risk of SARS-CoV-2 infection.

It is also worth considering that HCQ is a lysosomotropic drug may influence the functions of proteins involved in antigen presenting pathways and in...
B-cell activation involved in antibody responses and may influence vaccine efficiency negatively.\(^\text{20}\) Trained immunity is known to enhance the innate immune response and thereby facilitates the defense against infections. HCQ forestalls the trained immunity and therefore may not be beneficial for clearing viral infections like SARS-CoV-2 and contends against its use as a CP for COVID-19.\(^\text{21}\) No negative influence of IVR on immune response has been documented yet, rather worldwide database has only strengthened the correlation of its prophylactic effect against SARS-CoV-2, also supported by several recent findings reported in literature.\(^\text{22}\) Until, vaccine availability improves along with its reach, CP with IVR seems a promising alternative.\(^\text{23}\)

This study was conducted when no vaccine for COVID 19 was available. Role of CP in COVID 19 vaccine beneficiaries is extremely debatable. It is important to consider well designed studies to understand the CP and vaccination interaction. Though this survey helped gathering information from a varied cohort, it was a small sample of physicians. Additionally, inconsistency in recall precision may have affected our results. Further compliance could have also affected our results in terms of the risks of contracting the SARS-CoV-2 infection among those prescribed CP apart from the missing follow-up data, which was not captured by our questionnaire. To affirm these findings and avoid recall bias an appropriately designed randomized controlled study with a larger sample size is warranted.

References