INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None.

Efficacy of Hydroxychloroquine in Hand Osteoarthritis: a Protocol for Systematic Review and Meta-analysis of Randomized Clinical Trial

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Review question / Objective: **Population: patients ages with primary hand osteoarthritis according to the American College of Rheumatology classification criteria. Intervention: the study group, treated with hydroxychloroquine which range from 200 to 400 mg according to ideal body weight. Comparison: the control group treated with placebo which had identical appearance to hydroxychloroquine. Outcome: the evaluations of clinical function and pain were performed with 100-mm visual analog scale (VAS), Australian Canadian Hand Osteoarthritis Index (AUSCAN) and the Arthritis Impact Measurement Scale 2 short form (AIMS2-SF) at 6, 12, and 24 weeks from the beginning of the treatments. Style: randomized controlled trial (RCT) without published year, publication status limitations.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 November 2020 and was last updated on 03 November 2020 (registration number INPLASY2020110005).

INTRODUCTION

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Condition being studied: As a common form of osteoarthritis (OA), symptomatic hand osteoarthritis with an increased prevalence of 26% in women and 13% in men ages over 70 years, include pain and stiffness and lead to reduced hand mobility and grip strength, resulting in activity limitations and lower quality of life. Besides hand OA has a high burden of disease and an unmet medical need for effective therapeutic options. Current symptomatic treatment of hand OA consists of non-pharmacological, including education and exercise, and pharmacologic approaches, including paracetamol, topical non-steroidal anti-inflammatory drugs (NSAIDs), topical capsaicin, chondroitin sulfate, and intraarticular orticosteroids. But these therapies are modest because their effects are small and inconsistent, and long-term effectiveness is not investigated. Hydroxychloroquine (HCQ) has been used clinically in the treatment of mild rheumatoid arthritis and other autoimmune diseases by the suppression of inflammation for many years. Hand OA involves not only mechanical triggers but also local inflammation caused pain, stiffness, reduced motion and radiographical damage progression. Therefore, inflammation is a potential treatment target and HCQ might also be beneficial in hand OA.To further confirm the efficacy of HCQ in hand OA, we performed this systematic review and meta-analysis to explore the clinical outcomes.

METHODS

Participant or population: Inclusion criteria: patients ages with primary hand OA according to the American College of Rheumatology classification criteria. Exclusion criteria: 1.secondary hand OA caused by inflammatory rheumatic diseases such as rheumatoid arthritis, psoriatic arthritis, peripheral arthritis, or spondyloarthropathy, 2.use of HCQ within 3 months before enrolling the study, 3.use of NSAIDs or corticosteroids 7 days before enrolling the study, 4.retinopathy, 5.myasthenia gravis, 6.known allergy or intolerance for HCQ.

Intervention: The HCQ which range from 200 to 400 mg according to ideal body weight.

Comparator: The placebo which had identical appearance to HCQ.

Study designs to be included: Randomized controlled trial (RCT).

Eligibility criteria: Randomized controlled trial (RCT) without published year, publication status limitations.

Information sources: A systematic search of the literature will be conducted without language and year restrictions to identify all relevant RCT. We will search following electronic databases: PubMed, EMBASE, Cochrane Library and Web of Science from 2002 to Sep. 2020 using related search terms, including “hydroxychloroquine”, “hand osteoarthritis”, “Osteoarth”. In addition, congress and conference proceedings will be manually retrieved. Related articles and references of included research will also be tracked to find potential studies. If significant data was incomplete in included study, we will contact the authors to get unpublished data.

Main outcome(s): The 100-mm visual analog scale (VAS) at 6, 12, and 24 weeks from the beginning of the treatments.

Additional outcome(s): The Australian Canadian Hand Osteoarthritis Index (AUSCAN) and the Arthritis Impact Measurement Scale 2 short form (AIMS2-SF) at 6, 12, and 24 weeks from the beginning of the treatments.

Data management: After imported into the Endnote X7 and duplication, retrieved records will be independently screened by two reviewers. Firstly, we will read the titles and abstracts of all identified records to exclude clearly unrelated records based on the inclusion criteria. Then the full texts of the articles retained were reviewed to further determine their suitability. Any disagreement will be resolved by a third reviewer. We will show the selection process in details in the PRISMA flow chart.Two authors of this review will independently extract the data using a pre-defined form. The basic characteristics, related outcome and quality evaluation information of included studies will be collected. Similarly, any discrepancies will be resolved by a third reviewer. Data extracted will include author, year, study type, number of participants, intervention, control, demographics, complications, previous history, pain VAS, AUSCAN and AIMS2-SF at baseline and during the follow-up time.

Quality assessment / Risk of bias analysis: Included study bias will be independently assessed by two reviewers and any disagreement will be solved by a third reviewer. For randomized controlled trials, we will use the Cochrane risk of bias tools to evaluate potential bias in seven specific domains: (1) sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6)selective outcome reporting, (7) other bias.

Strategy of data synthesis: For dichotomous variables, The Relative Risk (RR) with 95% confidence intervals (CI) were calculated from each study. Continuous variables will be presented as Standard Mean Difference (SMD) with 95% CI. All endpoints will be combined and performed meta-analysis by using DerSimonian and Laird random effects model.We assessed statistical heterogeneity by using X^2 test and I^2 statistic. We will consider significant heterogeneity when P 0.10 for X^2 or $I^2$50%. All primary analyses were performed with STATA v15.1 (Stata Corp, College Station, TX).

Subgroup analysis: We will also conduct subgroup analysis to find more potential information based on pre-set criteria in different follow-up time.

Sensibility analysis: If the heterogeneity is high, we will conduct sensitivity analyses based on the patient age and follow-up time.

Country(ies) involved: China.

Keywords: pain, hand function, osteoarthritis, hydroxychloroquine.

Contributions of each author:
Author 1 - Qiangqiang Li - The author conceived the idea for this study, designed the meta-analysis and drafted the protocol.
Author 2 - Ya-Dong Xie - The author conceived the idea for this study, provided statistical advice and input and drafted the protocol.
Author 3 - Wen-Qiang Liang - The author provided statistical advice and input.
Author 4 - Guo-Qing Yang - The author designed the meta-analysis.
Author 5 - Huai-Bin Zhang - The author reviewed the protocol and provided critical feedback.
Author 6 - Yong-Ping Wang - The author reviewed the protocol and provided critical feedback.