Review Protocol

The aim of our project is to assess the efficacy and safety of hydroxychloroquine (HCQ) for the (1) treatment and (2) prevention of COVID-19 disease using data from randomized controlled trials.

Data sources and search strategy:

The literature will be searched by a medical librarian for the concepts of randomized controlled trials of chloroquine or hydroxychloroquine and COVID-19. Additional searches will be performed in the Medrxiv.org and Research Square preprint servers for eligible RCTs.

Inclusion and exclusion criteria:

We will include the following RCTs in our systematic review and meta-analysis:

1- Open label or double blinded RCTs that assessed the efficacy and safety of hydroxychloroquine therapy in comparison to placebo or standard care (SOC) in hospitalized patients with COVID-19 disease.

2- Open label or double blinded RCTs that assessed the efficacy and safety of hydroxychloroquine therapy in comparison to placebo or standard care (SOC) in outpatients with COVID-19 disease.

3- Open label or double blinded RCTs that assessed the efficacy and safety of hydroxychloroquine therapy in comparison to placebo in the prevention of COVID-19 disease among individuals with high risk exposure.

4- Studies with less than 30 patients will be excluded.

5- Studies with combination therapies that did not include hydroxychloroquine alone will be excluded.

Data Collection

Two reviewers will independently identify eligible studies and extract the data into a pre-specified data collection form. Discrepancies will be resolved with a third reviewer. Data will be collected on the following prespecified outcomes:

The treatment RCTs

1- Mortality,

2- viral clearance,

3- disease progression,

4- symptom resolution and clinical recovery,

5- need for mechanical ventilation,

6- hospital length of stay, and

7- requirement for hospitalization (outpatient trials).

The prevention RCTs.

1- Risk of acquiring COVID-19 infection in individuals with high-risk exposure for the

Safety outcomes

1. Arrhythmias,
2. elevated liver enzymes,
3. gastrointestinal adverse events (diarrhea, vomiting),
4. neurologic adverse events (dizziness, fatigue, irritability),
5. headaches,
6. visual symptoms and

7. rashes.

Assessment of methodological quality (risk of bias):

Two reviewers will independently assess the risk of bias for each study using the Cochrane risk-of-bias tool for randomized trials (RoB 2).

Assessment of the certainty of evidence:

Certainty of evidence for each outcome will be assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. This method evaluates the certainty of evidence by assessing the following domains: Limitations, indirectness, inconsistency, imprecision, and publication bias.

Statistical analysis

All statistical analyses will be performed using Review Manager 5.4.The efficacy outcomes of interest in this review (in the treatment RCTs) and the incidence of infection in patients with high risk exposure (in the prevention RCTs) and the safety outcomes will be pooled using the Mantel-Haenszel method for dichotomous data. Fixed and random-effects models will be used depending on statistical heterogeneity. Subgroup analyses to assess the safety outcomes will be restricted only to patients enrolled in the double blinded RCTs. We will pool RD and 95% CI when studies had zero events and use RD to calculate number needed to harm (NNH) and 95% CI for each adverse event. We will construct funnel plots to assess for asymmetry and publication bias.