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Response of the intravenous versus oral antibiotic regimen in brucellosis bacteremia

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ABSTRACT

BACKGROUND & OBJECTIVE: More than 500,000 new cases are reported globally annually. The World Health Organization recommends doxycycline with rifampicin or an aminoglycoside for brucellosis bacteremia. Some experts prefer to use doxycycline and rifampicin. We aimed to observe the response rate of intravenous versus oral anti-brucella therapy regimens in brucellosis bacteremia patients and compare the frequency of side effects and complications in both groups.

METHODOLOGY: This observational study included adult brucellosis bacteremia patients treated in a hospital in Makkah, KSA for four years. According to the method of treatment (oral versus IV antibiotics), patients were grouped into two categories. Following the treatment, all these patients' records were evaluated. The negative blood culture was the primary endpoint whereas complications and all-cause mortality were secondary endpoints. The chi-square test, Fisher's exact test, and Mann-Whitney U test were applied accordingly to analyze the two groups' characteristics.

RESULTS: A total of 93 cases were enrolled, the majority were males i.e., 64 (68.8%); with a mean age group (44.33 ±19.22 years). In total, 37 (39.8%) of patients were given IV regimens and the remaining 56 (60.2%) of patients were given oral regimens. Follow-up negative blood culture after 4 weeks was 90.3% (n = 84). The recovery rate was 93.5% (n = 87). No death was reported over this period. No difference was observed (P-value 0.309) between the oral and IV treatment regimens regarding the blood culture negativity.

CONCLUSION: Oral doxycycline-rifampicin (DR) and IV gentamicin-doxycycline-rifampicin (GDR) regimens have similar response rates in bacteremia brucellosis.

KEYWORDS: Brucellosis, Acteremia, Antibiotic, Treatment.

INTRODUCTION

Human brucellosis is one of the most frequently presented global zoonotic disorders. It represents a public health threat in high-prevalence regions like the Middle East, the Mediterranean region, Latin America, and Africa [1]. The Brucella (gram-negative, facultative, intracellular coccobacillus) is the causative organism of brucellosis. Brucella abortus, Brucella suis, and Brucella melitensis are the most frequent species causing human brucellosis [2].

Consuming contaminated food products and contact with a source directly or indirectly are important transmission modes for brucellosis. Patients suffering from brucellosis typically experience non-specific symptoms. The non-specific symptoms of brucellosis include fever, chills, headaches, arthralgia, fatigue, anorexia, myalgia, and weight loss. Clinical symptoms can differ depending on whether brucella infections are hematogenous or localized. Human brucellosis is usually not lethal, but if ignored, a chronic intracellular infection can lead to serious sequelae which can cause a significant impairment. Even after having prompt diagnosis and care, 10–30% of individuals still had complications after being diagnosed with chronic brucellosis [2,3].

Brucellosis was the most reported bacterial infectious disease in Saudi Arabia between 2018 and 2019 and later with a decreasing trend [4, 5]. "According to the Ministry of Health 2021 Statistics book, the incidence rate has been gradually increasing since 2014 to 2018"[6].

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Human brucellosis can affect any organ of the body system. Disease clinical diagnosis can be readily mistaken with other medical conditions because of vague symptoms [6]. Three distinct methods are used in the microbiological diagnosis of human brucellosis: serology, culture, and nucleic acid amplification tests (NAATs). The gold standard test for brucellae detection in blood cultures allows for the confirmation of the disease's presence in its early stages when serological test results are still negative or exhibit low or borderline antibody titers. Patients with bacteremia brucellosis are diagnosed based on positive culture results for Brucella species, while patients with nonbacteremic brucellosis are classified based on negative culture results for Brucella species. Therefore, brucellosis-related clinical characteristics, antibody titers, and agglutination tests are used to diagnose nonbacteremic patients [6].

The main goals of brucellosis treatment are to manage the illness and avoid negative consequences, relapse, and complications. The management of a zoonotic infection aims at treating the infection with an appropriate antibiotic medication over an extended period; however, it is unknown which antibiotics work best and how long treatments should last. So, the efficacy of any therapeutic regimen is determined by curing disease, and evaluating the rate of relapse or treatment failure [7].

Bacteremia brucellosis is not uncommon, but its epidemiology and management data are not well documented. The global standard of brucellosis therapy is a dilemma in the absence of multiethnic, randomized trials for different treatment regimens, along with other multiple factors. The usage of two or more antibiotics is currently recommended treatment regimens [8].

The antibiotic regimen and duration are determined by the primary disease or co-morbid diseases that preclude certain antibiotics from being used [9]. The doxycycline-rifampicin regimen (DR) for 45 days duration is considered affordable, and simple with good compliance first-line therapy for non-focal mild cases in most endemic areas [9].

There is an inconsistency in the recommendation of antibiotic regimes in different countries. Consideration of an intravenous antibiotic regimen was usual practice for the management of bacteremia and complicated brucellosis. Currently, brucella bacteremia and complicated brucellosis are being treated successfully with the oral antibiotic regimen by some experts. The purpose is to reduce the resistance against mycobacterium tuberculosis by using rifampicin- and aminoglycoside [10]. Spinal brucellosis alternative treatment regimen is ciprofloxacin and rifampin instead of the classical regimen (doxycycline plus streptomycin) [11].

We aimed to observe the response rate of intravenous versus oral anti-brucella therapy in brucellosis bacteremia patients and the frequency of side effects and complications in these two groups.

METHODOLOGY

This observational, single-center study was done at Security Forces Hospital Makkah. The study was started after ethical approval was obtained from the Medical Research Ethics Committee of the hospital (# 0429-020621). Confidentiality and anonymity of the subjects were maintained as per the rules/policies of the hospital, and no names of the study participants were mentioned. A total of 198 cases of brucellosis were reviewed retrospectively (from January 1st, 2017, to December 31st, 2020). Patients were selected randomly according to inclusion criteria. The included patients were > 14 years of age, of either gender, with a diagnosis of brucella bacteremia confirmed by blood culture. Blood cultures were performed by the BACTEC 9120 (Becton Dickinson, Sparks, MD, USA) method.

The confirmed case of brucellosis is labeled when a positive blood culture for Brucella spp. or a four-fold or larger elevation in brucella antibody titer between acute and convalescent serum samples is found. An antibody titer of 160 in either acute or convalescent-phase serum is defined as laboratory evidence of probable brucellosis. So, the cases diagnosed as brucellosis with negative blood cultures were excluded from this study. According to the inclusion criteria, bacteremia patients (N=93) were enrolled in the study. Patients' data, including demographics, clinical presentation, and laboratory characteristics, were documented. All patients were separated into two groups (oral Rx vs IV Rx group) as exposed to treatment regimens. (IV regimens included gentamicin-doxycycline-rifampicin and oral included doxycycline-rifampicin or ciprofloxacin).

These patients' responses were assessed by clinical improvement along with a decrement of inflammatory markers and negativity of blood culture (which was performed 4 weeks after therapy). Patients were assessed for up to 6 months of period. Patients were considered recovered if clinically no signs and symptoms were observed during six months. The patients whose clinical signs and symptoms were improved than before were categorized as having partial remission.

The third category comprised those patients who suffered from relapse or reinfection characterized by the re-appearance of the disease clinical presentation moreover, either Brucella species growth in cultures and/or the serological parameters positivity, once completely symptom-free. Comorbidities and complications were assessed, investigated, and managed appropriately with a multidisciplinary approach. Side effects were assessed and managed accordingly. Although clinical management of brucellosis presents challenges due to a high frequency of the above factors.

The data were analyzed using version 27 Statistical Package for the social sciences. The descriptive data is presented by numbers, means, and standard deviations. The inferential data is expressed by applying an independent t-test to compare the two groups' continuous variables; Pearson's Chi-Square test / Fisher's exact test was applied to analyze categorical variables

depending upon the number of variables. The Mann-Whitney U test was applied to compare the two groups' causative organism titers and the patient's final diagnosis because of the non-uniform distribution of the variables. The statistical significance of the P value was important if it was < 0.05.

RESULTS

Total of 93 study participants, 64 were males (68.8%), and 29 were females (31.2%). The studied population's mean age was 44.33±19.22 years. Among the total 93 patients, 40 males (43%) and 16 females (17.2%) were given the oral treatment regimens. The other 24 males (25.8%) and 13 females (13.9%) received IV treatment. Potential risk factors, clinical presentation, and comorbidities are elaborated in Table 1. Frequent presentations were fever (97.8%), fatigue (52.7%), and musculoskeletal pain (23.6%). Common comorbidities were diabetes mellitus (20.4%), hypertension (17.2%), liver diseases (5.4%), and chronic kidney disease (2.1%).

Table-I:Comparisons of Potential Risk Factors, Comorbidities, and Clinical Features between the Two Groups.

Variables	Oral Rx n%	IV Rx n%
H/O Raw Milk Ingestion	29(31.1)	19(20.4)
H/O Cheese Ingestion	9(9.7)	12(12.9)
H/O Diabetes Mellitus	12(12.9)	7(7.5)
H/O Hypertension	7(7.5)	9(9.7)
H/O Chronic Liver diseases	4(4.3)	1(1.1)
H/O Chronic Kidney disease	2(2.1)	0(0)
H/O Fever	55(59.1)	36(38.7)
H/O Muscle pain	16(17.2)	6(6.4)
H/O Weight loss	3(3.2)	4(4.3)
H/O Fatigue	24(25.8)	25(26.9)
H/O Other complaints	20(21.5)	23(24.7)

Table-II: Comparison of laboratory parameters between two groups.

Parameters	Group & Number	Means	Std. deviation	P-value
Hemoglobin (g/dl)	Oral Rx 56	13.2786	1.64369	0.667
	IV Rx 37	12.932	1.9751	
Neutrophils (Cells percentage/cu mm)	Oral Rx 56	2.5304	1.3201	0.063
	IV Rx 37	3.2124	2.1838	
Lymphocytes (cells percentage/cu mm)	Oral Rx 56	2.5343	0.9267	≤0.001
	IV Rx 37	1.9316	0.9470	
Platelets count (Cells count/cu mm)	Oral Rx 56	233.58	86.8040	0.361
	IV Rx 37	216.27	69.5196	
ESR (mm after 1st hour)	Oral Rx 56	46.375	11.5389	0.763
	IV Rx 37	47.108	12.2447	
CRP (mg/L)	Oral Rx 56	20.339	6.08880	0.226
	IV Rx 37	18.216	8.5866	
Total duration of therapy (weeks)	Oral Rx 56	6.4286	1.5592	0.091
	IV Rx 37	6.811	2.0795	

Laboratory parameters and total duration of therapy were compared to keep patients into two groups (oral vs IV) of patients as elaborated in Table-II.

The final clinical diagnosis of brucella patients and their agglutination titer data were compared according to their exposure to treatment by the two groups: either oral or IV. A Mann-Whitney U test was performed, and no statistically significant difference was found either between the agglutination titers of oral and IV groups for the final diagnosis of the patients. The results are well elaborated in Table- III.

In total, 37 (39.8%) patients were treated with the intravenous regimen and 56 (60.2%) patients took the oral regimen. In the oral group, 46 (49.5%) patients were given doxycycline plus rifampicin, 7 (7.5%) were given doxycycline plus ciprofloxacin, and 1 (1.1%) patient was given rifampicin + ciprofloxacin. Initially, thirty-five (37.6%) patients in the IV group received gentamicin along with rifampicin and doxycycline for almost seven days. One (1.1%) patient was treated with rifampicin and doxycycline along with intravenous ceftriaxone for 30 days, and one (1.1%) patient took ceftriaxone with doxycycline + ciprofloxacin for 30 days, then stepped down to oral therapy to complete the course as documented in Table -IV.

Table-III: Comparison of two groups regarding their agglutination titer and final diagnosis.

Variables	Oral Rx	IV Rx	Total	U value	Z value	P-value
Agglutination Titre.						
B. Melitensis	28	18	47	252.50	-0.31	0.756
B. Abortus	29	19	48	206.00	-1.58	0.112
Final diagnosis.						
Non focal brucellosis	48	29	77	916.00	-1.25	0.209
Septic arthritis	1	3	4			
Epidydmo- orchitis	3	1	4			
Spondylitis	3	2	5			
Neuroborreliosis	0	1	1			
Infective endocarditis	0	1	1			

Table-IV: Comparison of drug therapies in two groups.

Initial Drugs Used (Induction Rx)	Oral Rx	IV Rx	Total	P-Value
Doxycycline/Ciprofloxacin/ceftriaxone/gentamicin	7	36	43	≤0.001*
Doxycycline/Rifampicin/Ceftriaxone/Ciprofloxacin	49	1	50	
Total	56	37	93	
Step down Drugs used (Maintenance Therapy)				
Doxycycline/Ciprofloxacin/Bactrim/Ceftriaxone	6	6	12	0.438*
Doxycycline/Rifampicin/Ciprofloxacin	50	31	81	
Total	56	37	93	

***Chi-Square Test**

Blood culture for brucella became negative after four weeks of therapy in 84 (90.3%) of these patients, while two (2.2%) of them did not do it. The results indicate that since the p-value is greater than the 0.05 level of significance, we are inclined to accept the null hypothesis and conclude no significant difference in the proportion of follow-up blood cultures after 1 month between the oral and IV groups. $p > 0.05$. It's elaborated below in Table-V.

Table-V: Comparison of the outcomes and side effects of two groups.

Variables	Response	Oral Rx	IV Rx	Total	P- Value
Follow Up Blood Culture (After 4 weeks)	Positive	7	2	9	0.309*
	Negative	49	35	84	
Final Outcome	Cured	51	36	87	0.397*
	Relapsed	5	1	6	
Side Effects.	Nil	49	31	80	0.761*
	Present	7	6	13	

***Fishers Exact Test**

Generally, patients' tolerance was good, moreover, some mild and transient adverse effects were observed without any association (p-value 0.590) between the oral and IV groups of patients.

A total of 87 (93.5%) patients were documented as cured. Two (2.2%) patients lost their follow-up. The relapse rate after six weeks of completion of treatment was observed to be 6.4% (n = 6). There was no in-group (oral vs IV) difference statistically (p-value 0.309) regarding cure and relapse cases. The mortality rate was nil during this period (Table -V).

So, the two groups (oral vs IV) showed no difference that could be statistically significant concerning the following outcomes: blood culture negativity, clinical cure, all-cause mortality, and patient parameters including gender, comorbidities, CRP (C-reactive protein), WBCs (white blood cells), ESR (erythrocyte sedimentation rate), agglutination titer, and side effects except the age of patients.

DISCUSSION

Adult brucellosis has a non-specific broad-spectrum clinical exhibition. Early diagnosis and remission of difficult cases is the optimal goal to prevent treatment failure and deaths due to disease relapse and drug resistance. Commonly, brucella bacteremia patients' clinical features and laboratory characteristics did not differ from non-bacteremia brucellosis patients, but bacteremia patients were present early in their course of illness [12]. So, the purpose of this study was to observe the blood culture negativity and cure rate of intravenous versus oral anti-brucella therapy in bacteremia brucellosis patients.

The rate of brucellosis blood culture positivity differs from 15% to 90% according to the phase of the disease. Bacteremia in brucellosis was documented in almost 55% of Chinese studies [13,14], 45.6% in an Indian study [15], and 40% in Saudi Arabia [16]. The current study observed bacteremia in 46.97% of adult brucellosis patients, which is almost comparable to previous literature.

In this study, the two groups (oral vs. IV) were almost similar in terms of demographics, clinical presentations, and laboratory parameters. So, these two groups were similar enough to allow a comparison between the results of the antibiotic regimens in bacteremia patients. During the first six weeks of therapy, both groups had a cure rate of 93.5% and a relapse rate of 6.4%, with a P-value of > 0.397. In other words, patients in both groups had almost the same recovery rate from bacteremia, and the relapse rate was similar in both groups.

The mean age of the patients in our study was 45.3 ± 18.75 years, which is almost like the Chinese study (47.1± 14.4) [12], and KSA study (50 years) [16], But it was higher than the mean age (29.5 years) reported in another study in Saudi Arabia [3].

This disease is frequently seen more in men, as reported in other local and international literature [3,12,16]. This age and gender difference is likely because drinking raw milk and eating raw dairy products is more frequent among elderly males.

In our study, the most common presenting symptoms were fever (97.8%), fatigue (52.7%), and musculoskeletal pain (23.6%). Common comorbidities were diabetes mellitus (20.4%), hypertension (17.2%), liver diseases (5.4%), and chronic kidney disease (2.1%), which were almost comparable with our studies with some variations. Different populations and study settings can explain these differences.

To my knowledge, no study compares the efficacy of antibiotic regimens (oral vs. IV) in only brucellosis bacteremia adult patients. Multiple regimens are being followed in different countries for brucellosis treatment because of the lack of multiethnic, randomized trials for different treatment regimens. Using two or more antibiotics to treat brucellosis is the currently recommended treatment regimen [8].

Data documented that the doxycycline-rifampicin regimen (DR) for six weeks still seems like a convenient first-line treatment for non-focal mild cases in most endemic areas [17].Studies showed that the combination of doxycycline plus gentamicin appeared to be similarly effective as streptomycin plus doxycycline (the traditional therapy) in some studies [9].

Traditionally, a duration of antibiotic treatment was required in focal brucellosis. International studies showed the recovery rate with the DR regimen was 88% and 90.5% with the co-trimoxazole–rifampin–gentamicin regimen [18].

Another trial compared the doxycycline-rifampin regimen with the doxycycline-rifampin-gentamicin regimen. A relapse rate of 13.8% was observed in the doxycycline-rifampin group, as compared to 4.6% in the doxycycline-rifampin-gentamicin group [18].Recent local and international literature shows that in both complicated and uncomplicated brucellosis, symptom resolution and clinical cure were nearly equal in the two groups (on dual and triple therapy) [19,20].

The literature demonstrates that “doxycycline with co-trimoxazole is equivalent to doxycycline-rifampicin in efficacy and should be preferred in countries with a high prevalence of tuberculosis. Nonetheless, rifampicin should be part of the treatment regimen for neuro brucellosis and endocarditis and is the mainstay in pregnant women and children” [21,22].

Similarly, another local article found no difference in cure rates in non-focal brucellosis when using the regimens of oral doxycycline with rifampicin or aminoglycoside, versus doxycycline with co-trimoxazole [23].

The cure rate was 96%. Different studies have been performed on the relapse rate of brucellosis after an appropriate course of treatment. Our study observed a relapse rate of 6.4%. Internationally, the relapse rate with various treatment regimens ranged from 6.7% to 15% [24].

The relapse of the disease depends upon multiple factors and one of them is the intracellular position of the organism (which protects it from the antibiotic effects and the immune mechanisms of the host), and the second one is re-exposure to the organism. This factor is seen more in KSA because of the traditional usage of camel and sheep products.

Given that the gentamicin-doxycycline-rifampicin (GDR) IV regimen and the doxycycline-rifampicin (DR) oral regimen both cure bacteremia focal and non-focal brucellosis in adult patients, although the duration of therapy is longer in complicated brucellosis, So, the above literature

interpretation concluded that the doxycycline and rifampicin regimen (oral) still seems like a reasonable, effective, cheap, and suitable first-line treatment in non-focal and focal bacteremia brucellosis in most endemic areas.

CONCLUSION

Most cases of brucellosis bacteremia in adults can be readily treated with the combination of doxycycline and rifampicin (in a dose adjusted to body weight) for six weeks. So, it will improve adherence and outcomes and avoid parenteral drugs when feasible. Complicated cases of brucellosis need a more careful evaluation of the patient and therapeutic intervention. This local expertise's findings can serve as guidance for the future.

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Authors' Contribution:

Imran Nazir: Substantial contributions to the conception and design of the work.
Mohammed A Al-Mat Rafi: The acquisition and analysis of data for the work.
Fozia Bashir Basal: Interpretation of data for the work.
Nouf Alsahaf: Drafting the work.
Ahmed F Aboelazm: Reviewing it critically for important intellectual content.
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