Is hydroxychloroquine/chloroquine effective and safe to use as treatment for COVID-19 in children?

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This rapid review summarizes the available evidence on the efficacy and safety of hydroxychloroquine/chloroquine in treating children with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

There is insufficient evidence on the effectivity and safety of chloroquine and hydroxychloroquine to be routinely recommended for use as COVID-19 therapy in children.

- Quinoline-based basic compounds such as chloroquine and hydroxychloroquine, originally manufactured as antimalarials, is being used as anti-inflammatory drugs for various diseases like rheumatoid arthritis and systemic lupus erythematosus.
- In-vitro studies showed that antiviral properties of chloroquine and hydroxychloroquine against SARS-CoV-2 can be attributed to its ability to increase endosomal pH and interference on the terminal glycosylation of ACE-2 receptor thereby blocking viral entry and replication.
- Although hydroxychloroquine is considered to be generally well tolerated, toxicities like retinopathy and dysrhythmias have been reported, hence the recommendation of baseline ophthalmologic and cardiac evaluation and screening.
- At present, there are three low-quality published observational studies (1 case report, 2 case series) on the use of hydroxychloroquine as treatment in children with COVID-19 which showed inconclusive results. Due to lack of proven efficacy and increasing concern of safety, the use of these investigational drugs for COVID-19 treatment must be restricted in the context of formal clinical trials.
- There are currently six ongoing clinical trials on chloroquine and hydroxychloroquine involving children, mostly adolescents 16 years and older, diagnosed with COVID-19.
- WHO and CDC stated that there are no drugs approved for the treatment of COVID-19 and investigational anti-COVID-19 therapeutics should only be used in approved, randomized, controlled trials.
- The Pediatric Infectious Disease Society of the Philippines recommended the use of investigational therapeutic interventions like hydroxychloroquine or chloroquine only for severe or critically-ill children with COVID-19 provided there is proper informed consent.

RESULTS

Characteristics of Included Studies

As of May 16, 2020, there are three published observational studies (1 case report, 2 case series) on the use of hydroxychloroquine as treatment in children with COVID-19. In May 2020, there was a case report about late-onset neonatal sepsis in a patient with Covid-19 hospitalized at Houston, Texas, United States. This 3-week-old male preterm neonate, who was exposed to an untested symptomatic 49-year old female household contact, presented with respiratory symptoms and signs of poor perfusion hence was worked-up for SARS-CoV-2 via nasal swab and was subsequently managed with empiric antibiotics (ampicillin and gentamicin) for sepsis and was intubated. Results of the reverse transcriptase-polymerase-chain-reaction(rtPCR) for COVID-19 became available on the 7th day of admission and was shown to be positive. At this point when COVID-19 was confirmed, there was already clinical improvement with the patient being extubated at day 5 and transferred out of PICU. He was able to complete the 5-day course of hydroxychloroquine and azithromycin and was discharged on the 9th hospital day without oxygen support [22].

A case series was done on 48 children diagnosed with COVID-19 admitted to pediatric intensive care unit (PICU) in North America receiving experimental therapies, most commonly hydroxychloroquine (21 out of 48 patients or 44%) as treatment. Of the 48 children with COVID-19 admitted to participating PICUs, 25 (52%) were male, and the median (range) age was 13 (4.2-16.6) years. They were diagnosed to have COVID-19 infection by polymerase chain reaction from nasal swabs. Most of these children presented with respiratory symptoms (73%) and in a severe (33%) or crtical (35%) condition requiring support via intubation/tracheostomy (38%) and noninvasive ventilation (44%) upon admission. Significant comorbidities were mostly medically complex (40%) including those who had long-term dependence on technical support associated with developmental/genetic abnormalities. Some of patients has immune suppression/malignancy (23%), obesity (15%), diabetes (8%), seizures (6%), congenital heart disease (6%), sickle cell disease (4%), chronic lung disease (4%), and other congenital malformations (4%). Hydroxychloroquine was given either as a single agent (21 out of 48 patients), or in combination with other drugs such as azithromycin. The dose, frequency, and duration of these drugs were not specified. Twenty patients (42%) received no pharmacotherapy aside from supportive care. Outcomes observed include number of patients who died, remain hospitalized and requiring mechanical ventilation, and those discharged. Mortality was documented in two patients, aged 12 and 17 years old with preexisting comorbidities and developing multisystem complications, bringing the case fatality rate at 4.2% at the time of this report. Fifteen patients are still hospitalized, 9 of which are in severe or critical condition and 6 have mild to moderate symptoms. Most of the pediatric patients (31 out of 48 children, 65%) were eventually discharged [23].

Another case series was conducted in 46 children admitted in a medical center in New York, United States and was laboratory-confirmed to have SARS-CoV-2 infection. These patients were clinically managed given empiric antibiotics, respiratory support, and some investigational drugs such as hydroxychlorouine (22%), methylprednisolone (24%), and remdesivir (17%). There was no control group available. Most of the children (89%) were eventually discharged. Out of the 13 patients admitted at PICU, 4 patients remained hospitalized in the ICU and on ventilatory support at day 14. There was 1 mortality upon withdrawal of supportive therapy because of comorbidity with metastatic cancer. [24]. Characteristics of these included studies are tabulated on Appendix 1.

Although the direct evidence of treating COVID-19 confirmed children with hydroxychloroquine/chloroquine is limited to these descriptive studies, a rapid review in the adult population showed that based on two randomized clinical trials involving 92 participants with RT-PCR confirmed COVID-19, treatment with HCQ 400mg daily for 5 days caused improvement in chest CT scan findings compared to standard therapy alone. However, there were no significant differences in terms of symptom improvement and disease progression. Adverse events documented include diarrhea, fatigue, rash, headache, and transient elevation of aspartate aminotransferase which resolved upon discontinuation of treatment [25].

Critical Appraisal

The overall strength of evidence of the included observational studies in determining the effectivity and safety of hydroxychloroquine in treating COVID-19 in children is low. There is high risk of bias because randomization, allocation concealment, and blinding of participants, caregivers, and outcome assessors were not done.. The clinical data of 97 patients available are just anecdotal since the presentation of the results are purely descriptive and we are unable to make any conclusion and recommendation. Therefore, there is still no hard evidence to conclude that hydroxychloroquine or chloroquine is effective and safe to be used as treatment for COVID-19 in children. Details on the critical appraisal of these articles are shown on Appendix 4.

Effectiveness Outcomes

These observational studies showed that most of the hospitalized COVID-19 confirmed children given investigational therapy like hydroxychloroquine were eventually discharged, however, there is no direct evidence that the clinical improvement of these patients was due to hydroxychloroquine since the clinical data gathered was limited and the results were inconclusive.

Safety Outcomes

The safety profile of hydroxychloroquine in terms of occurrence of adverse events were not mentioned. Its association with mortality in children treated for COVID-19 is not specified clearly in the articles.

Ongoing Studies

In addition to these studies, there are currently six ongoing clinical trials on chloroquine and hydroxychloroquine involving children, mostly adolescents 16 years and older, diagnosed with COVID-19 in different countries like Iran, Egypt, Mexico, United States, South Korea, and Thailand. Most of these studies are randomized open label clinical trials on the recruitment phase targeting 40 to 500 participants. Further illustration of the characteristics of these ongoing clinical trials are summarized on Appendix 2.

Recommendations from Other Guidelines

The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) stated that currently, there are no drugs approved by the U.S. Food and Drug Administration and there is no sufficient evidence or data to recommend any pharmaceutical intervention for the prevention or treatment of COVID-19. They emphasized that investigational anti-COVID-19 therapeutics should only be used in approved, randomized, controlled trials[1].

The National Institutes of Health recently provided interim guidelines for the medical management of COVID-19. In line with the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, there are insufficient clinical data available for its recommendation. The COVID-19 Treatment Guidelines Panel, however, recommends against using high-dose chloroquine (600mg twice daily for 10 days) for the treatment of COVID-19 based on the best evidence gathered at present on its associated toxicities. The Food and Drug Administration warns against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 outside the setting of a hospital or clinical trial given the risk of dysrhthmias [26].

Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment published by China National Health Commission suggested chloroquine phosphate (for adults weighing above 50 kilogram, 500 mg twice daily for 7 days and those below 50kg 500mg twice daily for day 1 to 2 and once daily for day 3 to 7) as antiviral treatment for COVID-19 pneumonia with contraindication in patients with heart disease. It is not recommended to use three or more antiviral drugs simultaneously [27].

The American Pediatric Infectious Disease Society proposed to do supportive care alone in managing mild to moderate pediatric COVID-19 cases, reserving the use of hydroxychloroquine only as an alternative for remdesivir, preferably in the context of clinical trials. Combination therapy with

hydroxychloroquine and azithromycin has been discouraged due to observed increased risk of dysrhythmias. The panel suggested that hydroxychloroquine loading dose be given on day 1 with a maximum treatment duration of 5 days [28].

Philippine Pediatric Society with the Pediatric Infectious Disease Society of the Philippines recommended investigational therapeutic interventions like hydroxychloroquine or chloroquine only for severe or critically-ill children with COVID-19. Informed consent must be acquired from legal guardian prior to giving hydroxychloroquine or chloroquine in pediatric COVID-19 patients [29].

CONCLUSION

Recent studies revealed that chloroquine and hydroxychloroquine were found to be effective against SARS-CoV-2 in in vitro studies but its application for treatment of COVID-19 in humans remains to be inconclusive due to limited clinical trials with small sample size mostly done in adult population.

The safety profile of these drugs in terms of adverse events and dose-dependent toxicities is yet to be explored in the pediatric population. Although it is previously considered to be generally well tolerated from its previous use for other diseases like rheumatoid arthritis and systemic lupus erythematosus, WHO and CDC still advise for proper medical guidance from healthcare professionals due to fatal risks like dysrhythmias.

Studies on the use of chloroquine and hydroxychloroquine as treatment for COVID-19 in children are limited to case report and case series as well as ongoing multinational randomized open label clinical trials. The clinical data available is purely descriptive and inconclusive.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	Late Onset Neonatal Sepsis in a Patient with Covid-19./ Munoz, AC. *et al.*	Case report	United States	3-week-old male preterm neonate with COVID-19	5 day-course of hydroxychloroquine and azithromycin	None	Clinical resolution of symptoms and discharge	He was able to complete the 5-day course of hydroxychloroquine and azithromycin and was discharged on the 9th hospital day without oxygen support.
2	Characteristics and Outcomes of Children with Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units/ Shekerdemian, LS. *et al.*	Case series	United States	48 children (4.2-16.6 years) with comorbidities diagnosed with COVID-19 admitted at the pediatric intensive care unit	Experimental pharmacotherapy including hydroxychloroquine, azithromycin, remdesivir, and tocilizumab as single agent or in combination	No experimental pharmacotherapy	Number of patients who died, remained hospitalized and mechanically ventilated, and discharged	Most of the children (65%) were eventually discharged. Fifteen patients remained hospitalized, 9 of which are on severe or critical condition while 6 have mild to moderate symptoms. Two patients with significant comorbidities and developed multisystem complications died.
3	Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 (COVID-19) at a Tertiary Care Medical Center in New York City/ Chao, JY. *et al.*	Case series	United States	46 children aged 1 month to 21 years old admitted with laboratory-confirmed SARS-COV-2 infection	Investigational therapy including hydroxychloroquine, remdesivir, or methylprednisolone	None	Length of hospital stay, PICU stay, number of days on respiratory support, number of patients discharged or died	Most of the children (89%) were eventually discharged. Out of the 13 patients admitted at PICU, 4 patients remained hospitalized in the ICU and on ventilatory support at day 14. There was 1 mortality upon withdrawal of supportive therapy because of metastatic cancer.

Table 2. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04376814/ Evaluation of Safety and Efficacy of Hydroxychloroquine Plus Favipiravir Drug Regimen in Comparison With Hydroxychloroquine Plus Kaletra on the Need for Intensive Care Unit Treatment in Patients With COVID-19; a Randomized, Multicenter, Parallel Groups, Open Label Study	Enrolling by invitation	March 29, 2020 to May 25, 2020	Nonrandomized open label clinical trial	Iran	Hospitalized patients 16 years to 100 years old diagnosed with COVID-19 based on ground glass appearance in chest CT scan or positive RT-PCR test for COVID-19	Patients will be given a stat dose of 1600mg Favipiravir tablets for the first time, and for next time they will be given 600mg of favipiravir tablets three times per day for 7 days, plus 200mg of Hydroxychloroquine two times per day	Patients will be given a stat dose of 400mg Hydroxychloroquine tablets plus 200/50 mg of Kaletra two times per day for seven days.	Primary: Admission to ICU (up to 28 days) Secondary: 1. Mortality 2. Length of stay in hospital 3. Radiological treatment response 4. Laboratory treatment response (blood cell count, CRP)

							will be given to patients for 7 days		5. fever 6. dyspnea 7. oxygen saturation without supplemental oxygen 8. allergic drug reaction 9. oxygen therapy 10. adverse drug reaction
2	NCT04353336/ Clinical Study Evaluating the Efficacy of Chloroquine in COVID-19 Treatment	Not yet recruiting	April 17, 2020 to December 1, 2030	Randomized open label clinical trial	Egypt	Child, Adult, Older Adult COVID-19 patients	Chloroquine treatment	No intervention	Number of patients with virological cure (time frame: 6 months)
3	NCT04341493/ Treatment With Hydroxychloroquine vs Nitazoxanide + Hydroxychloroquine in Patients With COVID-19 With Risk Factors for Poor Outcome	Recruiting	April 6, 2020 to December 30, 2020	Randomized single-blinded clinical trial	Mexico	COVID-19 positive patients 5 years and older treated at the Helath Institute of the State of Mexico, with risk factors to get complicated: age more than 60 years old, diabetes mellitus or obesity grade II or more	Hydroxychloroquine 400 mg PO every 12 hours for two days and then 200 mg PO every 12 hours for four days + Nitazoxanide 500 mg PO every 6 hours for six days	Hydroxychloroquine 200 mg PO every 12 hours for 7 days	Mechanical ventilation requirement (time frame: since the diagnosis until 2 weeks after)
4	NCT04335552/ Pragmatic Factorial Trial of Hydroxychloroquine, Azithromycin, or Both for Treatment of Severe SARS-CoV-2 Infection	Recruiting	April 17, 2020 to August 1, 2020	Randomized open label clinical trial	United States	Hospitalized patients 12 years and older with suspected or confirmed SARS-CoV-2 infection	1.Standard of care plus hydroxychloroquine for 5 days 2.Standard of care plus azithromycin for 5 days 3.Standard of care plus hydroxychloroquine plus azithromycin for 5 days	Standard of care	Primary:WHO ordinal scale measured at 14 days after enrollment Secondary: 1.rates of death during the index hospitalization 2.number of days on mechanical ventilation for patients who were on mechanical ventilation at baseline 3. Proportion of patients not receiving mechanical ventilation at baseline who progress to requiring mechanical ventilation during the index hospitalization [Time Frame: Index hospitalization, up to 46 days]

									4. WHO ordinal scale measured at 28 days after enrollment 5. Hospital length of stay in days for the index hospitalization [Time Frame: Index hospitalization, up to 46 days] 6. Rates of all-cause study medication discontinuation [Time Frame: Index hospitalization, up to 46 days] 7. Rates of severe adverse events [Time Frame: Day 14]
5	NCT04307693/ Randomized Controlled Clinical Trials of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	Recruiting	Multicenter, open labelled, randomized clinical trial	March 11, 2020 to May 2020	South Korea	Patients 16 years old to 99 years old with confirmed mild COVID-19	1.Lopinavir/ritonavir 200mg/100mg 2 tablets by mouth, every 12 hours for 7-10 days 2. Hydroxychloroquine 200mg 2 tablets by mouth, every 12 hours for 7-10 days	No lopinavir/ritonavir and hydroxychloroquine	Primary: Viral load [Time Frame: hospital day 3, 5, 7, 10, 14, 18] Secondary: 1. Viral load change [Time Frame: hospital day 3, 5, 7, 10, 14, 18] 2. Time to clinical improvement (TTCI) [Time Frame: up to 28 days] 3. Percentage of progression to supplemental oxygen requirement by day 7 4. Time to NEWS2 (National Early Warning Score 2) of 3 or more maintained for 24 hours by day 7 5. Time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission 6. Rate of switch to Lopinavir/ritonavir or hydroxychloroquine by day 7

									7. adverse effects [Time Frame: up to 28 days] 8. Concentration of Lopinavir/ritonavir and hydroxychloroquine [Time Frame: 1, 2, 4, 5, 12 hours after taking intervention medicine]
6	NCT04303299/ A 6 Week Prospective, Open Label, Randomized, in Multicenter Study of, Oseltamivir Plus Hydroxychloroquine Versus Lopipinavir/ Ritonavir Plus Oseltamivir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine in Mild COVID-19 AND Lopipinavir/ Ritonavir Plus Oseltamivir Versus Favipiravir Plus Lopipinavir / Ritonavir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine Versus Favipiravir Plus Darunavir and Ritonavir Plus Hydroxychloroquine in Moderate to Critically Ill COVID-19	Not yet recruiting	Randomized open label clinical trial	April 15, 2020 to November 30, 2020	Thailand	Patients 16 to 100 years old diagnosed with COVID-19	1. Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 800 mg per day In mild COVID19 2. Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus plus Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 400mg per day in Mild COVID19 3. Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In mild COVID19 4. Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In moderate to critically ill COVID19 5. Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5	Patient who unwilling to treatment and willing to quarantine in mild COVID19	Primary: SARS-CoV-2 eradication time (up to 24 weeks) Secondary: Time Frame[up to 24 weeks] 1. Number of patient with Death 2. Number of patient with Recovery adjusted by initial severity in each arm 3. Number of day With ventilator dependent adjusted by initial severity in each arm 4. Number of patient developed Acute Respiratory Distress Syndrome After treatment 5. Number of patient with Acute Respiratory Distress Syndrome Recovery

							mg/kg) per day plus Favipiravir 2400 mg, 2400 mg, and 1200 mg every 8 h on day 1, and a maintenance dose of 1200 mg twice a day in Mild COVID19 In moderate to critically ill COVID19 6. Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day plus Hydroxychloroquine 400 mg per day In moderate to critically ill COVID19 7. Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus Favipiravir 2400 mg, 2400 mg, and 1200 mg every 8 h on day 1, and a maintenance dose of 1200 mg twice a day plus Hydroxychloroquine 400 mg per day In moderate to critically ill COVID19		