Review Article

Chemoprophylaxis in COVID-19 — Where Do We Stand Today?

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Till December 16th, 2020, World has witnessed 72,196,732 confirmed cases of COVID-19 including 1,630,521 deaths, reported to WHO. This huge toll to human civilization has been created an unprecedented fear among world population complicated with loss of job, economic shutdown as well. Naturally, with the passage of time, people need to move out to earn their daily bread in the face of opening the economy. This increases the risk of acquiring the infection and put an extra load over the hard-pressed health care system. Many frontline workers including healthcare personnel have succumbed in the battle against Covid -19. Before a safe and effective vaccine becomes available to all, an useful chemoprophylaxis along with adequate personal protection may come as a rescue. In this article we are only trying to explore this issue.

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Prevention is better than cure' the age - old proverb is universally true even in case of infectious diseases like COVID-19. Chemoprophylaxis or Chemoprevention refers to the administration of a medication for the purpose of preventing a disease or infection. Presently during the Covid -19 pandemic, where medical and scientific fraternity is desperately trying for a remedy, it is not surprising to search for an effective chemoprophylaxis against SARS-Cov-2 infection too. While talking about chemoprophylaxis, medicines can be administered well before or immediately after the actual exposure of the infection among high risk population and contacts, are well-known as preexposure (PrEP) and postexposure prophylaxis respectively (PEP).

In fact, several drugs in modern medicine have been repurposed for both treatment and chemoprophylaxis of COVID-19, similar trend is being observed in other branches of medicine as well. Noteworthy, healthcare and other frontline workers are exposed to infection repeatedly and carry more risk of acquiring disease and are appropriate candidates for chemoprophylaxis. There are various measures of prevention against SARS-Cov-2. One is universal masking and physical distancing. But, during long work schedule and in crowded environment these measures are often not followed. Vaccine is undoubtedly the most important prophylactic measure against viral infections but a highly effective and safe vaccine is yet to come in near future. Here lies the role of chemoprophylaxis and we can buy time for developing a safe and effective vaccine. Several agents are being proposed, few of them are recommended by different national and state health authorities in India and abroad.

Editor's Comment :

- Chemoprophylaxis in COVID-19 has been a highly discussed topic since the emergence of the disease.
- Many studies and guidelines in favour or against of prophylactic use of hydroxychloroquine and ivermectin are on record.
- Adequate personal protection and covid appropriate behaviour should always be followed on the top of any prophylaxis

Hydroxychloroquine : The 'Queen' in disguise !

The mostly discussed and controversial molecule is hydroxychloroquine (HCQ). The advantage of this molecule is it is cheap and relatively safe though many arguments, counterarguments and concerns are still in the air about it's possible adverse effects[1].

A handful of basic science and clinical research studies speak for the usefulness of HCQ both in the prophylaxis and treatment of COVID-19 infection. HCQ has a good safety profile and a long half-life and have demonstrated in vitro efficacy against SARS-CoV. There are several proposed mechanisms as follow **:** HCQ raises the pH level of endosomes preventing viral entry, increases the intracellular concentration of zinc blocking viral replication or as immunomodulator limiting the cytokine storm.

We know that the Indian Council of Medical Research (ICMR) acted promptly to recommend hydroxychloroquine for prophylaxis among

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asymptomatic health care workers and household contacts of confirmed patients (published bulletin dated March 21, 2020). In the revised advisory they again retained the original recommendation of 400 mg twice a day on Day 1, followed by 400 mg once weekly to be taken with meals for next 7 weeks in case of frontline workers and for 3 weeks in case of household contacts. Before issuing the recommendation, ICMR scientists have performed in-vitro testing of HCQ for antiviral efficacy with log reduction in viral RNA copy of SARs-CoV-2. They further recommended for its use beyond 8 weeks on weekly dosage with strict monitoring of clinical and ECG parameters under supervision [2].

Accordingly the revised guideline has been issued following some beneficial study reports eg, a retrospective case-control analysis at ICMR has found that there is a significant dose-response relationship between the number of prophylactic doses taken(four and more) and reduction of frequency of SARS-CoV-2 infection in symptomatic healthcare workers[3]. Similarly few observational studies - one from AIIMS and other from three diferrent hospitals, New Delhi have shown a beneficial effect of HCQ prophylaxis among healthcare workers (HCW)[2].

Based on the available evidence and long track record of it's daily use in some chronic ailments, it has been opined that HCQ is relatively safe and barring few contraindications may have some beneficial effects as a prophylactic option.

But many people are not confident with these reports and demand for a randomised control study (RCT) of adequate sample size.

As per the published Randomized Controlled Trial (RCT) in JAMA, on efficacy and safety of daily HCQ at a dose of 600mg versus placebo as preexposure prophylaxis, did not find any significant difference in acquiring infection among hospital based HCW at high risk, but the trial was limited by small sample size and all of the SARS Cov2 positive HCW developed mild disease, did not require hospitalisation and all recovered. Adverse events, although more among HCQ users (45% *versus* 26%, p=0.03), were mostly gastrointestinal, without any cardiovascular toxicity (syncope or arrhythmia) and no significant difference of QTc prolongation was observed[4].

In another PrPEP RCT (Rajasingham R *et al*), HCQ was given at a loading dose of 400mg twice at an interval of 6-8 hours followed by (i) 400 mg once weekly or (ii) 400 mg twice weekly for 12 weeks, in a matched fashion with a placebo, randomly among healthcare workers, showed no significant reduction in COVID-19 incidence among them.

But studies with evidence of beneficial effect are also on record. An encouraging result of PrEP with HCQ has also been reported from West Bengal (preprint version medRXiv).The executed cohort study demonstrated that voluntary consumption of HCQ as prophylaxis(ICMR schedule) by HCW at high risk, significantly reduced the rate of RTPCR positivity as compared nonusers ($p<0.001$)[5]. Another retrospective study of HCQ as PrEP (ICMR schedule) involving HCW also significantly (relative risk of 0.1046, 95% confidence interval: 0.0510–0.2147, $P<0.0001$), reduced SARS-Cov-2 infection among compliant versus noncompliant users.[6]

Few published studies also deny the role of hydroxychloroquine as postexposure prophylaxis (PEP) against SARS Cov 2 infection, although a small but potentially valuable benefit still exists[7]. Here, a long delay between perceived exposure to SARS-CoV-2 and the initiation of hydroxychloroquine ($\geq$3 days in most participants) (Boulware *et al*), might be the reason of failure of prevention of infection rather that reduced clinical symptoms and severity. Even in this study there was a 2% risk reduction of infection in HCQ arm (statistically not significant) but upon extrapolation in a larger population, that may have a significant impact in preventing further spread of the pandemic[8]. According to another study from PGI, Chandigarh, the absolute risk reduction of COVID-19 infection by HCQ as PEP was 8.9%, which was statistically significant[9].

In a preprint study by Mitja *et al* showing an infection rate of 17.8% in control compared to 18.7% in treatment (HCQ prophylaxis) group (no significant difference), thus disfavouring PEP with HCQ. However, on serology test, there are significantly more participants with IgM/IgG positivity on day 14 in HCQ arm compared to control (14.4% *versus* 8.7%, $p<0.0006$), thus proposing HCQ can increase activation of adaptive immunity. It is also suggested that using HCQ on day 1, day 0 and pre-exposure can have better protection against symptomatic COVID-19.There was no serious side effect reported in those studies. So, it can be concluded that if used early HCQ can provide some benefit as PEP[8].

On the otherhand, in a population-based cohort study among rheumatology patients where prior hydroxychloroquine use before SARS-CoV-2 infection found no significant difference in standardised cumulative COVID-19 mortality (0·23% among hydroxychloroquine users and 0·22% among non-users). with an adjusted hazard ratio of 1·03 (95% CI 0·80–1·33)[10].

Zhong *et al* analyzed 42 families and concluded

that rheumatic diseases increased risk of infection (OR 2.68, p<0.023).Adjusted for all other factors, rheumatology patients who were taking HCQ had a lower risk of COVID-19 infection than patients taking other disease-modifying anti-rheumatic drugs (OR 0.09, p=0.044).

Overall, the retrospective studies about HCQ as a prophylaxis give conflicting results. Patients with rheumatic diseases may be more susceptible to the infection thus may negate the potential prophylactic benefit of HCQ as shown in some studies. However, no firm conclusion can be made using these observational studies.

A substantial uncertainity still prevails among medical fraternity about the role of HCQ as a prophylaxis against SARS-Cov-2 infection, demanding more data from large, well designed studies. Still, many countries continue to recommend HCQ for treatment and prophylaxis.

In fact many arguments for and against the effectiveness of HCQ as prophylactic and therapeutic agent against SARS-Cov-2 are in the air and a consencious guideline is yet to be released. Many studies are ongoing and hopefully in the coming days we will get the evidence based scientific verdict on this issue.

Ivermectin : The 'Nobel' drug for a 'Noble' cause !

Another drug which attained much enthusiacism is ivermectin, well known for the treatment of helminthic diseases in humans, now being tried for SARS-CoV-2 infection. Usual oral anthelmintic dose is 0.15 mg/kg–0.2 mg/kg body weight for most infestations and is well tolerated. The half-life of ivermectin is 12–36 hours in human, and its metabolites may persist for up to 12 days due to high liposolubility. In-vitro studies are on record promoting it's antiviral effects against several DNA and RNA viruses.

The anti-SARS-CoV-2 action of ivermectin is likely occuring through multiple mechanisms – (i) Viral replication inhibition, (ii) Viral entry blockage into the host cell, (iii) Ionophore Molecule like activity, (iv) Microvascular thrombosis prevention, (v) Affinity and deposition to the pulmonary tissue[11].

Caly *et al* found that a single dose of ivermectin (5 ìM),almost completely eliminated (5000-fold reduction in viral RNA) SARS-Cov2 infection in Vero-hSLAM cells at 48 h, which formed the basis for it's consideration in the treatment and prophylaxis of COVID-19 disease[11,12].

While extrapolating this in-vitro study dose into equivalent human dose, it comes to a very large one which is far beyond the usual anthelmintic human dose of ivermectin and effective human dose for SARS-CoV-2 infection is yet to be established[13]. Other anti Covid actions may be important here and cumulative effect of those actions need further exploration.

A handful of clinical trials, observational studies and case reports covering the entire severity spectrum of COVID-19 are available, and many are yet to be published. Taking reference from these study reports and local experience gained from pilot studies different state governments in India have already incorporated ivermectin in the treatment and chemoprophylaxis of COVID-19[14].

In West Bengal ivermectin has been incorporated in the guideline as pre exposure prophylaxis at a dose of 12mg once daily preferably a fatty meal in day1 and day7 followed by day 30 and to be repeated monthly[15]. As post exposure prophylaxis it is recommended as 12 mg at day 1 and to be repeated at Day 7 in some other states in India[14,16].

Some studies are reported regarding prophylactic use of ivermectin. One randomized controlled trial was done in Zagazig university, Egypt which used ivermectin at a dose of 300mcg/kg as postexposure prophylaxis at Day 1 and Day 3 showed statistically significant benefit in preventing COVID-19 disease among asymptomatic close contacts of confirmed cases.[17]Similarly taking clue from this, a recently completed study published as a preprint version from AIIMS, Bhubaneswar showed a 73% reduction in contacting COVID-19 infection in the following one month among HCW taking ivermectin at 300mcg/kg once a day with a gap of 72 hours[18]. One recently published study using monthly single dose of oral ivermectin (12mg) tablet and another study of four hourly oral ivermectin drop along with carrageenan nasal spray appeared as highly effective PrEP modalities among HCW respectively[19,20]. According to another study, as PrEP weekly ivermectin (at a dose of 0.2mg/kgbw) is superior to monthly intake which is even better than no prophylaxis[21].

All of those studies documented no mortality and any serious adverse events due to ivermectin. So ivermectin could play a major role in prevention of COVID-19 both as PrEP and PEP.

Considering the role of ivermectin as immuno-potentiating agent when administered along with few vaccines as revealed through some animal studies[22], a thorough research is urgently required on usefulness of ivermectin chemoprophylaxis in covid vaccinated people as breakthrough infections and even deaths are on record after full dose vaccination.

HCQ and Ivermectin Combination Prophylaxis — Are They Better ?

Another point needs to be discussed is combination chemoprophylaxis. Although no COVID-19 guidelines recommend this approach, many healthcare workers are consuming both hydroxychloroquine and ivermectin chemoprophylaxis concomitantly. No study is available till date in this issue but few authors have opined towards better therapeutic and prophylactic response by way of different and synergistic actions. But a well designed RCT can only be decisive in this regard[23].

Quadruple Therapy — Is It Promising?

As a better and successful prophylactic and therapeutic measure, a quadruple therapy regimen has been proposed involving four medicines namely ivermectin, doxycycline, zinc fortnightly with weekly vitamin D3 claiming high efficacy. Ivermectin-doxycycline-zinc triple drug therapy may possess a synergistic action but emergence of resistance to doxycycline among other pathogens is also a matter of concern.

Other Drugs and Agents :

Among other drugs Mefloquine and Tafenoquine are proposed to have effect against SARS-Cov-2 infection as weekly PrEP but are not recommended in any guideline in India or abroad.

Moreover, many people are taking preparations from other branches of medicines along with the drugs from modern medicine. This is not recommended as there is every chance of unknown drug drug interactions and thus can lead to serious adverse events.

Regular habit of consumption of multivitamins, Vitamin D, Zinc, some readily available spices as prophylactic measure for COVID -19 needs to be explored through a well designed study.

Strict adherence to the public health measures such as physical distancing and wearing protective equipment is difficult to follow than simply taking a drug. Thus proper use of personal protective equipments like mask, face shield, maintaining physical distancing and hand hygiene is to be stressed even after the use of any chemoprophylactic agent. There should be no complacency among HCW and they never should loosen their guard in their work place or other risk zones.

Conclusion

Active chemoprophylaxis is necessary till an effective and safe vaccine is available to all eligible people in the face of opening economy, school, colleges and work places. The successful PrEP and PEP for diseases like malaria, /AIDS encourage to adopt this strategy among larger population to prevent the spread and halt the COVID-19 pandemic. On the hindsight, people, may desperately venture for a 'cure' or 'prevention' will often believe 'something is better than nothing' in the hour of crisis. This could also lead to widespread self-medication and undue adverse events.

Thus, it is important to conduct and analyze the gold standard randomized controlled trials using different chemoprophylactic agents in question to prove or refute their efficacy conclusively. Till then we need to abide by the National and State guidelines strictly to confront this deadly enemy of human civilization.

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