THE ROLE OF CHLOROQUINE AND HYDROXYCHLOROQUINE IN PROPHYLAXIS OF COVID-19: A LITERATURE REVIEW

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ABSTRACT

Background: A pandemic potential Covid-19 spread rapidly worldwide. Ministry of Health, Republic Indonesia recommended one of the Covid-19 treatments with combination of hydroxychloroquine/chloroquine and azithromycin. However, the effectiveness and safety of antimalaria regime remain debating topic. This study aimed to investigate the role of chloroquine and hydroxychloroquine in prophylaxis of Covid-19.

Subjects and Method: A systematic review was conducted by searching from PubMed, SpringerLink, and Cochrane Library databases. The keywords were “prophylaxis”, “chloroquine” OR “hydroxychloroquine” “SARS-CoV-2” OR “Covid-19”. The inclusion criteria were phase IIb clinical trials, double masking, comparative observational studies, open access articles published until August 2020. The exclusion criteria were inaccessible and duplicate articles. The quality of selected articles was critically appraised. The data were reported by PRISMA flow chart.

Results: Three articles out of 117 articles met the criteria inclusion. The findings showed that hydroxychloroquine could not prevent Covid-19 compatible disease or confirmed infections when used as post-exposure prophylaxis. High dose chloroquine was not recommended for critically ill COVID-19 patients because of its potential side effects, especially when administered with azithromycin and oseltamivir. Covid-19 patients with the need for oxygenation were not suggested to use hydroxychloroquine.

Conclusion: There is scarce evidence to support prophylaxis and treatment effects of chloroquine or hydroxychloroquine in COVID-19 patients. Further research on the safety and use of chloroquine or hydroxychloroquine is required in the management of Covid-19.

Keywords: prophylaxis, Chloroquine, Hydroxychloroquine, SARS-CoV-2, Covid-19

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BACKGROUND

The most important thing in human life is health. Human health is recently facing a pandemic of the COVID-19 disease caused by the Coronavirus (Oktavia, 2020). There are at least two Coronavirus types that cause severe symptoms such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Coronavirus Disease 2019 (COVID-19) is a new disease that has never been previously identified in humans. The virus that causes COVID-19 is called SARS-CoV-2. Research showed that

SARS was transmitted from Civet cats to humans. Meanwhile, the animal that is the source of transmission of COVID-19 is still unknown (Ministry of Health RI, 2020).

Common symptoms include symptoms of acute respiratory distress such as fever, cough, and shortness of breath. The incubation period is 5-6 days on average, and the longest is 14 days. In cases of severe COVID-19 can cause pneumonia, acute respiratory syndrome, kidney failure, and even death. The clinical symptoms reported in the majority of cases were fever, some cases had difficulty breathing, and X-rays showed ex-

tensive pneumonia infiltrates in both lungs (Ministry of Health RI, 2020). Severe complications such as hypoxemia, ARDS (Acute Respiratory Distress Syndrome), arrhythmias, shock, and acute kidney injury had been reported among COVID-19 patients (Huang et al., 2020; Chen et al., 2020).

A study among 99 patients found that approximately 17% of patients had ARDS, and 11% died of organ failure (Chen et al., 2020). The average duration from the first symptom to ARDS is 8 days (Wang et al., 2020). The effort to control the spread of COVID-19 by carrying out isolation quarantine through screening and diagnostic tools. WHO had released guidelines for monitoring COVID-19 cases on January 31, 2020 (WHO, 2020). For someone who meets the criteria, which recommends going for the first screening. If a negative result is found, the sample should be sent to a reference laboratory.

WHO had put forward a case definition of suspected COVID-19 as people (a) with acute respiratory infection (history of fever and cough requiring hospitalization) and without other etiologies explaining clinical presentation and travel history to or places in China during 14 days before the onset of symptoms; or (b) a patient with acute respiratory illness and at least one of the following during the 14 days before the onset of symptoms: contact with a confirmed or probable case of SARS-CoV-2 infection or work in a health care facility where a patient confirmed with acute respiratory disease or probable SARS-CoV-2 is being treated (WHO, 2020). For patients who met the diagnostic criteria for SARS-CoV testing, the CDC (Centers for Disease Control) recommended collecting nasopharyngeal and oropharyngeal swab specimens, if possible, sputum, tracheal aspiration, or bronchoalveolar lavage (CDC, 2020).

The uncertain weather and incubation period make it difficult to make an early diagnosis and start treatment on time (Lee et al., 2020; Cao et al., 2020). To contain the spread of SARS-CoV among community members, the CDC and WHO implemented strict infection control measures (Hoffman et al., 2020; Zhou et al., 2020).

According to an investigation by To et al. (2020), patients with SARS-CoV infection had the highest viral load which had peaked at the time of hospitalization, early use of potent antiviral drugs may be of benefit in controlling the severity of COVID-19 (Liu et al., 2020). Here, the roles of several drugs, including antiviral agents, antibiotics, anti-inflammatory, and antimalarial agents, were reviewed to explore their efficacy in fighting SARS-CoV-2. Chloroquine antimalarial agent, chloroquine itself, is often used clinically to treat malaria and connective tissue diseases (Lee et al., 2019). Due to the lack of a cure for COVID-19, the disease is spreading rapidly, and the death rate is relatively high.

The use of the antimalarial drug hydroxychloroquine as a treatment for Covid-19 patients has been licensed by the FDA (BBC News, 2020). There are currently no drugs directly active against SARS-CoV-2; however, several antivirals and antimalarials have emerged as potential therapies. Current guidelines recommend combination treatment with hydroxychloroquine/azithromycin or chloroquine. Remdesivir and convalescent plasma may be considered in critically ill patients with respiratory failure. However, access to this therapy may be limited (CEBM, 2009). No drug has been validated to significantly affect the clinical care of COVID-19 patients in large-scale studies (Chen et al., 2020; Wang et al., 2020).

Chloroquine and its derivatives hydroxychloroquine had been used for generations to treat malaria. However, the drug may have activity against SARS-CoV 1 and SARS-

CoV 2 in vitro. Research conducted in 2005 found that the ability of Chloroquine to increase endosomal pH so that it can inhibit the virus replication process and is effective in reducing the spread of infection to other host cells (CDC, 2020; Vincent et al., 2020). Chloroquine also has immunomodulatory effects through suppressing the release of Tumor Necrosis Factor- and alpha-6, which help prevent cytokine storms that lead to rapid deterioration in patients with COVID-19 (WHO, 2020). Besides, chloroquine has shown effectiveness in treating pneumonia associated with COVID-19 in a multicenter clinical trial with >100 patients in China (Gao et al., 2020). Subsequent studies found that hydroxychloroquine increased potency and a more tolerable safety profile than chloroquine (Yao et al., 2020).

In this new non-randomized clinical trial, 14 patients were treated with hydroxychloroquine alone, and 6 patients were treated with a combination of hydroxychloroquine and azithromycin. A substantial decrease in viral load faster viral and elimination saw in patients treated with the combination of hydroxychloroquine and azithromycin. However, most of the patients treated with hydroxychloroquine alone showed upper or lower respiratory tract infection (Gautret et al., 2020).

Given the broad accessibility of antimalarial, compared to antivirals, combination treatment with hydroxychloroquine and azithromycin is recommended for hospitalized patients with moderate to severe COVID-19. The FDA recently granted emergency authorization for hydroxychloroquine to treat COVID-19 infections. Although the FDA has not approved it, its use is permitted to be added in therapy in hospitals (FDA, 2019). As a result, there has been a surge in chloroquine and hydroxychloroquine (The Hill, 2020; ASHP 2020). Several ongoing clinical trials investigate the prophylactic and thera-

peutic effectiveness of these drugs against SARS-CoV-2 (Yao et al., 2020).

However, the regimen antimalarial provides good effectiveness in the management of COVID-19 is still a debate. Further study is needed to provide information for the health workers involved (To et al., 2020). This study aimed to investigate the role of chloroquine and hydroxychloroquine in the prophylaxis of COVID -19.

SUBJECTS AND METHOD

1. Study Design

This study was a systematic review. The articles used in this study were obtained from several databases, including PubMed, Spring link, and the Cochrane Library. The keywords for finding articles were as follows: "Chloroquine", "Hydroxychloroquine", "Coronavirus", "Coronavirus dis-ease", "CO-VID - 19", "SARS - CoV - 2", "Pro-phylaxis", and "therapy".

2. Inclusion Criteria

The articles included in this study were full text articles published in English. The study designs included were randomized controlled trial (RCT) and observational studies. Selected articles are then critically appraised to determine validity and applicability using the relevant criteria from the evidence-based Oxford Center for Medicine.

3. Exclusion Criteria

The study did not include articles not relevant, lack of data, and met exclusion criteria.

4. Data Analysis

The data were reported by PRISMA flow chart.

RESULTS

From the search results online, there were 3 articles selected that met the inclusion and exclusion criteria: 2 studies Randomized, the Controlled Trial by Boulware DR, et al and Borba MGS, et al and 1 Comparative Observational Study by Mahévas et al. After conducting a critical assessment, it was found

that the first, second and third articles were valid. Table 1. Searching strategy using database from PubMed, Springer link, Cochrane Library. Table 1 showed the searching strategy using database from PubMed, Springer link, Cochrane Library. The results of the summary source presented in Table 2. Figure 1 showed the PRISMA flow chart of the articles reviewed.

DISCUSSION

The results of the analysis of 3 selected articles stated that the use of chloroquine or hydroxychloroquine in sufferers of COVID-19 did not provide significant improvement, even the administration of a higher dose of chloroquine should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when consumed in conjunction with azithromycin and oseltamivir.

One article stated that giving chloroquine high doses indicate a QTc interval greater than 500 milliseconds. It should be noted that when misused, chloroquine and to a lesser extent, hydroxychloroquine, are highly toxic and can cause dysrhythmias and electrolyte disturbances (Olano et al., 2019).

Another critical study is that toxicity chloroquine has a narrow margin of safety and causes several cardiovascular side effects, such as prolonging the QT interval. Hydroxychloroquine is relatively safer. However, an unrestricted acute over-dose can cause serious toxicity. Besides, this side effect can be increased because the drug does not inhibit viral replication in the cytochrome P-450 system, even in combination with other drugs such as azithromycin, so it is recommended to be evaluated (Cao et al., 2020). In the absence of strong inhibitors in vivo and clinical evidence, it seems too early to recommend chloroquine and hydroxychloroquine as drugs for prophylaxis for COVID-19, in the current pandemic (Cao et al., 2020).

To date, there is scarce evidence to support the efficacy of chloroquine or hydroxychloroquine in treating COVID-19. Considering safety concerns, the use of chloroquine or hydroxychloroquine against people with COVID-19 needs to be thoroughly evaluated.

Table 1. Searching strategy using database from PubMed, Springer link, Cochrane Library

Database	Search strategy	Hit	Selection
PubMed	(Prophylaxis [All Fields] AND Treatment [All Fields] AND ("Chloroquine" [MeSH Terms] AND ("Hydroxychloroquine" [MeSH Terms] AND ("Coronavirus" [MeSH Terms] OR (Coronavirus disease [All Fields] OR (COVID-19[All Fields] OR (SARS - CoV - 2 [All Fields]	32	5
Cochrane Library	Prophylaxis AND treatment of AND Chloroquine AND Hydroxychloroquine AND Coronavirus disease OR COVID-19 OR SARS - CoV - 2	47	6
SpringerLink	(Treatment [All Fields] AND ("Chloroquine" AND ("Hydroxychloroquine" AND ("Coronavirus" OR (Coronavirus disease [All Fields] OR (COVID-19[All Fields] OR (SARS - CoV - 2 [All Fields]	38	5

Figure 1. PRISMA Flow Chart

Table 2. Summary Source

Title	Author (year)/ Country	Study Design	Total Sample	Intervention	Comparison	Outcome
Randomized Testing of Hydroxychloroquine as Prophylaxis Post Exposure to Covid-19	Bo et al., (2020)	RCT	821 participants	Hydroxychloroquine Tablets 200-mg; 800 mg orally once, followed in 6 to 8 hours for 600 mg, then 600 mg once daily for 4 consecutive days	4 tablets placebo once, followed in 6 to 8 hours with 3 tablets, then 3 tablets once daily for 4 consecutive days	<p>Main Results:</p> <ol style="list-style-type: none"> 1. Incidence of COVID19 among those who were asymptomatic at baseline [Time Frame: 14 days] Number of participants on 14 days after registration with active COVID19 disease. 2. Overall change in disease severity for 14 days among those symptomatic at baseline [Time frame: 14 days]. Remeasure the mixed regression model changes in: Visual Analog Scale 0-10 score overall symptom severity ranking score (0 = no symptoms; 10 = most severe) <p>Secondary Outcomes:</p> <ol style="list-style-type: none"> 1. Incidents of Hospitalization [Time Frame: 14 days]. Results are reported as the number of participants in each group requiring hospitalization due to COVID-19 related illnesses. 2. Incidence of Death [Time Frame: 90 days] Results are reported as the number of participants in each group who have expired due to late illness COVID-19. 3. Incident of Confirmed SARS-CoV-2 Detection [Time Frame: 14 days]. Results were reported as the number of participants in each group who had been confirmed as infected with SARS-CoV-2. 4. Incidence of Symptoms Compatible with COVID19 (probable disease) [Time Frame: 90 days]. Results were reported as the number of participants in each group who self-reported symptoms compatible with COVID19 infection. 5. Incidents of Discontinuation or All-Cause Study Drug Withdrawal [Time Frame: 14 days]

						<p>Outcomes are reported as the number of participants in each group who discontinued or withdrew drug use for any reason.</p> <p>6. Overall symptom severity at 5 and 14 days [Time Frame: 5 and 14 days]. Visual Analog Scale 0-10 overall symptom severity rating score (0 = no symptoms; 10 = most severe).</p> <p>7. Ordinal Level Scale COVID-19 Disease Severity at 14 days among those symptomatic at trial entry [Time Frame: 14 days]. Participants will self-report disease severity status as one of the following 3 options; there was no COVID19 disease (score 1), COVID19 disease without hospitalization (score 2), or COVID19 disease with hospitalization or death (score 3). An increased scale score indicates greater disease severity. Results are reported as the percentage of participants who fall into each category per group.</p> <p>Results:</p> <p>821 participants without symptoms. Overall, 87.6% of the participants (719 out of 821) reported high-risk exposure to contacts Covid-19 confirmed. The incidence of novel compatible Covid-19 diseases did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was -2.4 percentage points (95% CI= -7.0 to 2.2; p= 0.350). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs 16.8%), but no serious adverse reactions were reported.</p>
Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive	Mahevas et al., (2020)/ Brazil	RCT	81 participants	Treated with high-dose CQ (ie, 600 mg CQ twice daily for 10 days)	Treated with low-dose CQ (ie, 450 mg twice daily on day 1 and once daily for 4	<p>Main Results:</p> <p>The mortality rate was 39% in the high dose group compared with only 15% in the low dose group. The data presented here refer primarily to safety outcomes and mortality during treatment at day 13.</p>

Therapy for in patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection (SARS-CoV-2): Randomized Clinical Trial					days)	<p>Secondary Results:</p> <p>Status participant clinical, laboratory examination, and electrocardiogram results. Results will be presented on day 28. RNA detection of respiratory viral secretions was carried out on days 0 and 4.</p> <p>Results:</p> <p>Of the predetermined sample sizes of 440 patients, 81 were enrolled (41 [50.6%] to the high dose group and 40 [49.4%] to the low dose group). The enrolled patients had a mean age (SD) of 51.1 (13.9) years, and most (60 [75.3%]) were men. Older age (mean [SD] age, 54.7 [13.7] years vs 47.4 [13.3] years) and more heart disease (5 of 28 [17.9%] vs 0) seen in the high dose group. Viral RNA was detected in 31 of 40 (77.5%) and 31 of 41 (75.6%) patients in the low dose arm. The mortality rates up to day 13 was 39.0% in the high dose group (16 of 41) and 15.0% in the low dose group (6 of 40). The high-dose group showed more instances of a QTc interval greater than 500 milliseconds (7 of 37 [18.9%]) than the low-dose group (4 of 36 [11.1%]).</p>
Clinical efficacy of hydroxychloroquine in patients with Covid-19 pneumonia who require oxygen: observational comparative study using routine care data	Zhou et al., (2020)	Comparative observational studies	181 patients aged 18-80 years with documented coronavirus 2 pneumonia (SARS-CoV-2) with severe acute respiratory syndrome requiring oxygen but not intensive care.	Hydroxychloroquine at a dose of 600 mg/ day within 48 hours of admission to hospital	standard care without hydroxychloroquine	<p>Main Outcome:</p> <p>Survival without transfer to the intensive care unit at day 21.</p> <p>Secondary Outcomes:</p> <p>Overall survival, survival without acute respiratory distress syndrome, weaning off oxygen, and hospital discharge to home or rehabilitation (all on day 21). Analyses were adjusted for confounding factors with inverse probability of weighted treatment.</p> <p>Results:</p> <p>In the main analysis, 84 patients who received hydroxychloroquine within 48 hours of admission to hospital (treatment group) were compared with 89 patients who did not receive hydro-chloroquine</p>

						(control group). Eight additional patients received hydroxychloroquine more than 48 hours after admission. In a weighted analysis, the survival rate without transfer to the intensive care unit on day 21 was 76% in the treatment group and 75% in the control group (weighted hazard ratio 0.9, 95% confidence interval 0.4 to 2.1). Overall survival at day 21 was 89% in the treatment group and 91% in the control group (1.2, 0.4 to 3.3). Survival without acute respiratory distress syndrome at day 21 was 69% in the treatment group compared with 74% in the control group (1.3, 0.7 to 2.6). On day 21, 82% of patients in the treatment group were weaned from oxygen compared with 76% in the control group (risk-weighted ratio 1.1, 95% confidence interval 0.9 to 1.3). Eight patients in the treatment group (10%) underwent electrocardiographic modifications requiring treatment discontinuation
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