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Combination of doxycycline, streptomycin and hydroxychloroquine for short-course treatment of brucellosis: a single-blind randomized clinical trial

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Abstract

Purpose Previous studies have shown the effect of hydroxychloroquine in the treatment and prevention of recurrence of brucellosis. The aim of this study was to compare the effect of 4 and 6 week regimen containing hydroxychloroquine in the treatment of brucellosis.

Methods In a single-blind randomized clinical trial, 92 patients with acute brucellosis were randomly divided in two treatment groups who received a triple drug regimen including doxycycline, streptomycin, and hydroxychloroquine (DSH] for 4 and 6 weeks. All patients were followed up for up to 6 months. Response to treatment, relapse rate, complications, and results of serological tests were compared in both groups. Data were analyzed by SPSS software version 16.

Results Of the 92 patients studied, 46 received a 4 week course and 46 received a 6 week course of therapy. There were no significant differences between the two groups in terms of age and sex distribution. The response rate, treatment failure, and relapse in the 4 week treatment group were 82.6%, 17.3%, and 7.89%, respectively, and in the 6 week treatment group were 91.3%, 8.7%, and 9.52%. The frequency of negative 2ME test at 24 weeks after treatment was 11.1% in the 4 week group and 8.7% in the 6 week group. No significant differences were found between the two groups in terms of response to treatment, treatment failure, relapse, and negative 2ME test.

Conclusion The 4 week and 6 week courses of the combination of DSH are equally effective in treating brucellosis. We recommend further studies to support the use of the short-course 4 week regimen for the treatment of uncomplicated brucellosis.

Keyword Brucellosis · Treatment · Hydroxychloroquine · Relapse

Introduction

Brucellosis is a zoonotic disease that has a wide global distribution. According to the World Health Organization, 500,000 cases of the disease are reported each year, with the highest number reported in the developing countries and the eastern Mediterranean [1, 2]. Burden of human brucellosis is significantly high in Iran, and it has also increased during the recent years [3, 4]. Clinical manifestations of brucellosis include fever, headache, musculoskeletal pain, general weakness, weight loss, and sweating. Complications of the disease include spondylitis, arthritis, meningitis, epididymitis, and endocarditis [5]. Relapse of brucellosis usually occurs in the first 6 months after stopping treatment. The lowest relapse rate and the best clinical response occur with the combination of doxycycline plus streptomycin at a rate of about 5–7%. [6]

Relapse of brucellosis may be due to the survival of Brucella inside phagocytes and the alkaline environment inside the cell, which protects them from certain antibiotics and host immune mechanisms. There are evidences that the intracellular effect of doxycycline can be increased by adding hydroxychloroquine and consequently alkalinization of the phagolysosome medium [7]. In a recent clinical trial

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study, hydroxychloroquine was added to the standard doxycycline-streptomycin treatment, the results of which showed a significant effect of this drug in the treatment and reduction of brucellosis relapse [8].

The aim of this study was to evaluate the response to treatment and recurrence of brucellosis in two groups receiving a triple drug regimen of doxycycline, streptomycin, and hydroxychloroquine (DSH) for 4 and 6 weeks.

Materials and methods

In a single-blind, randomized clinical trial conducted in 2019–2020 in Sina Hospital, Hamadan, Iran, all adult inpatients with brucellosis were included in the study after obtaining informed consent. The criteria for diagnosing the disease were clinical presentations consistent with brucellosis with positive serology including standard tube agglutination (Wright) test ≥ 1/160 and 2-mercaptoetanol (2ME) ≥ 1/80. Patients under 18 years of age, pregnant women, patients with neurobrucellosis, endocarditis, spondylitis and any serious complication of brucellosis, as well as those who did not want to continue clinical and laboratory follow-up were excluded from the study. Patients were randomly divided into 2 groups: 4-week treatment (doxycycline 200 mg daily for 4 weeks, hydroxychloroquine 400 mg daily for 4 weeks, and streptomycin 1 g daily for 3 weeks] and 6 weeks [doxycycline 200 mg daily for 6 weeks, hydroxychloroquine 400 mg daily for 6 weeks, and streptomycin 1 g daily for 3 weeks).

According to the study of Majzoobi et al. [8] at 95% confidence level with a power of 90%, the sample size was estimated for each group of 51 patients. Due to the COVID-19 pandemic condition, the number of patients enrolled in the study for each group was reduced to 46.

Response to treatment was assessed every 2 weeks until the end of treatment, and then, monthly follow-up was performed for 6 months for recurrence. Laboratory follow-up was performed with 2ME test at the end of treatment, the third month, and the sixth month after treatment (Fig. 1).

Improvement of signs and symptoms at the end of treatment without considering the change in 2ME titer was considered as an appropriate clinical response. Recurrence of clinical symptoms with increase in 2ME titer toward the end of treatment was defined as relapse.

Data were analyzed using SPSS software version 16. Statistical significance was determined by t test for quantitative variables and Chi-square for qualitative variables. A p value of less than 5% was considered significant.

This study was approved by the ethics committee of Hamadan University of Medical Sciences with the ID IR.UMSHA.REC.1398.022. Also, the study was registered in the Iranian Clinical Trial Database (IRCT) with the ID IRCT20160523028008N4.

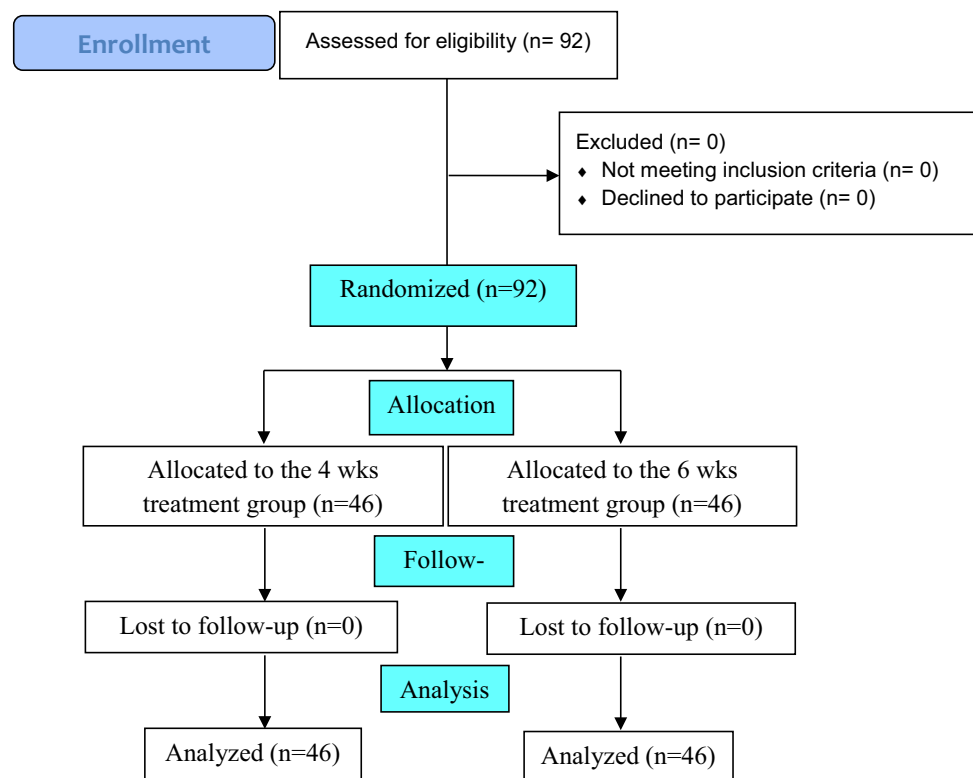**Fig. 1** Clinical trial flowchart of the study

Table 1 Demographic characteristics of patients in two groups receiving 4 and 6 week course triple drug regimens

Variable	4 wk course	6 wk course	P value
*Sex (male/female)	35/11	29/17	0.174
*Place(urban/rural)	16/30	10/36	0.165
†Age (year) mean ± SD	37.4 ± 12.5	40.5 ± 11	0.221

*Chi^2

† t test

Table 2 Comparison of symptoms of brucellosis in two groups receiving 4 and 6 course triple drug regimens

Symptoms	4 wk course N (%)	6 wk course N (%)	P value
Myalgia	36 (78.3)	38 (82.6)	0.599
Headache	17 (37)	20 (43.5)	0.524
Arthralgia	26 (56.5)	28 (60.9)	0.672
Fever	28 (60.9)	34 (73.9)	0.182

Results

Ninety-two patients with acute brucellosis who met the inclusion criteria were randomly divided into two groups of 46 patients receiving 4 week and 6 week drug regimens, with doxycycline + streptomycin + hydroxychloroquine (DSH). In the 4 week treatment group, 35 patients (76.1%) and in the 6 week treatment group, 29 patients (63.0%) were male P = 0.174, (Table 1).

Patients in the 4-week group had a mean of 37.4 ± 5 years and the 6 week group had a mean age of 40.11 ± 5 years (P = 0.221). Patients in the 4 week group had an average of 43 days before treatment and the 6 week group had 58 days before starting treatment. Thirty patients in the 4 week treatment group [65.2%] and 36 patients (78.3%) in the 6 week treatment group lived in rural areas (P = 0.165). The most common symptoms were myalgia and fever (Table 2).

Both groups had comparable conditions in terms of response to treatment in the second and fourth weeks, treatment outcome, and recurrence rate (Table 3).

The treatment regimen of eight patients in the 4 week group was continued for 6 weeks due to lack of proper response, and the drug treatment of four patients in the 6 week group was continued for up to 8 weeks.

The mean duration of fever after treatment was 2.4 ± 1 days in the 4 week group and 2.4 ± 1.1 days in the 6 week treatment group. There was no statistically significant difference between the two groups (P = 0.844).

Out of 38 patients who responded to treatment in the 4 week group, three patients (7.89%) had relapse in the first trimester and in the 6 week group of 42 patients who responded to treatment, four patients (9.52%) had relapse. Two patients recurred in the first 3 months and two patients recurred in the sixth month.

No serious complication was observed in patients following the use of drugs that led to discontinuation of treatment. The most common complication was gastrointestinal symptoms [nausea, epigastric pain] and dizziness (Table 4).

Discussion

The findings of this study showed that musculoskeletal pain, fever, and joint involvement are the most common clinical signs and symptoms in patients. These findings are consistent with the previous similar studies [6, 8].

In the present study, the 4 week and 6 week courses of the combination of DSH were equally effective in treating brucellosis. The relapse rate was about eight to 9.5% and no significant difference was observed between the two groups. These recurrence rates were higher than those reported with standard streptomycin–doxycycline regimen [6, 9]. However, in a recent clinical trial, the authors reported fewer relapses by adding hydroxychloroquine to the standard brucellosis regimen [8]. The reason for this difference may be due to the small sample size compared to the previous study of the authors. Accordingly, further investigation with new studies and sufficient sample size seems to be needed.

According to the findings of this study, the main complications observed were gastrointestinal and dizziness, which, of course, did not lead to discontinuation of treatment.

Table 3 Comparison of treatment outcome in the two study groups

Treatment outcome	4 wk course	6 wk course	P value
Clinical response to treatment (2nd wk)	21 (45.6)	20 (44.4)	1.00
Clinical response to treatment (4th wk)	38 (82.6)	36 (78.3)	1.00
Clinical response to treatment (6th wk)	–	42 (91.3)	–
Response to treatment	38 (82.6)	42 (91.3)	0.231
Therapeutic failure	8 (17.3)	4 (8.7)	0.231
Relapse	3/38 (7.89)	4/42 (9.52)	1.00

Table 4 Frequency of complications in two groups receiving 4 and 6 course regimens

Complication	Frequency	Percent
Gastrointestinal symptoms	15	16.3
Dizziness	15	16.3
Teeth discoloration	2	2.2
Nail discoloration	1	1.1
Itching	1	1.1

Gastrointestinal symptoms were also the most common drug side effects in brucellosis patients in the previous studies [6, 9, 10].

Doxycycline-induced nail and tooth discoloration occurred in a small number of patients, which improved with nail growth over time. However, tooth discoloration was constant during 6 months of follow-up. Although these complications are more common in children, they are also reported in adults [11, 12].

In the present study, no side effects of hydroxychloroquine were observed in patients. However, in some studies with higher doses and longer consumption, side effects, especially ocular disorders, have been reported that need to be considered in the follow-up of patients. According to studies, hydroxychloroquine side effects such as retinopathy and optic nerve involvement are less common than chloroquine and are rare as long as the total dose is less than 6.5 mg/kg, so screening for eye diseases in patients is not necessary [13, 14].

Hydroxychloroquine, in addition to being used in the treatment of Q fever endocarditis [15], malaria, brucellosis [1, 8], and infection caused by Staphylococcus aureus [16], has recently been studied in the treatment of patients with COVID-19, with conflicting results. Despite the reports of some benefits of hydroxychloroquine in patients with mild COVID-19, a recent meta-analysis of clinical trials found that its use is associated with increased mortality in COVID-19 patients [17, 18].

Current principles for the treatment of brucellosis include combination of antimicrobials that can reduce intracellular acidity or survive in acidic environment [19]. The main effect of hydroxychloroquine is related to intracellular alkalization and consequently inadequate pH for survival and proliferation of pathogens, increased intracellular effect of doxycycline and aminoglycosides, and also increased effect of doxycycline–aminoglycoside synergism [1, 15, 20].

According to the results of this study and the intracellular effect of hydroxychloroquine, it is suggested that further clinical trials be performed by adding it to other brucellosis drug regimens as well as studies on localized and complicated brucellosis.

In conclusion, the 4 week and 6 week courses of the combination of DSH were equally effective in treating brucellosis. Therefore, the short-course 4 week regimen may be recommended for the treatment of uncomplicated brucellosis. Further studies are needed to compare the proposed treatment regimen with standard regimens and support this recommendation.

Declarations

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