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HYDROXYCHLOROQUINE DRUG SAFETY REVIEW FOR THE PROPHYLAXIS OF SARS COV 2 PANDEMIC

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ABSTRACT: COVID19 outbreak, originated from Wuhan, china is now declared as pandemic by WHO. HCQ has got special attention after various advisories are being issued by health authorities to utilize it for the prophylaxis of SARS COV2. Therefore, drug safety evaluation based on its pharmacokinetic & pharmacodynamics parameters & literature rationale for Evidence Based Medicine is required for its justification to be utilize effectively in the COVID19 Pandemic. We have reviewed literature of HCQ antiviral properties, ADRs, Drug Interactions on PubMed, Google Scholar, CDC database *etc*. Based on the gathered evidences we have performed Evidence Based Medicine (EBM) Risk vs. Benefit Analysis to justify HCQ utilization in SARS COV 2 through U.S. Preventive Services Task Force guidelines. Adverse drug reactions & toxicities such as retinopathy & cardiotoxicity due to HCQ are dose dependent and preventable in nature. HCQ has a potency to combat the disease. Further confirmations are awaited by more clinical trials and their meta-analysis results. It has proven to be effective in inhibiting the viral entry into the cell membrane & decreasing the viral duration of SARS COV 2 in cell culture as well in RCT. In this hour of great disaster where no other safe option appears to be much effective, we conclude that HCQ prophylactic and therapeutic benefits against COVID19 epidemic outweighs the potential risks of adverse drug reactions, which are preventable in nature. For desired therapeutic response, careful monitoring is advised.

INTRODUCTION: Originated from China, Severe Acute Respiratory Syndrome Corona Virus 2 (SARS COV 2) infection is a global Health emergency. There is no known vaccine or specific drug is available for this viral infection.

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Health authorities are officially declaring Hydroxychloroquine (HCQ) as an armor against COVID-19 (coronavirus disease 2019) [1, 2]. Recently various studies have suggested HCQ as a potential drug to reduce the viral load and duration of COVID19 [3]. HCQ was first discovered during WWII, approved in 1955 for its antimalarial action. Since then, it has been approved for various autoimmune diseases such as SLE (Systemic Lupus Erythematous) & RA (Rheumatoid Arthritis) [4]. World Health Organization has placed HCQ in essential drug list [5].

Since its endorsement as an "Anti-Corona" drug, the self-medication practice has tends to be increased. Due to which reports of HCQ overdosing from Nigeria & USA has alerted the drug regulation stakeholders [6] to prevent any malpractice, Indian Drug authorities have banned the dispensing of HCQ without prescription [7].

So far, the clinical studies which are demonstrating HCQ effectiveness against SARS COV 2 have infeasible data to justify the drug safety in patients across the globe and many other studies are under pipeline [1]. Therefore it is an ethical obligation for healthcare researchers to update the authorities about drug safety review of hydroxychloroquine.

Antiviral Mechanism of HCQ: Hydroxychloroquine raise the pH in endosomes & at the surface of the cell membrane, this inhibits virus (like SARS COV 2) fusion into host cell membrane. HCQ also inhibits nucleic acid replication, new virus particle transport, virus assembly, virus release. SARS COV 2 target ACE2 (Angiotensin Converting Enzyme) for entry into the host cell, which is also inhibited by HCQ through the process of terminal glycosylation [8].

In some cases, patient's immune response to the SARS-CoV-2 virus increases cytokines Interleukin (IL-6 & IL-10). This cytokines increased further leads to multi-organ failure. HCQ is a proven immunomodulatory. As a potent DMARD (Disease Modifying Anti Rheumatoid Drugs) it exerts its effects through the inhibition of endocytosis (receptor-mediated) which alters various cell mechanisms like, Toll-like receptor (TLR) signaling, antigen presentation & post-transcriptional modification of proteins leading to significant reduction in the cytokines production. Therefore HCQ in SARS COV 2 can suppress the increase of immune response to prevent further complications [9, 10].

CQ (Chloroquine) and HCQ both raise the pH in host cell's intracellular organelles (like lysosomes & endosomes) which are membrane fusion targets for the virus. CQ has additional mechanism to inhibit virus entry by altering glycosylation of ACE2 receptor and spike protein. *In-vitro* studies have shown that, unlike CQ, HCQ not only inhibits the virus entry step into the host cell but also act upon post-entry stage as well in SARS COV 2. Inhibition of virus entry was studied while focusing on co-localization of virions. The immunofluorescence analysis (IFA) results shows CQ and HCQ to be effectively block the migration of SARS COV 2 from early endosomes (EEs) to endolysosomes (ELs). This transportation from EEs to ELs is the key requirement of virus to release its viral genome [11].

HCQ Pharmacokinetics & Pharmacodynamics: As an antimalarial HCQ inhibits polymerization of Heme molecules by targeting the acid vesicles in malarial parasite. Its antiviral properties are based on increase in pH at the cellular membrane surface, thus inhibition of viral infusion into cell occurs. Due to increase in C-peptide secretion & reduction in insulin clearance, HCQ also possess hypoglycemic activity. Arachidonic acid release inhibits platelets aggregation, makes HCQ a potent anti-thrombolytic agent too [4, 8, 12]. HCQ pharmacodynamics properties are summarized in **Table 1**.

TABLE 1: HCQ THERAPEUTIC PROPERTIES AGAINST VARIOUS DISEASES[4, 8, 12, 13-20]

Effect	Disease	Dose	Mechanism
Antimalarial	Malaria	400 mg/ day	As an antimalarial HCQ inhibits polymerization of heme molecules by targeting the acid vesicles in malarial parasite
Antimicrobial	Chronic Q fever, endocarditis	200 mg TDS	Alkalization of phagosome
Anti-viral	Influenza	400 mg/ day	Prevent the entry of adenovirus and influenza into cells by inhibition of endocytosis (receptor-mediated)
	Corona Virus	200 mg TDS	HCQ increase in pH at the cellular membrane surface, thus inhibition of viral infusion into cell occurs
	Retrovirus (HIV)	6.5 mg per kg per day	Inhibition of virus replication
Anti-Inflammatory & Immunomodulatory	SLE and RA	200-400 mg/ day and 400-600 mg/ day	Inhibition of endocytosis (receptor-mediated) which alters various cell mechanisms like, Toll-like receptor (TLR) signaling, antigen presentation & post-transcriptional modification

			of proteins leading to significant reduction in the cytokines production
Anticancer	Solid tumors	600 mg BD	Activation of caspase-3
Antithrombotic	Prevention of thromboembolism in immobilized patients	400 mg OD	Arachidonic acid release inhibits the platelets aggregation
Antidiabetic	Hypoglycemic in diabetes mellitus	400 mg OD	HCQ inhibits the degradation of insulin that reduces the clearance and enhance the sensitivity of insulin

OD (Once a day), BD (Both times a day), TDS (Thrice a day), HIV (HumanImmune deficiency Virus), TLR (Toll like Receptor), SLE (Systemic Lupus Erythematous), RA (Rheumatoid Arthritis)

HCQ is well absorbed on oral administration from the stomach & small intestine, maximum concentration of the drug in blood 129.6 ng/ml attains in maximum 3.26 hours' time, whereas in plasma, maximum concentration is 50.3 ng/ml attains in maximum 3.74 hours. HCQ shows a good bioavailability of 67%-74% on oral administration and an adequate protein binding in plasma of 50%. Metabolism is take place in liver by CYP3A4. The active metabolite of HCQ is Desethylhydroxy-chloroquine. HCQ possess a very long half time of 22 days in blood & 123 days in plasma. Complete excretion takes plays in almost 6 months. It is eliminated majorly through renal route (40-65%) out which 20% excreted out in unchanged form. Rest of elimination takes place *via* skin & feces [12]. Tabular description of HCQ pharmacokinetic properties is presented in **Table 2**.

TABLE 2: HCQ PHARMACOKINETICS PROPERTIES [8, 12]

HCQ Pharmacokinetics	
Absorption	200mg oral dose:-
	Blood: C-max 129.6ng/mL in T-max 3.26h
	Plasma: C-max of 50.3ng/mL in T-max3.74h
Bioavailability	67-74%
Volume of distribution	Blood -5522L
	Plasma - 44,257L
Protein binding	50% protein bound in plasma.
Metabolism	HCQ is metabolized by CYP3A4.
	Active metabolite: desethylhydroxychloroquine,
	Inactive metabolites: bidesethylchloroquine & desethylchloroquine.
Route of elimination	40-50% renal + 2 5% skin + 24-25% feces
Half life	Blood - 537 hours or 22.4 days,
	Plasma- 2963 hours or 123.5 days

Mg (Milligram), C-max (Maximum Concentration), T-max (Maximum Time), CYP3A4 (Cytochrome P450 3A4)

HCQ Toxicity Consideration: HCQ is considered to be safer than Chloroquine (CQ). An extra hydroxyl ring differs Hydroxychloroquine from chloroquine, although both the drugs exhibit almost similar chemical properties, therefore, for the toxicity evaluation of HCQ, chloroquine should also be included. These antimalarial are contraindicated to use in patients with history of retinopathy and in patients with known hypersensitivity to quinines. Although, the safety margin of CQ is narrow & a 30 mg/kg single dose is lethal, it is considered as a safe drug, when taken in therapeutic doses [21]. Precautions such as hemolysis monitoring is required when prescribed to patients with glucose-6-phosphatedehydrogenase (G6PD) deficiency. In most cases, acute chloroquine toxicity occurs when rapid high doses are administered *via* parenteral routes. Primarily, toxicity affects central nervous system (CNS) and the cardiovascular system. CNS manifestations like confusion, convulsions, and coma whereas the cardiovascular manifestations like reduced myocardial function, vasodilatation, hypotension, arrhythmias & eventual cardiac arrest could also be possible. A high HCQ cumulative dose of more than 1 g of base per kilogram body weight can results into irreversible retinopathy and ototoxicity [4, 22-24]. HCQ alter the recycling of all-trans-retinol as it act upon organic anion transporting polypeptide 1A2 (OATP1A2) [25]. This occurs mainly due to accumulation of drug in melanin-rich tissues which could be preventable by adequate therapeutic dosing.

Studies have shown that HCQ can cross placental barrier as well as could be secreted through breast milk [26]. Although significant fetal toxicity or congenital abnormalities are not documented with the use of Hydroxychloroquine in pregnancy, [27, 28] proper screening and routine monitoring is advisable. Therefore, HCQ utilization in pregnant patients can also be recommended.

Toxicity & Prognosis: Hydroxychloroquine alter the lysosomal enzymes activity, which leads to impairment in intra-cellular degradation processes & the pathologic metabolic products accumulate in the host cell. The alpha-galactosidase A (GLA) is involved in the pathophysiology of hydroxy-chloroquine cardiotoxicity. The deficiency of alpha-galactosidase a (lysosomal enzyme) is seen in Fabry disease. Fabry disease is a genetic storage disorder considered as evidence of HCQ related cardiotoxicity. Along with Fabry disease other cardio abnormalities such as valvular dysfunction, left ventricular hypertrophy, microvascular angina, and other conduction abnormalities may also present in cardiotoxicity individuals [29, 30].

Overdose patients may experience headache, visual disturbances, drowsiness, convulsions, hypo-kalemia, cardiovascular collapse, rhythm and conduction disorders like QT prolongation, torsades de pointes, ventricular tachycardia, and ventricular fibrillation. Overdosing complications include cardiac and respiratory failure. Immediate gastric lavage followed by activated charcoal (dose 5 times the HCQ dose) is recommended in HCQ overdosing or HCQ poisoning cases. Diazepam via parenteral route can also be administered to manage cardiotoxicity. To promote urinary excretion ammonium chloride could be utilized. Dilution of drug serum concentrations should be achieved through transfusion of fluids. Further, toxicity monitoring of patient is recommended [12].

TABLE 3: SEVERE HCQ COMPLICATIONS [25-29]

	Retina Toxicity	Cardio Toxicity
Mechanism	Mechanism behind Retina-toxicity: HCQ inhibit autophagy which increase lysosomal pH of retinal pigment epithelial cells that stops auto-phagosomes attachment with lysosomes. This increase lipofuscin level in retinal pigment epithelial cells that is associated with photoreceptor degradation. HCQ, affects the visual cycle through retinal pigment epithelial cells all-trans-retinol recycling process by inhibiting the organic anion transporting polypeptide (OATP) 1A2 activity.	HCQ cardio toxicity as explained by chatre et al is of following 2 types ACUTE TOXICITY occurs due to high-dose administration or self-ingestion which block the sodium, calcium and potassium (hERG) channels. This increases the QT interval that leads to ventricular rhythm trouble, negative inotropic effect. Peripheral vasodilatation occurs due to blockade of alpha as the secretion of histamine stops. QRS prolongation leads to Atrioventricular Block. CUMULATIVE TOXICITY occurs in Long-term therapy or a high cumulative dose leading to drug accumulation. Increased lysosomal pH which Impair the lysosomal protein degradation also leads to Accumulation of ineffective auto-phagosomes, phospholipids & glycogens with myocyte vacuolization.
Dose	Cumulative Dose- 6.5 mg/kg over 5 years	Poisoning Dose- 4g to 14 g (cases reported) Cumulative Dose- 1235g over 7 years (case reported of 65 g over 1 year)
Complications	Mild stage retinopathy (Mild damage in the parafoveal zone), Moderate stage retinopathy (parafoveal ring of damage of 50–100% and parafoveal retina thinning), Severe stage (irreversible bull's-eye retinopathy with retinal pigment epithelium (RPE) damage). Other complications (loss of cone structure and foveal thickness)	Cardiac arrhythmias, Cardiac conduction disorders like AVB unknown, Complete AVB, First- or second-degree. Other conduction disorders (RBBB, LBBB). Cardiac valve disorders, Pulmonary artery wall hypertrophy, Right & left ventricular failures, Coronary artery disorders, MI & related disorders, HF, Ventricular hypokinesia, diastolic dysfunction, biventricular hypertrophy, elevated troponin, left ventricular ejection fraction.
Symptoms	Corneal changes (edema and opacities), visual disturbances, photophobia color vision abnormalities decreased dark adaptation, halo around lights & blurred vision.	Arrhythmias, torsade de pointes, vasodilation, hypotension, suppressed myocardial function, QT interval prolongation, cardiomyopathy, cardiac failure & eventual cardiac arrest
Prognosis	Poor	Poor
Risk Factors	High dose, longer duration, co-morbidity	High dose, longer duration, co-morbidity, self-poisoning
Prevention	Body weight calculated dose with routine investigations	Body weight calculated dose with routine investigations

hERG (human Ether-à-go-go-Related Gene), mg (milligram), kg (Kilogram), MI (Myocardial Infarction), RPE (Retinal Pigment Epithelium), RBBB (Right Bundle Branch Block), LBBB (Left Bundle Branch Block), HF (Heart Failure), AVB (Atrioventricular Block)

HCQ withdrawal after cardiac complications may not bring complete recovery of heart functioning. Recovery from HCQ induced atrioventricular block is not documented. Some patients undergo irreversible damage that may require implantation of pacemaker or heart transplant. Fatality due to HCQ induced cardiotoxicity is also reported in several patients, mostly short after the diagnosis [29, 31, 32]. Severe HCQ complications are tabulated in **Table 3**.

HCQ Adverse Drug Reactions: HCQ is a relatively safe drug. Specific drug reactions like aplastic anemia, agranulocytosis, hemolysis (in patients with G-6-phosphate dehydrogenase deficiency), thrombocytopenia, leukopenia & Exacerbation of psoriasis could be prevented with proper screening of patients before initiation of therapy. Some common ADRs associated with HCQ use are nausea, vomiting, headache, abdominal cramping, irritability, ataxia, dizziness, nervousness, emotional changes, lassitude, nightmares, psychosis, seizure, vertigo, anorexia, diarrhea, abnormal liver function, pigmentation changes (skin and mucosal; black-blue color), rash, pruritus and tinnitus are also well documented. HCQ related major adverse drug reactions are tabulated in **Table 4**.

Complicated adverse drug effects of HCQ therapy are seen mainly in drug accumulation cases which leads to Cardiopathy & Retinopathy. Cardiac changes such as arrhythmias, torsade de pointes, vasodilation, hypotension, suppressed myocardial function, QT interval prolongation, cardio-myopathy, cardiac failure & eventual cardiac arrest may be present. In retinopathy patient may experience corneal changes (edema and opacities), visual disturbances, photophobia color vision abnormalities decreased dark adaptation, halo around lights & blurred vision [12].

TABLE 4: VARIOUS ADVERSE DRUG REACTIONS ASSOCIATED WITH HYDROXYCHLOROQUINE [12]

S. no.	System Organ specific disorders	Adverse Drug Reactions
1	Connective tissue & Musculoskeletal disorders	Skeletal muscle myopathy or neuro-myopathy, depression of tendon reflexes, sensorimotor disorder, abnormal nerve conduction, progressive weakness and atrophy of proximal muscles.
2	Psychiatric disorders	Irritability, nervousness, nightmares, psychosis, Irritability, emotional imbalance.
3	Neuro-otology disorders	Tinnitus, nystagmus, vertigo, deafness.
4	Nervous system disorders	Seizure, headache, ataxia, dizziness, and extrapyramidal disorders such as dyskinesia, dystonia and tremors.
5	Cardiac system disorders	QT interval prolongation, ventricular arrhythmias & torsade de pointes, cardiomyopathy, cardiac failure.
6	Retina disorders	Photophobia, blurred vision, decreased dark adaptation, bull's eye appearance(Irreversible retinopathy with retinal pigmentation changes), color vision abnormalities, visual disturbances (visual acuity), and visual field defects (paracentral scotomas), maculopathies (macular degeneration) corneal changes (edema and opacities).
7	Hepatic disorders	Acute hepatic failure, abnormal Liver function tests.
8	GIT & general disorders	Abdominal pain, diarrhea, nausea & vomiting.
9	Metabolic disorders	Hypoglycemia, porphyria, appetite decreased, weight decreased.
10	Skin disorders	Skin rashes and photosensitivity, pruritus, exfoliate-dermatitis, AGEP, Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation disorders in skin & mucous membranes, DRESS syndrome, Dermatitis bullous eruptions including erythema multiform, *etc*.
11	Others	Angioedema, urticaria, bronchospasm & fatigue.

GIT (Gastro Intestinal Tract), AGEP (Acute Generalized Exanthematous Pustulosis), DRESS Syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms)

Contraindications & Precautions: HCQ should not be prescribed to individuals with known history of hypersensitivity to amino-quinolones. HCQ should be used with precaution in co-morbid conditions including GIT, neurological, hematological, hepatic& renal disorders and also in alcoholic patients. HCQ has complication warning of retinal damage, cardiac function impairment, exacerbation of psoriasis, myopathy & neuropathy, hypoglycemia and hemolysis in G6PD deficiency [12]. Safety advisory related to the use of Oral HCQ is represented in **Table 5**.

TABLE 5: ORAL HCQ SAFETY ADVISORY [12]

Contraindication	Precautions	Warnings
Contraindicated in patients with known hypersensitivity to 4-amino-quinolone compounds	Gastrointestinal disorders	Irreversible retinal damage
	Neurological disorders	Fatal Cardiac effects, including Cardiomyopathy and QT prolongation
	Blood disorders	Worsening of psoriasis and porphyria
	Sensitivity to quinine	Proximal Myopathy and Neuropathy
	Hepatic/Renal Disease	Hypoglycemia
	Alcoholism or conjunction with hepatotoxic drugs	Hemolysis in G-6-PD deficiency

G6PD (Glucose 6 Phosphate Dehydrogenase Deficiency)

HCQ Drug Interactions: HCQ should be used with other concomitant drugs only after screening their drug interaction profiles. There are many common drugs such as digoxin, insulin, cyclosporine, Antacids, ampicillin *etc*., which have the potential to antagonize or synergies each other pharmacological & therapeutic response if administered together 12. Drug with established QT prolongation activity have potential to bring lethal results when used as concomitant with HCQ. Antagonistic & synergistic drug-drug interactions are described in **Table 6**.

TABLE 6: HCQ/CQ DRUG INTERACTIONS SUMMARY [12]

Action	Concomitant Agents	Effect
Antagonistic	Antiepileptic	Antiepileptic drugs response alters.
	Antacids and kaolin	Chloroquine absorption reduces
	Praziquantel	Praziquantel bioavailability reduces
	Cimetidine	Metabolism of chloroquine inhibited by cimetidine
	Ampicillin	Ampicillin bioavailability decreases
Synergistic	Cyclosporine	Cyclosporine plasma level increases
	Hypoglycemic drugs	Antidiabetic drug's hypoglycemic activity increases.
	Digoxin	Digoxin serum levels increases
	Drugs that prolong QT interval	QT prolongation drugs response increases

HCQ in Pregnancy & Lactating Mothers: From the perspective of pregnancy, HCQ utilization is considered to be safe. Studies have shown that HCQ can cross placental barrier as well as could be secreted through breast milk [26]. HCQ utilization safety in pregnancy has already been evaluated in several studies. Auto immune diseased pregnant patients treated with HCQ have not experienced any complication such as pre-mature delivery or decreased numbers of live births, spontaneous abortion, any congenital abnormalities or significant fetal toxicity or fetal death during pregnancy. Although, HCQ can cross the placenta, it have the potential to cause significant abnormalities in fetal development therefore proper screening and routine monitoring is advisable. Hence, HCQ can be utilized in pregnant patients. As infants are extremely sensitive to 4-aminoquinolines toxic effects, therefore precautions should be taken in nursing mothers too as HCQ can be excreted in breast milk [4, 12, 26, 33- 34].

HCQ Evidence-Based Medicine & Risk *vs.* Benefit Evaluation: The explicit, conscientious, judicious & reasonable use of best available evidence in taking decisions for individual patient care is termed as Evidence-based medicine (EBM). To practice EBM, updated skills along with clinical expertise, including regular information retrieval from credible resources, and the application of available scientific evidences in evaluation of literature are required. EBM is lifelong continuous, problem-oriented learning practice. Diagnosis, prognosis, selection of therapy and health care issues are analyzed on the basis of patient oriented care through systematic evaluation clinically relevant information [35].

Individual clinical practice: HCPs such as physicians, pulmonologist who have updated knowledge about HCQ and have treated SARS patients should consider this drug for their patients. They should also evaluate themselves the available recent evidences of HCQ utilization in COVID19 outbreak. HCPs should rank the clinical evidences on the basis of their freedom and relevancy. RCTs are considered as of gold standard in clinical judgment as compared to a case report. Health professionals must focus on HCQ risks such as

toxicity, ADRs (dose dependent & preventable in nature) versus benefits like early recovery in young patients and reduction in SARS progression in geriatric and co-morbid conditions as majority of mortality is seen in later group of patients.

Evidence-based medicine has categorized various clinical evidences based on their credibility in medical research and ranks them according to help the Health care professionals in decision making in risk vs. benefit analysis. Here we have performed EBM analysis based on the best available evidences of HCQ prophylaxis in SARS COV 2 as on April 2020, so far, to make judgment weather to or not consider this drug against corona virus. HCQ Utilization Risk *vs.* Benefit Analysis based on Guyatt *et al*., grading recommendation & level of evidence provided by US Preventive Services Task Force is represented in **Table 7**.

TABLE 7: HCQ UTILIZATION RISK *vs.* BENEFIT ANALYSIS BASED ON GUYATT *et al.* GRADING RECOMMENDATION & LEVEL OF EVIDENCE PROVIDED BY US PREVENTIVE SERVICES TASK FORCE [36, 37, 38, 39]

Level	EBM Prerequisite clinical evidences	Benefit Vs Risk and Burdens	HCQ Evidences in Prophylaxis of SARS COV2	Implications
I	Evidence obtained from at-least one properly conducted RCT	Benefits clearly outweigh risk and burdens or vice versa	√	Strong recommendation, can apply to most patients in most circumstances without reservation. [3]
II 1	Evidence obtained from well-designed controlled trials without randomization	Weak recommendation, best action may differ depending on circumstances or patients' or societal values	×	Clinical data without randomization is not available so far in open access therefore benefits closely balanced with risks and burden
II 2	Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one center or research group	Weak recommendation, best action may differ depending on circumstances or patients' or societal values	×	Clinical data from well-designed cohort or case-control analytic studies is not available so far open access therefore benefits closely balanced with risks and burden
II 3	Evidence obtained from multiple time series with or without the intervention.	Very weak recommendations; other alternatives may be equally reasonable	×	Clinical data from multiple time series is not available so far in open access therefore benefits closely balanced with risks and burden
III	Opinions of respected authorities, based on clinical experience descriptive studies and case reports or reports of expert committees	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	√	Strong recommendation but may change when higher quality evidence becomes available. [1]

RCT (Randomized Controlled Trial)

U.S. Preventive Services Task Force risk *vs*. benefit analysis model when employed to evaluate current situation indicates that HCQ has fair scientific evidence which suggests the therapeutic benefit outweighs the potential risks of adverse drug reactions, which are preventable in nature. Therefore health care professionals should consider the drug for the prophylaxis of SARS COV 2.

DISCUSSION: In current scenario, COVID-19 pandemic has affected almost every human being on the planet, directly or indirectly. SARS COV 2 is global threat. So far lakhs of people across the globe are already died in almost every corner of the world and many lives are at risk. In-spite of all the measures taken by authorities from quarantine of suspected individuals to lockdown of entire country, has not proven to be effective in establishing the trust among the public. COVID-19 and other recent outbreaks are much different from previous century ones, people today are more aware as technology has made them updated about all activities, across the globe. Everybody is hoping for either a cure or effective treatment to fight with this virus. So far, by this day there is no known treatment options available to HCPs rather than supportive care. Research is going on towards vaccines as well as discovery of novel therapeutics against SARS COV2 [37].

Antiviral drug development has basic concerns such as pharmacological action & therapeutic response of drug along with Risk *vs*. Benefit assessment. Antiviral targeting a pandemic virus also focus on the drug availability to a larger population in short period of time. A vaccine approval or a novel drug approval is a time consuming process that passes through strict protocols for public safety. Repositioning existing drugs with established safety profiles is a much better option in this situation. HCQ has been better known for its safety in humans as compare to its subsequent chloroquine. HCQ antiviral potency in SARS COV 2 has both *in-vitro* as well *in-vivo* base. [3, 11]

Many trials are under pipeline to evaluate HCQ efficacy in various population. In this study, we have evaluated HCQ's pharmacological parameters & EBM analysis to suggest its use as a potential prophylactic antiviral drug.

Due to several factors like large scale production, stock availability, low cost *etc*. HCQ is currently the best option with HCPs as efficacy & safety is established and ADRs are dose dependent, hence preventable.

CONCLUSION: HCQ is a relatively safe drug used for treating many medical conditions, since a very long time. The high doses, prolonged duration of treatment and co-morbidity (such as renal impairment) that could result in drug accumulation may bring toxic consequences. HCQ has a potency to combat the disease. Further confirmations are awaited by more clinical trials and their meta-analysis results. It has proven to be effective in inhibiting the viral entry into the cell membrane & decreasing the viral duration of SARS COV 2 in cell culture as well in RCT. In this hour of great disaster where no other safe option appears to be much effective, we conclude that HCQ prophylactic and therapeutic benefits against COVID 19 pandemic outweighs the potential risks of adverse drug reactions, which are preventable in nature. For desired therapeutic response, careful monitoring is advised.

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