Review Paper

Comparing the Efficacy of Gentamicin and Streptomycin on Brucellosis: A Systematic Review

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ABSTRACT

Background: Brucellosis is the most common zoonotic infection, which is transmitted to humans through direct contact with infected animals or their products (e.g. milk). Choosing an appropriate antibiotic regimen that minimizes recurrence and treatment failure has always been a challenging aspect of treating brucellosis. In recent years, several studies have compared the efficacy of streptomycin and gentamicin in treating brucellosis, but it is still not completely clear which antibiotic is superior.

Methods: Medline and Scopus databases were searched. All English articles published from January 2006 until January 2020 that assessed the efficacy of streptomycin and gentamicin in treating human brucellosis were carefully evaluated.

Results: In total, 11 studies met the inclusion criteria. Of these, 2 were reviews, 2 were clinical trials, and the other 7 studies were lab experiments. Four studies had been performed in Iran. The number of subjects in the evaluated articles ranged from 50 to 323. Most studies focused on the adult population, with only one specifically focusing on children above 8 years old. Human brucellosis agents were almost equally sensitive to streptomycin and gentamicin in lab experiments. In clinical trials, both antibiotics were effective in treating brucellosis.

Conclusion: Streptomycin and gentamicin could safely be used with doxycycline to treat brucellosis successfully.

Keywords: Brucellosis, Treatment, Gentamicin, Streptomycin, Zoonotic infection

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Introduction

Brucellosis is the most common human-animal infectious disease (zoonosis) transmitted through infected animals and their products, such as milk and dairy products. Symptoms of this disease in humans include fever, chills, sweating, joint pain, muscle pain, headache, etc. The high prevalence of this disease, not only in Iran but also in the world, has made it one of the most important zoonotic diseases [1].

According to the World Health Organization (WHO) reports, more than 122000 new cases of brucellosis occur annually in the world and they are distributed in different regions. The cause of this disease is a gram-negative bacillus called *Brucella*, which is eliminated by pasteurization and boiling. This disease is very important in most parts of the world, especially in developing countries, in terms of public health and its impact on the socio-economic status of society. In many developed countries, control of the disease in animals has significantly reduced its prevalence in humans. However, brucellosis is still common in developing countries, especially in the Mediterranean, West Asia, Africa and the United States [1].

The type and severity of brucellosis vary depending on the type of bacteria transmitted from the animal. *Brucella melitensis* is the most pathogenic species that causes severe symptoms and tissue damage in the body's organs, systems, or tissues. This species is transmitted directly or indirectly from infected sheep, goats, or their products. It is the most common cause of human brucellosis in the world and Iran.

Brucella suis is another bacterium that causes brucellosis, which can cause necrosis and abscess formation. *Brucella abortus*, which is usually the source of infection in cattle, has the least pathogenicity. Still, it can produce tissue damage by forming abscesses, although it is much less common than *B. melitensis*.

Brucella canis, which causes brucellosis in dogs and other canids, is rare but causes clinical manifestations similar to those of other species. Brucellosis occurs in two types, acute and chronic, with various clinical manifestations. Therefore, physicians often have difficulty diagnosing this disease. Symptoms of brucellosis can occur days to months after infection. Signs and symptoms are similar to influenza, including fever, chills, sweating, weakness, fatigue, back pain, joint and muscle aches, and headaches.

In some people, brucellosis can become chronic and remain for years or even after treatment. Long-term signs and symptoms include fatigue, fever, arthritis, and spine inflammation. It should be noted, however, that these symptoms occur in acute, subacute, chronic, and localized forms, depending on the type of *Brucella* and the severity of the disease [1].

As mentioned, brucellosis is one of the most common infectious diseases and has several different treatment protocols. Choosing an effective treatment protocol for brucellosis from among the various protocols associated with a lower risk of recurrence and failure in treatment has always been one of the challenges of medical knowledge. One of the controversial issues in determining the appropriate treatment protocol for brucellosis is the selection of the appropriate antibiotic. In recent years, various studies have compared the effects of the two antibiotics gentamicin and streptomycin in treating brucellosis. However, the final result of choosing one of these two treatment regimens has never been achieved [2].

Methods

Study plan

A systematic review was conducted using a predefined protocol based on PRISMA. This study used PubMed, Embase, Google Scholar, Science Direct, Scopus, ProQuest, and Web of Science databases to search for articles. All prospective and retrospective laboratory, clinical, interventional, descriptive, and cohort articles published in English from July 2006 to July 2020 were examined. The initial search result was 34 studies in the Medline database and 47 in the Scopus database. After deleting similar articles, systematic review articles, and articles published in languages other than English, the titles of the articles were reviewed, and unrelated articles were removed, leaving a total of 24 articles related to the present study. Two independent reviewers assessed articles to ensure their eligibility for inclusion. Finally, 11 articles were included in the study according to the inclusion criteria.

Search strategy

In this systematic review, we reviewed databases (PubMed, Embase, Google Scholar, Science Direct, Scopus, Embase, and Web of Science) for studies evaluating the efficacy of gentamicin and streptomycin in the treatment of brucellosis in humans from July 1. We searched from 2006 to July 1, 2020, limited to English articles. The main terms MeSH used in electronic searches were

as follows: (ALL [gentamyc *] AND ALL [brucell * OR "malta fever" OR "gibraltar fever" OR "rock fever" OR "cyprus fever" OR "undulant fever "] AND ALL [streptomyc *]). ([Gentamycins] OR [garamycin] OR [gentacycol] OR [gentamicin sulfate] OR [sulfate, gentamicin] OR [gentamicin sulfate (USP)] OR [gentave] OR [OR [G-myticin] OR [G myticin] OR [Gmyticin] OR [gentamicin] OR [gentamycin]) AND ([brucelloses] OR [malta fever] OR [fever, malta] OR [gibraltar fever] OR [fever, gibraltar] OR [rock fever] OR [fever, rock] OR [Cyprus fever] OR [fever, Cyprus] OR [*Brucella* infection] OR [*Brucella* infections] OR [infection, *Brucella*] OR [undulant fever] OR [fever, undulant] OR [brucellosis, pulmonary] OR [brucelloses, pulmonary] OR [pulmonary brucelloses] OR [pulmonary brucellosis]) AND ([streptomycine panpharma] OR [streptomycin grünenthal] OR [estreptomycin CEPA] OR [strepto-hefa] OR [strepto hefa] OR [Streptomycin Clariana] OR [estreptomycin normon] OR [smtreptol] OR [strepto sulfate] OR [streptomycin sulfate (2: 3) Salt] OR [streptomycin sulphate]).

Inclusion criteria

An article is included if it meets the following criteria:

All articles that examined the effectiveness of gentamicin and streptomycin in treating brucellosis. Their publication date was from July 1, 2006, to July 1, 2020. Articles were published in the English language and are accessible in full text.

Exclusion criteria

After reviewing articles, studies with the following criteria were excluded:

The article's content is irrelevant to the subject under study (reviewed and approved by 2 reviewers separately). Articles that were published before July 2006. Articles that were published in any language except English. The full text of the published article is not available. Two reviewers independently coded and extracted data on study details, design and relevant results from the included studies. Studies were critically appraised for potential bias using a predefined set of criteria based on the CONSORT checklist (Figure 1).

Results

During the searches and review process, 11 studies met the inclusion criteria and were reviewed. Of these 11 studies, 2 were review studies, 2 were clinical trials, and 7 were laboratory studies. Four studies were related to our country, Iran, and others were conducted in Saudi Arabia, Kazakhstan, Turkey, Greece, Qatar, Brazil and Spain. In non-review studies (9 cases), the samples var-

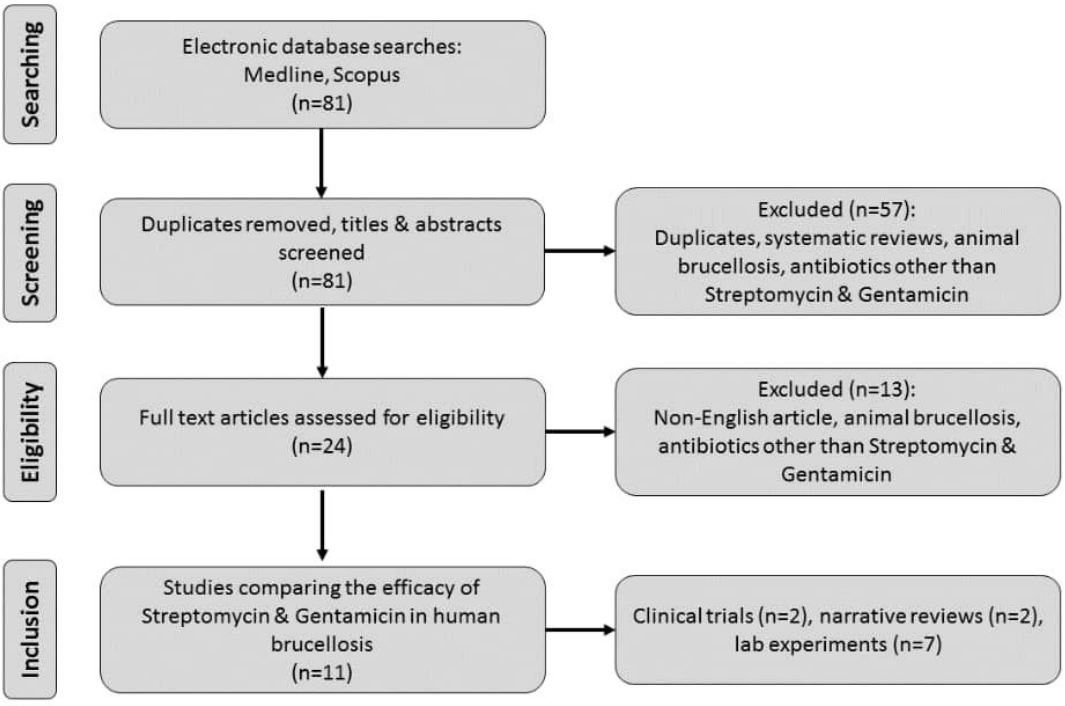

Figure 1. Study inclusion criteria flowchart

ied from 50 to 323. Most studies were performed on the adult population, and only one study (review type) was conducted specifically on children older than 8 years. The sex composition of the studies showed that in most studies, the number of men was more than that of women. A summary of the findings and the characteristics of the studies can be seen in the Table 1.

Discussion

According to the WHO report, out of 1709 pathogens, 832(49%) are transmitted from animals to humans. Because of the frequent use of animal products during the day, the possibility of transmission of these diseases is very high. Despite the efforts of many organizations to control this disease, it still causes death and disability in many people. One of the most common diseases transmitted from animals to humans is brucellosis, which is transmitted by *Brucella* species. Endemic brucellosis areas include the Mediterranean basin countries, the Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa, and parts of Mexico and Central and South America [3].

Approximately 500000 cases are reported annually, and an estimated 2.4 billion people are at risk. All age groups and both sexes are affected. The prevalence of brucellosis has increased due to growing international tourism and migration. Consumption of unpasteurized dairy products (especially raw milk, soft cheese, butter, and ice cream) is the most common means of transmission. Since fermentation occurs, hard cheese, yogurt,

Table 1. Baseline characteristics of the studies

Authors, Year	Country	Population (n)	Age Range/ Mean Age (y)	Gender (Male/ Female)	Study Design	Result
Hasanjani Roushan et al. 2010 [7]	Iran	164	>10	108 men / 52 women	Clinical trial	Gentamicin for 5 days plus doxycycline for 8 weeks is no more effective than streptomycin for 2 weeks with doxycycline for 45 days.
Hasanjani Roushan et al. 2006 [8]	Iran	191	34.95	109 men / 82 women	Random clinical trial	Oral doxycycline for 45 days with intramuscular gentamicin for 7 days is equivalent to oral doxycycline for 45 days with streptomycin for 14 days.
Ariza et al. 2007 [9]	Spain	-	-	-	Review	Suggested diet doxycycline with streptomycin (streptomycin 15 mg/kg daily intramuscularly for 2-3 weeks) doxycycline with gentamicin (5 mg/kg daily intravenously for 7 days)
Shevtsov et al. 2017 [10]	Kazakhstan	329	-	-	Laboratory	Sensitivity of all samples to streptomycin / 97.3% sensitivity of samples to gentamicin
Etiz et al. 2015 [11]	Turkey	50	-	33 men/ 17 women	Laboratory research	Complete sensitivity of all samples to streptomycin and gentamicin
Hasanjani Roushan & Amiri, 2013 [12]	Iran	-	Children <8	-	Review	Suggested diet doxycycline for 45 days or 8 weeks with gentamicin for 7 or 5 days, respectively doxycycline for 45 days and streptomycin for 14 days
Torkaman Asadi et al. 2017 [13]	Iran	149	82-11 (2.17±1.41)	105 men / 44 women	Laboratory	Complete sensitivity of all samples to streptomycin and gentamicin
Turkmani et al. 2006 [14]	Greece	74	-	-	Laboratory	Complete sensitivity of all samples to streptomycin and gentamicin
Deshmukh et al. 2015 [15]	Qatar	231	-	-	Laboratory	Complete sensitivity of all samples to streptomycin and gentamicin
Barbosa Pauletti et al. 2015 [16]	Brazil	147	-	-	Laboratory	96.6% sensitivity of samples to gentamicin / 98.6% sensitivity of samples to streptomycin
Ozhak-Baysan et al. 2009 [17]	Turkey	77	-	-	Laboratory	Suitable sensitivity of all samples to streptomycin and gentamicin

and sour milk are less hazardous. Due to *Brucella* RB51 (a live attenuated cattle vaccine strain that can be shed in milk), infection has been acquired via consumption of unpasteurized milk. Consumption of raw or undercooked muscle tissue or organ meat (such as liver and spleen) is a less common transmission mode [4].

Brucellosis is an occupational disease in shepherds, abattoir workers, veterinarians, dairy-industry professionals, and laboratory personnel (including laboratory workers handling *Brucella* cultures and workers preparing brucellosis vaccines for animal use [5].

Rare cases of human-to-human transmission due to blood transfusion, tissue transplantation, breastfeeding, sexual contact, congenital transmission, and nosocomial infection have been described [6].

This study reviewed 11 studies, including 2 review studies, 2 clinical trials, and 7 laboratory studies, to evaluate the effectiveness of gentamicin and streptomycin in treating brucellosis in humans. Most studies have shown that the bacterium that causes brucellosis in laboratory studies has almost the same sensitivity to gentamicin and streptomycin. In the clinic, both drugs have almost the same effectiveness in treating brucellosis, so both medicines can be combined with doxycycline.

Hasanjani Roushan et al. evaluated the effectiveness of gentamicin and streptomycin in treating brucellosis in a 2010 clinical trial in Iran. The study was performed on 164 people, including 108 men and 52 women; all participants were over 10 years old. In this study, the effect of gentamicin for 5 days with doxycycline for 8 weeks was not superior to streptomycin for 2 weeks plus doxycycline for 45 days [7].

In another study by the same author and colleagues in Iran in 2006, which was conducted as a randomized trial, 191 people participated, 109 of whom were men and 82 were women. The mean age reported in the study was 34.95 years. The study found that oral doxycycline for 45 days plus intramuscular gentamicin for 7 days was as effective as treatment with doxycycline for 45 days plus streptomycin for 14 days [8].

A review study by Ariza et al. in Spain, in 2007, found that the efficacy of doxycycline with streptomycin intramuscularly at a daily dose of 15 mg/kg for 2-3 weeks is similar to doxycycline with gentamicin, which is given intravenously daily at 5 mg/kg for 7 days [9].

Shevtsov et al. conducted a study in Kazakhstan in 2017. In this study, which was performed on 329 samples, it was stated that all samples were sensitive to streptomycin and 97.3% to gentamicin [10].

Another study by Pinar Etiz from Turkey, published in 2015, looked at 50 samples, 33 of which were male and 17 of which were female. According to the results of this study, all samples were sensitive to streptomycin and gentamicin. Sampling in this study was done between 2008 and 2014 [11].

A review study by Hasanjani Roushan et al. was performed in Iran in 2013. It is mentioned that the preferred treatment for brucellosis in children older than 8 years is doxycycline for 45 days with streptomycin for 14 days or with gentamicin for 7 days [12].

Torkaman Asadi et al. conducted a laboratory study in 2013 and 2014 in Hamedan City, Iran, collecting 149 blood samples from patients with clinical suspicion of brucellosis, which was confirmed in 57 people with brucellosis. Examination of antibiotic susceptibility tests showed that all 57 samples were completely sensitive to both gentamicin and streptomycin antibiotics [13].

Turkmani et al. conducted a laboratory study in 2006 in Greece. They investigated 74 brucellosis samples, including 57 human and 17 animal samples, which were tested for sensitivity to various antibiotics. In this study, all samples were completely sensitive to gentamicin and streptomycin [14].

The results of another study conducted by Anand Deshmukh et al. in 2015 in Qatar were consistent with this study, which examined 231 samples. All samples were equally sensitive to gentamicin and streptomycin [15].

Another laboratory study in Brazil was conducted in 2015 by Barbosa Pauletti et al. They studied 147 blood samples taken from infected animals and the sensitivity to gentamicin and streptomycin was 96.6% and 98.6%, respectively [16]. Another laboratory study conducted in 2009 by Ozhak-Baysan et al. in Turkey showed that gentamicin and streptomycin had good effects on brucellosis samples [17].

Four studies were related to our country, Iran, and others were conducted in Saudi Arabia, Kazakhstan, Turkey, Greece, Qatar, Brazil and Spain. As expected, brucellosis is a common problem in Asian and Middle Eastern countries, and finding a suitable and effective antibiotic regimen to treat the disease in these areas is a high priority.

The results of the present study indicate that streptomycin and gentamicin are equally effective in treating brucellosis in humans and, consequently, in cases where only one of these two drugs is available, or in cases where it is possible to use one. It is not possible to use alternative antibiotics that can be used with the same effectiveness and efficiency.

Most studies on brucellosis treatment have been performed in vitro by examining the sensitivity of the samples to various antibiotics. Due to the small number of clinical trial studies that have evaluated the effectiveness of different antibiotic regimens in the treatment of brucellosis and the age of most such studies, it is suggested that more clinical trials will be more extensive in future research. To determine the ideal treatment regimen for brucellosis.

Conclusion

Due to the high prevalence and unwanted side effects of the disease (relapse and treatment failure), special attention to treatment is of particular importance. Brucellosis treatment aims to control the disease and prevent complications, recurrence, and sequelae. Since *Brucella* is an intracellular microbe, long-term treatment combines treatment elements. Depending on the type of malta fever (focal and non-focal involvement), the treatment method, duration and combination of treatment differ. The preferred treatment method for brucellosis is to use the combination of doxycycline plus streptomycin, which improves the patient's symptoms faster and reduces the disease's recurrence.

Also, compared to the treatment recommended by the WHO (rifampin plus doxycycline), the mentioned treatment does not cause the possibility of resistance to anti-tuberculosis drugs. At the same time, streptomycin sometimes becomes scarce in some regions of our country, which causes concern for patients looking for a faster treatment method to improve symptoms. It is important to find a treatment that is equally effective as a treatment with streptomycin. Another aminoglycoside, gentamicin, is expected to have the same therapeutic efficacy as streptomycin, although it will impose a lower treatment cost on the patient. This review investigates the equal effectiveness of gentamicin compared to streptomycin by performing a meta-analysis, which will greatly help treat this disease. The present study was a systematic review conducted to compare the efficacy of gentamicin and streptomycin in treating brucellosis in humans. To conduct this study, the Medline and Scopus databases were searched from July 2006 to July 2020, and two independent judges evaluated 11 studies according to the inclusion criteria. The study of these articles showed that streptomycin and gentamicin are equally effective in the treatment of brucellosis in humans and, as a result, both alternative antibiotics can be used effectively in treating patients. However, it should be noted that most studies in this field are laboratory studies. To confirm these tests and obtain more reliable results, it is necessary to conduct clinical trials to determine the ideal treatment regimen for brucellosis.

Study limitations

Among the weaknesses and limitations of the present study is the restriction of the search to English-language articles. Because brucellosis is a common problem in Asian and developing countries, restricting the search to English-language articles may result in ignoring a significant portion of relevant clinical findings and evidence.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Theoretical formalism, data analysis, supervision and numerical simulations: Reza Ahmadi; Final approval: Vida Vakili and Parsa Sharifpour.

Conflict of interest

The authors declared no conflict of interest.

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