Systematic Review

Treatment of brucellosis: a systematic review of studies in recent twenty years

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Abstract

Background: The treatment of human brucellosis is controversial. The purpose of this study was to search published clinical trial papers to provide a simple and effective treatment in brucellosis.

Methods: Many studies on brucellosis treatment in a twenty- year span from 1993 to 2012 were searched in PubMed, Web of Science (ISI), Scopus, Google Scholar, Magiran, Iranmedex and SID. The studies that were searched and classified in groups according to combination therapy and monotherapy and their results in treatment outcome were compared. Regimens with lower treatment failure or relapse were considered as more suitable for brucellosis treatment.

Results: The comparison of combined doxycycline and rifampicin (DR) with a doxycycline plus streptomycin (DS) favors the latter regimen. The combined doxycycline/cotrimoxazole (DCTM) showed similar effect with DR. The treatment with the combined regimen including quinolones was similar to DR but with higher relapse rates. Higher relapse rate was searched in monotherapy (13% vs. 4.8%) and in short-term (less than 4 weeks) treatment regimen (22% vs. 4.8%), respectively. Although in children, clinical trials were limited but showed cotrimoxazole plus rifampin for six weeks was the best treatment regimen.

Conclusion: In uncomplicated brucellosis in adult patients, doxycycline-aminoglycoside combination is the first choice with doxycycline- rifampin and doxycycline-cotrimoxazole should be the alternative regimens. The other oral regimens including quinolones may be considered as alternatives. Cotrimoxazole plus rifampin for six weeks may be the regimen of choice for the treatment of patients younger than 8 years old. Gentamicin for 5 days plus cotrimoxazole for six weeks may be a suitable alternative regimen.

Keywords: Brucellosis, Treatment, Streptomycin, Doxycycline, Relapse

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Brucellosis is not only the most common zoonotic disease, but as a re-emerging disease has engaged the mind of health policymakers worldwide (1-3). More than 500000 new cases have been reported annually in the world, most of them occur in the developing regions where the disease is endemic (4). Brucellosis in both human and animal is a prevalent disease in Iran (5-6). Brucellosis as an occupational disease as well as a traveler's disease is a major public health problem, therefore, its treatment and treatment failure is considered as a major issue in controlling the disease (3, 7, 8). Brucellosis is treated with a variety of goals. Shortening the duration of symptomatic period, preventing relapse, reducing or preventing complications of brucellosis such as arthritis, sacroiliitis, spondylitis, endocarditis, meningoencephalitis, epididimoorchitis and ending abortion are the most important treatment goals (9-11).

In 1986, the World Health Organization (WHO) recommended antibiotic regimen of oral doxycycline 100 mg twice a day for 6 weeks plus oral rifampicin 600 to 900 mg daily for 6 weeks or streptomycin 1 g intramuscularly daily for 2-3 weeks for the treatment of brucellosis (9, 10). This treatment is still accepted as the preferred treatment for most infectious diseases specialists (11). Despite employing this regimen, treatment failure and relapse rise to between 5-15% cases (9-11).

Although some studies have pointed to a number of risk factors for treatment failure or relapse, but the best treatment regimen has not been clearly determined (12, 13). The efficacy of the different regimens in special circumstances such as pregnancy, chronic brucellosis, complicated cases, immunocompromised patients or dialysis are associated with the different results (14-16). The use of other drugs such as gentamicin, quinolones and cotrimoxazole (CTM) either alone or in combination with other drugs have been associated with the different results (14, 17-21).

There are a number of questions to be answered, the first choice treatment regimen, the best treatment for complicated cases, the appropriate treatment in special circumstances, the need for antibiotic injection, the relapse and treatment failures, the danger of rifampicin resistance M. tuberculosis, and treatment compliance. The aim of this study was to provide the most appropriate treatment for brucellosis by comparing the studies conducted in the different countries.

Method

In this study, we reviewed the articles in which brucellosis patients were being treated with various antibiotic regimens. The results of treatment failure or relapse with respect to the composition and duration of treatment were compared. Many studies on brucellosis treatment in a twenty years span from 1993 to 2012 were searched in PubMed, Web of Science (ISI), Scopus, and Google Scholar. The studies were searched and classified into groups according to combination therapy (2 or 3 antibiotics) and monotherapy and the results were compared. The regimens with lower treatment failure or relapse were considered as more suitable for the treatment of brucellosis. In these studies, the patients with brucellosis who were diagnosed through serology or culture were assessed. The acceptable serology titers of Wright ≥1/160 2 Mercapto Ethanol (2ME) ≥1/80 in the presence of clinical findings and brucellosis risk factors (10). Treatment failure or relapse was considered if there was an evidence of any signs or symptoms of the disease or increase in antibody titer or a positive culture at the end of treatment and follow up period (11, 13). In these studies, discontinued treatment for any reason, including severe gastrointestinal intolerance or drug side effects or renal failure were excluded.

The comparison of the results was performed using SPSS version 16 and chi -square test.

Results

Of the total 73 searched studies in initial review, 49 including 13 due to incomplete data, 28 due to lack of access to full text and 8 due to lack of compliance with the criteria defined in the method of study were excluded and finally only 24 studies in the field of adult cases of brucelosis and three in the field of childhood brucellosis were reviewed.

Standard regimen of streptomycin plus doxycycline (SD): The reviewed studies (18,19, 22-25) showed the overall failure rate of 7.4% in the range of 2-10% and relapse rate of 4.8% in the range of 0-9.7% (table 1). In Iran, the rates of treatment failure and relapse were 4.6-11% and 4.6-6.1%, respectively.

Table 1: Treatment failure and relapse of standard treatment with streptomycin plus doxycycline.

Study (Reference)	Failure rate %	Relapse rate %
Solera, et al. (22)	2	5.3
Hashemi, et al. (19)	4.6	4.6
Bayindir, et al. (23)	10	0
Roushan, et al. (24)	11	6.1
Roushan, et al. (36)	7.4	3.2
Erosy, et al. (25)	9.7	9.7

Combination of doxycycline plus rifampicin (DR): The overall treatment failure and relapse rates in reviewed studies were 7.8% between 3.1-15% and 10.7% ranged 3.5-16%, respectively (21-23, 26-29) (table 2). Although, the efficacy of this regimen is similar with the streptomycin plus doxycycline ($p>0.05$) but this indicates a higher relapse rate.

Table 2. Treatment failure and relapse with rifampicin plus doxycycline.

Study (Reference)	Failure rate %	Relapse rate %
Solera, et al. (22)	8	16
Bayindir, et al.(23)	15	10
Akova, et al. (26)	3.3	3.3
Ranjbar, et al. (27)	11.8	9.3
Agalar, et al. (29)	3.8	10
Karabay, et al. (28)	3.1	14.3
Alavi, et al. (5)	9.8	11.7

Combination of doxycycline plus gentamicin (DG): In some studies, the substitution of gentamicin for streptomycin has shown a failure rate of 0-10.8% (average of 5.2%) and relapse rate of 2.4-12.3% (average of 5.9%) (18, 19, 24, 30) (table 3). Although some studies had reported its effectiveness more than streptomycin but the difference in this study did not show any significant difference (10, 18).

Table 3. Treatment failure and relapse with gentamicin plus doxycycline

Study (Reference)	Failure rate %	Relapse rate %
Hashemi, et al, (19)	10.8	12.3
Roushan, et al. (24)	4.9	2.4
Roushan, et al. (18)	5.1	3.1
Solera, et al. (12)	0	5.9

Combination of cotrimoxazole plus rifampicin (RCTM): Cotrimoxazole (CTM) in combination with rifampin in the treatment of children with brucellosis showed the failure rate of 0-16.4% and relapse rate of 3.1-10% that was not significantly different with doxycycline plus rifampicin treatment (17-31).

Treatment regimens containing quinolones: The use of quinolones such as ciprofloxacin (C) or ofloxacin (O) in combination with other antibiotics such as doxycycline, CTM, rifampicin has shown that failure or relapse rate ranged between 3.2-26% (19, 20, 23, 25-29, 31). Studies, the high levels of quinolone efficacy and low level of relapse have been reported (20, 32) (table 4).

Combination of streptomycin plus tetracycline (ST): The reviewed studies showed the failure rate in the range of 0-14% and relapse rate between 0-9% that was not significantly different with SD treatment ($p>0.05$) (22, 23, 28). Combination of co-trimoxazole plus doxycycline (DCTM) in the treatment of brucellosis showed the failure rate of 1.9-7.1% and relapse rate of 5.8-8.6% that was not significantly different with doxycycline plus rifampicin (17, 21).

Table 4. Treatment failure and relapse with regimen containing quinolones.

Study (Reference)	Failure rate %	Relapse rate %
Hashemi, et al. (19)	4.6	4.6
Bayindir, et al. (23)	26	26
Keramat, et al. (20)	8	8.3
Akova, et al. (26)	3.2	3.2
Agalar, et al. (29)	10	15
Karabay, et al. (28)	13.3	13.3
Erosy, et al. (25)	15	15

Treatment with single drug or monotherapy: There are few studies about treatment with cotrimoxazole or ciprofloxacin in the acute and uncomplicated brucellosis (10). The efficacy of this regimen was similar with the rifampicin plus doxycycline but it indicates a higher relapse rate (13%) ($p<0.05$).

Short-term combined therapy: Few studies have compared doxycycline-streptomycin regimen and the doxycycline-rifampicin regimen over the different periods (10, 35). The duration of less than 1 month was inferior to more than 1 month (relapse rate of 22% vs. 7.1%) (35).

Triple therapy: In a study, 3-antibiotic regimen containing streptomycin plus doxycycline and rifampicin (SDR) was compared with 2- antibiotic regimen DR in complicated brucellar spondylitis. The efficacy of this regimen was 100% with full recovery and without failure or relapse (23).

Discussion

Although, employing the standard brucellosis treatment recommended by WHO has changed the feature of brucellosis and its risk factors for treatment failure or relapse, but the best treatment for brucellosis has not been cleared yet. This review study showed that in the case of complicated brucellosis associated with spondylitis, arthritis

or endocarditis, prolonged treatment (8 weeks or more) with triple therapy regimen had better efficacy and less treatment failure and relapse. The combination of streptomycin or gentamicin plus doxycycline and rifampicin (SDR or GDR) should be considered as the first choice of triple therapy regimens (23, 27). Skalsky et al. suggested a combination of three drugs doxycycline, rifampicin and aminoglycoside for human brucellosis. They concluded a lower treatment failure (7.8%) rate associated with triple therapy. Whereas, this rate was 32% with DR (33). However, in patients with focal complications of brucellosis such as brucellar spondylitis, longer or more aggressive curative therapy may be necessary than in patients with uncomplicated brucellosis.

The present study showed that a combination of doxycycline and aminoglycoside as the most widely studied treatment regimen with overall relapse of 4.8% and treatment failure rate of 7.4% was the preferred treatment in acute or uncomplicated chronic brucellosis or complicated cases (except of endocarditis, spondylitis or arthritis). Eight weeks treatment regimen of two antibiotics has a high therapeutic success and a less treatment failure or relapse (11, 18, 19, 22-25). Two-drug regimen consisting of streptomycin and doxycycline (streptomycin for 2 to 3 weeks and doxycycline for 8 weeks) or gentamicin plus doxycycline (gentamicin for 5-7 days and doxycycline for 8 weeks) should be recommended as the treatment of choice for uncomplicated brucellosis. In none of the reviewed studies on the combined use of doxycycline and gentamicin in adults, there was no advantage over the combinations including gentamicin for streptomycin.

In rural limited source areas and for the avoidance of repeated injections, treatment with two oral drugs such as DR, DCTM, tetracycline / rifampicin, doxycycline / ofloxacin or ciprofloxacin / rifampicin can be used. For the prevention of multi-drug resistant tuberculosis (TB) as a major problem in public health in areas with high prevalence of TB, prescription of rifampin in the treatment of brucellosis should be limited (10-34). Therefore, we suggest that rifampicin in the treatment of brucellosis in Iran should not be used except in children, pregnant or lactating women where tetracycline is contraindicated or when there are limitations on the use of streptomycin or gentamicin. However, rifampicin should not be used alone (14). The duration of less than 4 weeks was inferior to those of more than 4 weeks (relapse rate of 22% vs. 7.1%). Most authors suggest that longer treatment periods (6-8 weeks) yield superior results. Indeed, short-term treatment regimen (less than 4 weeks), because of high treatment failure (18.5%) and relapse rates (22%) and low level of reliability due to low number of studies are not suitable for treatment of brucellosis (10, 35).

Although several studies have examined the quinolones alone in the treatment of brucellosis, but because of the risk of emergence of bacterial resistance even during therapy, their use may be considered with caution (16, 22). The determination of the effect of quinolones in monotherapy of brucellosis requires more trial work and we currently do not recommend it.

In children like adult, early diagnosis and proper treatment are crucial for the prevention of morbidity and mortality. Tetracycline or doxycycline is contraindicated in children younger than 8 years old due to the risk of staining teeth, therefore cotrimoxazole in combination with gentamicin or rifampicin is a useful antibiotic regimen for childhood brucellosis (36). Cotrimoxazole plus rifampin for six weeks may be the regimen of choice for the treatment of patients younger than 8 years old. Gentamicin for 5 days plus cotrimoxazole for six weeks may be a suitable alternative regimen (37, 38). Treatment of brucellosis in children older than 8 years is the same for the treatment of adults except quinolone-containing regimens which are not recommended in children under 18 years.

This study has some limitations. A small number of studies, particularly clinical trial research studies, and their restrictions to the previous years are the main limitations of this study. The large number of studies are related to the years before the year 2000. The reason for this is that, brucellosis is at present not a health problem in the developed countries and studies review have been done when the disease was more prevalent. To reduce the effect of a small number of annual studies, we reviewed the studies through a span of twenty years. To minimize the bias of old studies, new studies after the year 2000 from Iran and the other developing countries were added.

In conclusion, for the treatment of uncomplicated brucellosis, in addition to doxycycline-aminoglycoside combination as the first choice treatment, oral regimens such as DR and DCTM should be considered. The other oral regimen including quinolones (e.g. ciprofloxacin or ofloxacin) may be considered as alternatives. Triple therapy should be used only in severe complicated cases. For the prevention of multi-drug resistant tuberculosis, prescription

of rifampin in the treatment of brucellosis in TB high prevalence area should be limited. Monotherapy and short-term therapy are not suitable treatment regimens.

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