Original Article

Outcomes of treatment in 50 cases with spinal brucellosis in Babol, Northern Iran

Seyed Mokhtar Smailnejad Gangi[1], Mohammad Reza Hasanjani Roushan[2], Nasser Janmohammadi[1], Raheleh Mehraeen[3], Mohammad Jafar Soleimani Amiri[2], Elham Khalilian[2]

[1]*Department of Orthopedics, Shahid Beheshti Hospital, Babol Medical University, Babol, Iran*
[2]*Infectious Diseases Research Center, Babol Medical University, Babol, Iran*
[3]*Department of Radiology, Shahid Beheshti Hospital, Babol Medical University, Babol, Iran*

Abstract

Introduction: Duration of treatment for brucellar spondylitis in endemic regions is controversial. This study describes the outcome of treatment in 50 cases of brucellar spondylitis in Iran.

Methodology: From April 2001 to September 2010, we treated 20, 13, 11 and 6 cases with doxycycline plus rifampin (DR), streptomycin plus doxycycline plus rifampin (SDR), cotrimoxazole plus doxycycline plus rifampin (CDR), and gentamicin plus doxycycline plus rifampin (GDR), respectively. Gentamicin and streptomycin were administered for 14 days and the other agents for 3 months. When complete clinical response was not achieved, therapy was continued. All patients were followed for one year. The Kaplan Meier method and the log rank test were used to compare the duration of therapy between SDR plus GDR patients with those treated with CDR or DR.

Results: Eight (45%), 10 (76.9%), 7 (63.3%) and 6 (100%) cases treated for three months were cured with DR, SDR, CDR and GDR, respectively. Nine (45%), 4 (36.4%) and two (22.2%) were cured after four months with DR, CDR and SDR, respectively**.** Mean duration of therapy in the SDR plus GDR, CDR and DR was 3.26±0.17, 3.36±0.15 and 3.9±0.23 months, respectively (p=0.49 and p=0.015, respectively). Three cases with epidural or paravertebral abscesses recovered after six months. Relapse occurred in one (9.1%) and two (10%) cases treated with CDR and DR, respectively.

Conclusions: Brucellar spondylitis could be treated using different combinations of antimicrobials especially with a regimen containing aminoglycoside for four months; patients with epidural or paravertebral abscesses require longer treatment times.

Key words: brucellosis; spondylitis; treatment; therapeutic regimen

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Introduction

The spinal column is one of the most frequently affected sites in osteoarticular brucellosis with a reported incidence of between 2% and 54%, depending on the study population, the species of infecting *Brucella*, and the difficulty of diagnosis [1-6]. Spondylitis may be complicated by potentially devastating neurological defects and residual disability may result from even protracted treatment [7-9]. Treatment of brucellar spondylitis remains controversial regarding the selection of antibiotics, the duration of treatment, and the role of surgery. After three months of treatment, failure rates between 20% and 26% have been reported [9,10]. However, using a triple combination of antibiotics (streptomycin 1 g/day for 15 days and doxycycline 100 mg every 12 hours orally for 45 days plus rifampicin 15 mg/kg per day in a single morning dose orally for 45 days) a small series of cases had higher cure rates [11]. In a recent study in Greece, Ioannou *et al*. treated 18 cases of brucellar spondylodiskitis for between 6 and 18 months using a triple antibiotic combination and, based on clinical, radiological and serologic responses, no relapses were detected [12]. So far, consensus on the optimal regimen of antibiotics to be used and duration of treatment has not been reached, making the treatment of spinal brucellosis controversial. In this prospective study we addressed the treatment of brucellar spondylitis using different regimens of therapy according to clinical and inflammatory responses in Babol, northern Iran.

Methodology

From April 2001 through September 2010, a total of 1,623 cases of brucellosis were diagnosed in the Department of Infectious Diseases at Babol Medical

University in Iran and among them, 50 (3.1%) cases had brucellar spondylitis. These cases were treated and followed prospectively for one year. This department provides services to more than 1.7 million local residents in three large cities (Amol, Babol, and Ghaemshar) and the corresponding rural regions of Mazandran province located across the Caspian Sea. The diagnosis of brucellosis was established by standard tube agglutination test (STAT) with a titre ≥1:160 and a titre in 2-mercaptoethanol (2-ME) ≥1:80 for patients with clinical signs and symptoms compatible with brucellosis (fever, sweating, arthralgia, back pain). Three blood samples were obtained from each patient before initiation of treatment; blood inoculated in Castaneda diphasic medium and incubated for six weeks at 37°C. For all cases, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fever, risk factor for brucellosis, and concurrent involvement of other organs were recorded. Normal values of the laboratory test results were defined with regard to references [13].

For spondylitis, radiographic findings were recorded by determining epiphysitis of the anterosuperior angle of the vertebra, narrowing of the disc space, erosion, sclerosis, vertebral collapse and osteomyelitis. Diagnosis of spondylitis was established using magnetic resonance imaging (MRI). Two types of spinal involvement (focal and diffused) were considered [14]. We prepared a record for each case including clinical manifestations, laboratory test results, and outcome of treatment. After diagnosis, a body external brace was used for stabilization of involved vertebrae for three weeks.

All cases were treated with one of the following regimens of therapy: co-trimoxazole plus rifampin plus doxycycline (CRD), gentamicin plus doxycycline and rifampin (GDR), streptomycin plus doxycycline and rifampin (SDR) or doxycycline plus rifampin (DR). The dosages were co-trimoxazole 8 mg/kg/day (3 doses/day); rifampin 15 mg/kg/day (once daily); gentamicin 5 mg/kg/day single dose (maximum of 240 mg/day); doxycycline 100 mg (twice daily); and streptomycin 1 g/day single dose. Gentamicin and streptomycin were administered intramuscularly as a single dose daily for 14 days with monitoring of blood urea nitrogen (BUN) and creatinine every 5 days. SDR and GDR were administered to patients younger than 60 years. Duration of therapy for all regimens was three months. When complete clinical and inflammatory responses were not achieved after three months, therapy was continued until improvement of clinical symptoms and signs with normalization of CRP and ESR to normal values. All patients were hospitalized for two weeks and after discharge from the hospital they were followed up every two weeks during the treatment period and then at a three-month intervals for one year. The last patient follow-up was September 2010. The efficacy of all therapeutic regimens was recorded. Therapeutic failure was defined as persistence of clinical signs and symptoms of the disease for three months. Cure was defined as complete improvement of clinical symptoms and signs with normalization of CRP and ESR to normal values. Relapse was defined to occur when clinical symptoms and signs of brucellosis reappeared and reduced titer of STA or 2ME increased again, or isolation of *Brucella* from blood culture during the follow-up period. Antibiotic therapy was changed if adverse effects of the drugs were observed. Sequelae were considered to have occurred when pain, abnormal physical findings, or functional limitation persisted for longer than six months post-therapy.

Data were collected and analyzed with SPSS version 18 (IBM, Chicago, USA). The Kaplan Meier method a and log rank test were used to estimate the duration of therapy between SDR plus GDR with those treated with CDR or DR regimens.

Results

Demographic characteristics

The mean age of the patients (26 males, 24 females) was 51.8 ± 14.5 years (range 27 to77 years). The mean duration of the onset of disease to diagnosis for all cases was 67 ± 56 days (range 10 to 240 days). Of 50 cases, 10 were diagnosed within 3 weeks of initial presentation, 16 were diagnosed between 3-6 weeks, 9 were diagnosed between 5-10 weeks and 15 were diagnosed after more than 10 weeks of their initiation of clinical symptoms and signs. Sheepherders and consumption of unpasteurized dairy products were the main risk factors for brucellosis and were seen in 43 (86%) cases (Table 1). Thirty-seven (74%) patients were rural residents.

Clinical symptoms, signs and laboratory test results

The most common symptoms associated with spinal *Brucella* cases were sweating, fever and arthralgia. These symptoms were found in 48 (96%), 28 (56%) and 14 (28%) of the cases, respectively (Table 1). The median STAT titer was 1:640 (range

Table 1. Clinical manifestations and laboratory test results on 50 cases of brucellar spondylitis

Variable	Male N = 26	Female N = 24	Total N = 50
Fever, N (%)	17 (65.4%)	11 (45.8%)	28 (56%)
Sweating, N (%)	25 (96.2%)	23 (95.8%)	48 (96%)
Artheralgia, N (%)	7 (29.6%)	7 (29.2%)	14 (28%)
Normal Hb, N (%)	19 (73.1%)	15 (62.5%)	34 (68%)
Elevated CRP, N (%)	23 (88.5%)	22 (91.7%)	45 (90%)
Lecoucytosis, N (%)	6 (23.1%)	8 (33.3%)	14 (28%)
Overall risk factors, N (%)	24 (92.3%)	19 (79.2%)	43 (86%)
Normal ESR, N (%)	4 (15.4%)	2 (8.3%)	6 (12%)

CRP; C-reactive protein ESR; erythrocyte sedimentation rate, Hb; hemoglubin

1:320 to 1:2560), and 2ME titers in all patients were ≥ 1:80 (range 1:80 to 1:1280). *Brucella melitensis* was isolated in blood cultures of 10 (20%) patients

The spondylitis evident in 4 (8%) cases was focal and in 46 (92%) was diffuse. Spondylitis was seen in 44 (88%) cases in both lumbar and lumbo-sacral. Involvement of more than two vertebrae was seen in 4 (8%) cases (Table 2). Paravertebral or epidural masses were seen in 23 (46%) cases, in which three cases had paravertebral or epidural abscesses (one case also had psoas abscess). Cervical and thoracic and thoraco-lumbar involvements are shown in Table 2. No patient displayed any neurologic deficit.

Outcomes of treatment

With three months of treatment, 31 (62%) patients were cured and the remaining 19 cases continued to have clinical signs and symptoms without worsening of their clinical conditions. After four months of therapy, 15 (30%) cases were cured (Table 3). The mean duration of therapy in the aminoglycosides-treated patients was 3.26 ± 0.17 months (95% CI, 2.93 to 3.59). For CDR, mean duration of treatment was 3.36 ± 0.15 months (95% CI, 3.1 to 3.7), and for DR mean duration of treatment was 3.9 ± 0.23 months (95% CI, 3.45 to 4.35). The mean duration of therapy with GDR plus SDR was lower than that of the DR group ($p = 0.015$). There was no significant difference between the mean duration of therapy in the GDR plus SDR when compared with the CDR group (0.49). Only four cases required treatment for six months (three with epidural or paravertebral abscesses and one with involvement of more than two vertebrae.

Relapse was seen in one (9.1%) case treated with CDR and in two (10%) cases treated with DR regimens (Table 3). The treatment course of these cases was three months. Relapse in the CDR group occurred after three months of treatment and in the DR group after two and four months after treatment. All drugs were tolerated by the patients during the treatment period. No serious adverse effects causing discontinuation of any agent were observed during treatment.

Discussion

In this study we found that 31 (62%) subjects responded to a treatment course of three months with different regimens of therapy. Only one case with this duration of therapy had relapse. Colmenero *et al*. and Solera *et al*. reported failure rates for cases who received three months of therapy of 20% of 96 cases and 26% of 35 cases respectively, which was lower than our finding of 19 (38%) cases [9,10]. Most of their patients received streptomycin for two to three weeks and doxycycline for three months, while in our study a combination of rifampin and doxycycline was continued after discontinuation of streptomycin or gentamicin, which may be the reason for the lower failure rate in our study (Table 3).

By increasing the duration of therapy to four months, an additional 15 (30%) patients were cured. A total of 46 (92%) of the patients treated with the multiple antimicrobial regimens were cured after 4four months. The remaining four cases (three with paraverbral abscesses and one with multiple levels of vertebral involvement) required antibiotic treatment due to persistence of clinical signs and symptoms which were not detected after six months of treatment. Our findings and the results of other researchers showed that the longer duration of therapy, regardless of type of treatment regimen, is associated with a lower failure rate [12,15].

In our study, treatment with streptomycin 1 g/day for 14 days in addition to doxycycline plus rifampin for four months or using a regimen that included gentamicin did not result in any observed relapse. In Turkey 22 patients were treated with streptomycin for

Table 2. Spinal involvement in 50 cases with brucellar spondylitis

Vertebral level affected	N (%)	Epidural and/or paravertebral masses	Epidural and/or paravertebral abscess
Lumbar	34	15	1
L1-L2	5	2	-
L2-L3	7	3	1▪
L3-L4	7	4	
L4-L5	10	1	
L2-L3-L4	1	2	
L1-L2-L3	2		
L5	1		
L3	1		
Lumbo-sacral	10	4	1
L5-S1	9	3	1●
L4-L5-S1	1	1	
Thoraco-lumbar	1	1	
T12-L1	1	1	
Thoracic	2	1	
T9-T10	1	1	
T12	1		
Cervical	3		1
C5-C6	2	2	1*
C2	1		

▪ Psoas abscess * This case had paravertebral abscess, ● Epidural abscess

Table 3. Outcome of therapy with different regimens of therapy

Regimen of therapy (no. of cases)	Duration of therapy for 3 months N (%)	Duration of therapy for 4 months N (%)	Duration of therapy for 6 months N (%)	relapse	Cure rate N (%)
GDR (6)	6 (100%)	0 (0)	0 (0)	0 (0)	6 (100%)
SDR (13)	10 (76.9%)	2 (22.2%)	1 (7.7%)	0 (0)	13 (100%)
CDR (11)	7 (63.6%)	4 (36.4%)	0 (0)	1 (9.1%)	10 (90.9%)
DR (20)	8 (40%)	9 (45%)	3 (10%)	2 (2%)	18 (90%)

G: Gentamicin, D: Doxycycline S: Streptomycin C: Cotrimoxazole, R: Rifampin

15 days and doxycycline plus rifampin for 45 days, and no relapsed cases were described [11]**.** In 25 cases with brucellar spondylitis that were treated with different regimens of therapy, the mean duration of antimicrobial therapy was 130 ± 45 days [15].

Alp *et al*. treated 15 and 16 cases with streptomycin for two weeks plus doxycycline or ciprofloxacin plus doxycycline, respectively. In the doxycycline streptomycin group, the duration of the therapy was 12 weeks in eight patients, 14 weeks in three patients, 16 weeks in three patients and 24 weeks in one patient. In the ciprofloxacin doxycycline group the duration of the therapy was 12 weeks in twelve patients, 14 weeks in one patient, 16 weeks in two patients and 20 weeks in one patient. Relapse was not observed in any patient by the one-year follow-up [16]. Their findings were similar to the results obtained by our group when we used different regimens of therapy. Bayindir *et al*. (2003) reported no therapeutic failure or relapse in 22 patients with brucellar spondylitis who were treated with streptomycin 1g daily for 15 days and doxycycline plus rifampin for 45 days. Furthermore, with other regimens of therapy containing two combinations for 45 days (doxycycline plus rifampin, ofloxacin plus rifampin, streptomycin for 15 days plus doxycycline for 45 days), they found unacceptable therapeutic failure and relapse rates [11]. Thirty-five cases of brucellar spondylitis were treated with streptomycin plus rifampicin plus doxycycline for three months without therapeutic failure or relapse [17].

In this study we did not perform MRI for follow-up of these patients. Investigations have revealed that follow-up MRI of patients with vertebral osteomyelitis had a limited role and might give the impression of clinical progression even though there was otherwise clinical improvement. Use of follow-up MRI is necessary in patients with persistent elevation of inflammatory markers and in patients with persistent pain, or in patients who develop new neurologic signs and symptoms, which we did not see in our series [18]. We believe that with effective antimicrobial therapy, spontaneous fusion between adjacent infected vertebral bodies require longer periods of time.

A weakness of this study was that randomization for the administration of any of the regimens of therapy was not performed. However, our analyses showed that regimens containing aminoglycoside have better efficacy in comparison with other regimens of therapy. Our findings and the results of other researchers emphasize that the duration of therapy in brucellar spondylitis is should be based on each individual's conditions and the extent of the lesions.

In conclusion, although some patients with abscesses or more severe disease may require longer periods of therapy, most cases of brucellar spondylitis respond to treatment for up to four months with any of four antibiotic regimens, especially those regimens containing aminoglycoside.

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Corresponding author

Mohammad Reza Hasanjani Roushan
Infectious Diseases Research Center
Babol Medical University
Babol 4717641367, Iran
Telephone: +98 111 3234387
Fax: +98 111 2224032, +98 111 2227667
Email: hagar2q@yahoo.ca

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