Comparison of the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks versus streptomycin for 2 weeks plus doxycycline for 45 days in the treatment of human brucellosis: a randomized clinical trial

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Objectives: To compare the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks with streptomycin for 2 weeks plus doxycycline for 45 days in the treatment of human brucellosis.

Methods: In each arm of the study, 82 patients older than 10 years randomly received 5 mg/kg gentamicin once daily for 5 days plus 100 mg of doxycycline twice daily for 8 weeks or 1 g of streptomycin intramuscularly for 2 weeks plus the same dose of doxycycline for 45 days. Therapeutic failure and relapse in these two treatment groups were compared. This study was registered in the Iranian Registry of Clinical Trials (www.irct.ir) with registration number ID: IRCT138708191441N1.

Results: The clinical manifestations in these two groups were similar. Therapeutic failure was seen in two (2.4%) patients in the gentamicin/doxycycline group and in four (4.9%) patients in the streptomycin/doxycycline group [relative risk (RR) = 0.5, 95% confidence interval (CI) 0.09–2.66, P = 0.68]. Relapse was seen in two (2.4%) cases in the gentamicin/doxycycline group and in five (6.1%) cases in the streptomycin/doxycycline group (RR = 0.4, 95% CI 0.08–2, P = 0.44). The efficacy with the gentamicin/doxycycline regimen was 95.12% and that with the streptomycin/doxycycline regimen was 89% (RR = 1.07, 95% CI 0.98–1.17, P = 0.25). Cox regression analyses showed no differences among the two treatment groups for patients who had relapse or therapeutic failure and those who had not regarding baseline covariates such as sex, duration of disease before diagnosis, positive blood culture and focal disease.

Conclusions: The results show that the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks is not superior to that of streptomycin for 2 weeks plus doxycycline for 45 days.

Keywords: Malta fever, aminoglycosides, therapy regimen, RCT

Introduction

Brucellosis is an important public health problem throughout the world, especially in the Mediterranean region and other developing countries.1,2 Currently, streptomycin/doxycycline and doxycycline/rifampicin are considered as two optimal regimens endorsed by the WHO for the treatment of human brucellosis, but subsequent studies have reported that the efficacy of streptomycin/doxycycline is superior to that of doxycycline/rifampicin.3–10 In many endemic regions, especially in developing countries, tuberculosis is common. Therefore, mycobacterial resistance to rifampicin and the emergence of extensively drug-resistant (‘XDR’) tuberculosis are other problems when using rifampicin for the treatment of brucellosis.11,12 Thus, the selection of a regimen free of rifampicin is reasonable. Oral regimens, such as co-trimoxazole/rifampicin and co-trimoxazole/doxycycline for 8 weeks, have been studied in Iran, but the efficacy of these regimens was 76% and 84%, respectively.13 Shorter courses of treatment with different therapy regimens have been associated with relapse rates of 30%–40%.10–14 Many experts believe that the efficacy of aminoglycoside-containing regimens is better than that of others.1,15 With netilmicin for a week plus doxycycline for 45 days, the relapse rate was 12.5%.16 The administration of streptomycin for 2 weeks and doxycycline for 45 days has been
associated with a relapse rate of 5%–8%. When gentamicin was used for 7 days and doxycycline for 45 days, the success rates in three studies were between 86% and 94.8%.

The efficacy of gentamicin for 5 days plus doxycycline for 8 weeks was 100% in children with brucellosis. Since the efficacy of this regimen in adult cases of brucellosis has not been determined, the purpose of this study was to compare the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks versus streptomycin for 2 weeks plus doxycycline for 45 days in the treatment of human brucellosis.

**Methods**

**Patients**

Patients with brucellosis who attended the Department of Infectious Diseases of Yahyanejad University Hospital in Babol, Iran were entered into the study. This department serves >1.7 million local residents in three large cities (Amol, Babol and Ghaemshar) and the corresponding urban regions in the province of Mazandaran and locations across the Caspian Sea. Fortunately, due to the developing socioeconomic conditions of the people in these regions in recent years, we were able to keep in touch with all the patients during the study period by telephone. Inclusion criteria for this study were outpatient and inpatient cases aged >10 years. Patients who suffered from spondylitis, endocarditis and neurobrucellosis, those who were pregnant, and those who had received antibiotics for >2 days were excluded. The diagnosis of brucellosis was made by using standard tube agglutination (STA) titre ≥1:320 and 2-mercaptoethanol (2ME) titre ≥1:160, together with compatible clinical findings (fever, sweating, arthralgias, peripheral arthritis, sacroiliitis and epididymo-orchitis). It is known that >90% of patients with acute brucellosis with an STA titre of ≥1:320 have bacteraemia. Three blood samples were obtained from each patient before initiation of treatment, and were inoculated in Castaneda diphasic medium and incubated for 6 weeks. Radiological and other diagnostic imaging studies were performed on the basis of the clinical symptoms of the patients. Peripheral arthritis was diagnosed when the patients had swelling, effusion and limitation of motion in an involved joint. Sacroilitis was confirmed by using X-ray in prone position and then reconfirmed by bone scan. Epididymo-orchitis was diagnosed when patients had swelling and tenderness of the scrotal skin, testes and epididymis, and was confirmed by sonography. White blood cell count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, blood urea nitrogen (BUN), creatinine level and body weight (kg) were determined for all patients.

The study was approved by the Infectious Diseases Research Center of Babol Medical University and its Ethics Committee. All patients gave their written informed consent. For the literate patients, a consent form was given to them carefully, explained so that it was fully comprehended and, lastly, signed by them. The illiterate subjects were asked to be accompanied by a literate relative. The consent form was given to the literate relative to fully and carefully explain its content to the illiterate patient, and when satisfied the patient stamped her/his finger as a signature of approval. This study was registered in the Iranian Registry of Clinical Trials (www.irct.ir) with registration number ID: IRCT138708191441N1.

**Interventions**

In each arm of the study, patients received 5 mg/kg gentamicin once daily for 5 days plus 100 mg of doxycycline twice daily for 8 weeks (gentamicin/doxycycline group) or 1 g of streptomycin intramuscularly for 2 weeks plus the same dose of doxycycline for 45 days (streptomycin/doxycycline group).

**Objectives**

In this study, we tested the hypotheses that therapeutic failure, relapse and adverse effects with the gentamicin/doxycycline regimen were lower than with the streptomycin/doxycycline regimen.

**Outcomes**

The primary endpoints of this study were therapeutic failure due to lack of efficacy and relapse. The secondary endpoints included safety and compliance.

Therapeutic failure due to lack of efficacy was defined as the persistence or worsening of the symptoms or signs of the disease at the end of treatment, as judged clinically. Relapse was defined to occur when clinical symptoms and signs of brucellosis reappeared and reduced titres of STA or 2ME increased again, or the Brucella species was isolated from blood culture during the follow-up period. These tests and clinical symptoms and signs were reassessed at 3 month intervals as well as whenever clinical symptoms and signs reappeared. Failure of therapy and relapse cases were diagnosed and evaluated at our clinic.

Safety was assessed based on the adverse effects of drugs and the results of laboratory tests. BUN and creatinine levels were determined on days 4 and 6, and at the end of the treatment. Otoxotoxicity was examined clinically. Adverse effects of drugs were evaluated on days 10 and 20, and at the end of treatment.

Compliance was queried at each visit during the course of treatment; each patient was asked about taking the prescribed drugs. Efficacy (success rate) was defined as the rate of total cured cases in each arm.

**Sample size**

The sample size for each group was an estimated 82 cases, based on a therapeutic failure and relapse rate of 10% for the streptomycin/doxycycline regimen and a prediction of 0.5% for the gentamicin/doxycycline regimen. The α and β errors chosen for these calculations were 0.05 and 0.20, respectively.

**Randomization**

**Sequence generation**

Before administration of the regimens, we prepared 164 records and wrote gentamicin/doxycycline (82 records) or streptomycin/doxycycline (82 records) on each, separately. All records were mixed several times and inserted into a box.

**Allocation concealment**

For each patient, a record was drawn and the therapy regimen, which was noted on it, was administered. We could not predict the therapy regimen for any patient.

**Implementation**

Randomization and administration of therapy regimens were done by one of the authors (M. R. H. R.), and monitoring of the patients during the treatment period and post-therapy follow-up was done by four of the authors (M. R. H. R., M. J., M. S. H. and M. B.).

**Statistical methods**

Data were analysed by SPSS version 15. The Student’s t-test was used to compare continuous variables and the χ² test or Fisher’s exact test were used to compare categorical variables. We used relative risk (RR) with...
95% confidence interval (CI) for showing all outcomes. A Cox proportional hazards regression model (univariate and multivariate) was used to estimate the differences between the two therapy regimens after adjustment for baseline covariates such as sex, duration of disease before initiation of therapy, epididymo-orchitis, peripheral arthritis, sacroiliitis, spondylitis and isolation of organism in blood cultures. Time to relapse data were plotted using a Kaplan–Meier graph. The log rank test was used to compare the relapse rate in the two treatment groups. Differences with a \( P \) value of <0.05 were considered significant. All \( P \) values are 2-tailed.

Results

Flow of participants

Figure 1 shows a flow chart revealing how the patients in both arms were selected for analysis.

Recruitment

From April 2005 to September 2008, the eligible patients with brucellosis gave their written informed consent and were then randomized to receive the gentamicin/doxycycline or streptomycin/doxycycline regimen. After treatment, all patients were followed up for 1 year. The last follow-up visit of the patients treated in the gentamicin/doxycycline group or the streptomycin/doxycycline group was in September 2007. After 3 weeks from the initiation of the treatment regimens, the clinical manifestations in one subject from the gentamicin/doxycycline group and in two patients from the streptomycin/doxycycline group were worse, and they were diagnosed as having spondylitis by magnetic resonance imaging. Two subjects in the gentamicin/doxycycline group and five patients in the streptomycin/doxycycline group completed their treatment course, but did not attend post-therapy follow-up. Therefore, follow-up data from these patients were censored at the last visit. The median STA titre for all cases in the streptomycin/doxycycline group was 1:640 (range 1:320 to 1:10240) and that for the gentamicin/doxycycline group was 1:640 (range 1:320 to 1:40960). 2ME titres in all patients were \( \geq 1:160 \) (range 1:160 to 1:1280).

Baseline data

The baseline characteristics of the patients in both treatment groups are shown in Table 1.

Numbers analysed

For each arm, 82 patients were analysed.

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**Figure 1.** Flow chart summarizing the study process in the two treatment groups.
Outcomes and estimation

Therapeutic failure due to lack of efficacy

Therapeutic failure was seen in two (2.4%) cases from the gentamicin/doxycycline group and in four (4.9%) subjects from the streptomycin/doxycycline group (RR = 0.5, 95% CI 0.09–2.66, P = 0.68). Three cases with therapeutic failure had spondylitis (one in the gentamicin/doxycycline group and two in the streptomycin/doxycycline group) (Table 2). In these cases, rifampicin was added to doxycycline and both agents were continued for 4 months and resulted in cure. For other therapeutic failure cases, doxycycline was continued for another 30 days and favourable clinical responses occurred.

Occurrence of relapse

Relapse occurred in two (2.4%) cases from the gentamicin/doxycycline group and in five (6.1%) patients from the streptomycin/doxycycline group (RR = 0.4, 95% CI 0.08–2, P = 0.44). Among the relapsed cases from the gentamicin/doxycycline group, one case had bacteriological relapse 3 months after the treatment and he was asymptomatic. We called him to attend for retreatment. Seven days later, he developed sacroiliitis. The characteristics of other relapsed cases are shown in Table 2. Four of these subjects were treated with streptomycin and doxycycline, as specified in the above schedule, and three patients were treated with 100 mg of doxycycline twice daily and 600 mg of rifampicin once daily for 2 months; complete clinical response occurred in all cases. Among 55 patients with focal diseases except spondylitis in this study, only 3 (5.5%) cases experienced relapse without any evidence of therapeutic failure, in contrast to 3.9% of 106 patients without focal diseases (Tables 1 and 2).

Efficacy (success rate) of treated cases in the gentamicin/doxycycline group or the streptomycin/doxycycline group

Overall, success occurred in 78 (95.12%) patients in the gentamicin/doxycycline group and in 73 (89%) patients in the streptomycin/doxycycline group (RR = 1.07, 95% CI 0.98–1.17, P = 0.25).

Ancillary analyses

The cumulative probabilities of non-relapse cases in the two treatment groups are shown in Figure 2. Various sensitivity analyses did not show any significant differences in the success rates of the gentamicin/doxycycline group versus the streptomycin/doxycycline group. There were no differences among the two treatment groups for patients who suffered relapse or therapeutic failure compared with those who did not regarding some important clinical and laboratory data at baseline, except spondylitis, with bivariate and multivariate analysis (Table 3).
Table 2. Characteristics of the patients with relapse/therapeutic failure in the two treatment groups

<table>
<thead>
<tr>
<th>Therapy regimen</th>
<th>Age (years)/sex</th>
<th>Clinical manifestations(^a)</th>
<th>Blood culture(^a)</th>
<th>STA(^a)</th>
<th>2ME(^a)</th>
<th>Outcome</th>
<th>Time to relapse (months)</th>
<th>STA(^b)</th>
<th>2ME(^b)</th>
<th>Blood culture(^b)</th>
<th>Clinical manifestations(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEN/DOX</td>
<td>52/female</td>
<td>arthralgia, sweating</td>
<td>+</td>
<td>1:640</td>
<td>1:160</td>
<td>failure</td>
<td>—</td>
<td>1:1280</td>
<td>1:640</td>
<td>—</td>
<td>left knee arthritis</td>
</tr>
<tr>
<td>GEN/DOX</td>
<td>20/male</td>
<td>fever, arthralgia</td>
<td>+</td>
<td>1:2560</td>
<td>1:640</td>
<td>relapse</td>
<td>3</td>
<td>1:640</td>
<td>1:160</td>
<td>+</td>
<td>right sacroiliitis</td>
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<tr>
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<td>19/male</td>
<td>fever, sweating, sacralgia</td>
<td>–</td>
<td>1:2560</td>
<td>1:640</td>
<td>relapse</td>
<td>2</td>
<td>1:640</td>
<td>1:320</td>
<td>+</td>
<td>left knee arthritis</td>
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<tr>
<td>STR/DOX</td>
<td>17/male</td>
<td>fever, sweating, back pain</td>
<td>–</td>
<td>1:2560</td>
<td>1:640</td>
<td>relapse</td>
<td>8</td>
<td>1:640</td>
<td>1:320</td>
<td>+</td>
<td>left knee arthritis</td>
</tr>
<tr>
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<td>20/male</td>
<td>back pain, fever, left sacroiliitis</td>
<td>+</td>
<td>1:320</td>
<td>1:160</td>
<td>relapse</td>
<td>1</td>
<td>1:1280</td>
<td>1:640</td>
<td>–</td>
<td>fever, sweating, arthralgia</td>
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<tr>
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<td>fever, chills, right shoulder arthritis</td>
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<tr>
<td>STR/DOX</td>
<td>47/female</td>
<td>arthralgia, left knee arthritis</td>
<td></td>
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<tr>
<td>STR/DOX</td>
<td>20/female</td>
<td>fever, sweating, abortion</td>
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<tr>
<td>STR/DOX</td>
<td>21/male</td>
<td>sweating, fever, arthralgia, back pain</td>
<td></td>
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<tr>
<td>STR/DOX</td>
<td>32/male</td>
<td>low back pain, fever, sweating</td>
<td></td>
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<tr>
<td>STR/DOX(^c)</td>
<td>58/male</td>
<td>low back pain</td>
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<tr>
<td>STR/DOX(^c)</td>
<td>62/male</td>
<td>low back pain</td>
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<tr>
<td>GEN/DOX(^c)</td>
<td>52/male</td>
<td>fever, back pain</td>
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</tr>
</tbody>
</table>

GEN, gentamicin; STR, streptomycin; DOX, doxycycline.
\(^a\)At diagnosis.
\(^b\)At failure or relapsed cases.
\(^c\)These cases had spondylitis.
Compliance with doxycycline was queried in interviews during treatment on days 10, 20, 45 and 56. Therapy was well tolerated. In the gentamicin/doxycycline group, a photosensitivity reaction was observed in 11 cases, and mild abdominal discomfort and epigastric pain was observed in 12 cases; in the streptomycin/doxycycline group, these adverse effects were seen in 8 and 10 cases, respectively. Two out of 11 cases with a photosensitivity reaction in the gentamicin/doxycycline group had onycholysis, which developed after 6 weeks of receiving the regimen treatment and was related to doxycycline, but this agent was continued to 8 weeks. Onycholysis was repaired completely within 3 months after completion of treatment.

Overall, the rates of adverse effects in both groups were similar (28% in the gentamicin/doxycycline group and 22% in the streptomycin/doxycycline group) (RR = 1.3, 95% CI 0.74–2.15, P = 0.5). After completion of treatment, the mean serum creatinine level in the gentamicin/doxycycline group was 0.65 ± 0.2 mg/dL and in the streptomycin/doxycycline group it was 0.62 ± 0.17 mg/dL. No ototoxicity was found with either aminoglycoside.

**Discussion**

In this study, we found that the success rate of treatment with gentamicin for 5 days plus doxycycline for 8 weeks (95.12%) was not superior to that of streptomycin for 2 weeks plus doxycycline for 45 days (89%). Furthermore, the rate of relapse in patients with focal diseases except spondylitis in the gentamicin/doxycycline and streptomycin/doxycycline groups was 5.5% and 3.9%, respectively (Tables 1 and 2).

Experts believe that the duration of treatment for brucellosis with complications such as epididymo-orchitis, sacroiliitis and peripheral arthritis is similar to that of uncomplicated brucellosis.1,9 All cases with spondylitis in our study experienced initial therapeutic failure. Other studies recommend a longer duration of treatment in patients who have this condition.1,25

Using gentamicin for 7 days plus doxycycline for 30 days in adults and gentamicin for 5 days plus doxycycline for 3 weeks in children was associated with relapse rates of 12.3%–23.8%.20,21,26,27 Although childhood brucellosis is less serious than that in adults, a shorter duration of treatment with different therapy regimens was associated with higher relapse rates in both children and adults. The results obtained with the gentamicin/doxycycline regimen in this study are similar to those reported when using gentamicin for 7 days plus doxycycline for 45 days.19–21

In the current study, the number of patients suffering asymptomatic bacteriologic relapse was low (one case), but Solera et al.20 found six cases of bacteriological relapse without presentation of clinical signs and symptoms. The reason for a lower rate of relapse among asymptomatic patients in our study may be the lower sensitivity of the method we used for detecting the organism. We believe that asymptomatic bacteriologic relapse
cases eventually become symptomatic, as we saw in one case in this study and as Solera et al.\textsuperscript{21} showed in two relapsed cases in their study.

The results of this study show that the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks is not superior to that of streptomycin for 2 weeks plus doxycycline for 45 days. They are also compatible with the hypothesis that the two regimens are equivalent, although the study was not planned to prove equivalence. The gentamicin/doxycycline regimen (in adult patients with brucellosis) achieved a clinical response rate comparable to that of other regimens commonly in use. The decrease in duration of injections from 2 weeks for streptomycin to 5 days for gentamicin is advantageous, regarding toxicity, cost and ease of administration. Because the potential toxicity of aminoglycoside therapy is time dependent, a 5 day course may be preferable to a longer one. The only disadvantage of the gentamicin/doxycycline regimen is the length of doxycycline administration (~2 weeks more than that in the streptomycin/doxycycline group).

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Transparency declarations
We declare that we have no conflicts of interest.

Author contributions
M. R. H. R., M. J., M. S. H. and M. B. wrote the project. M. R. H. R. was the principal investigator of this study. Randomization/administration of both regimens was done by M. R. H. R. Monitoring of the patients during the treatment period and post-therapy follow-up data collection were done by M. R. H. R., M. J., M. S. H. and M. B. Our orthopedics consultant for patients who had skeletal complications was N. J. The microbiological study was done by M. J. S. A. and A. B. performed the statistical analyses. This manuscript was written by M. R. H. R. and was reviewed by all of the authors.

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