Original Article

J Babol Univ Med Sci
23; 2021. P: 252-258

# The Effectiveness of Vitamin A on the Symptoms of Brucellosis

**N. Ahmadvand (MD)[1], N. Zarinfar (MD)[*1], M. Soofian (MD)[1]**

1.Department of Infectious disease, School of Medicine, Arak University of Medical Sciences, Arak, I.R.Iran

**J Babol Univ Med Sci; 23; 2021; PP: 252-258**

**Received: Aug 14th 2020, Revised: Oct 5th 2020, Accepted: Oct 27th 2020.**

## ABSTRACT

**BACKGROUND AND OBJECTIVE:** Vitamin A in the immune system is considered as an anti-inflammatory vitamin that has anti-infective effects in infectious diseases. Therefore, this study was performed to evaluate the effectiveness of vitamin A as one of the complementary therapies in the treatment of brucellosis.

**METHODS:** In this experimental study, 110 people were selected as brucellosis patients based on serological test and were placed in two groups of control and intervention. In addition to the usual drugs for the treatment of brucellosis, patients in the intervention group received oral vitamin A at a dose of 25,000 units pre day for 6 weeks, and patients in the control group did not receive vitamin A. After the intervention, the response to treatment was evaluated based on the number of days of fever, chills, sweating, arthralgia, myalgia, anorexia, chronicity and recurrence using standard methods in the two groups.

**FINDINGS:** In terms of days with fever (14.72±27.61 vs. 53.45±141.14), sweating (19.27±28.98 vs. 61.09±142.35), arthralgia (56±96.83 vs. 53.45±158.18), myalgia (13.45±27.23 vs. 52.36±141.44) and anorexia (13.30±47.39 vs. 51.81±129.8), a significant decrease was observed in the intervention group compared to the control ($p<0.05$). There was no difference between the intervention and control groups in terms of chills ($p=0.122$). The recurrence rate in the control and intervention groups was 25.5% and 7.3%, respectively, and the chronicity rate was 3.6% and 0%, respectively, which was statistically significant ($p<0.05$).

**CONCLUSION:** Based on the results of the study, it can be said that vitamin A leads to faster improvement of brucellosis symptoms and it can be used as a complementary treatment for brucellosis.

**KEY WORDS:** *Brucellosis, Vitamin A, Treatment Outcome*.

**Please cite this article as follows:**

Ahmadvand N, Zarinfar N, Soofian M. The Effectiveness of Vitamin A on the Symptoms of Brucellosis. J Babol Univ Med Sci. 2021; 23: 252-8.

[*]**Corresponding Author: N. Zarinfar (MD)**
**Address:** Department of Infectious disease, School of Medicine, Arak University of Medical Sciences, Arak, I.R.Iran
**Tel:** +98 86 32241411
**E-mail:** nzarinfar@yahoo.com

## Introduction

Brucellosis is the most common zoonotic disease and is a major public health problem in many developing countries (1). According to the World Health Organization (WHO), brucellosis is considered a growing and neglected disease (2). The average incidence of this disease in Iran is 29.83 per 100,000 population (3). The clinical manifestations of this disease in humans are very diverse, so to diagnose this disease, microbial culture, serological tests (Serological tests) and nucleic acid amplification are used (4). In humans, the disease is known as Malta fever, Bang fever, ague, or Mediterranean fever (5).

The goal of treatment for brucellosis is to control the disease and prevent its complications, recurrence and subsequent consequences (6). General principles for brucellosis treatment include the use of antibiotics active in acidic intracellular environments (such as doxycycline and rifampin) and the use of combination therapy (due to the high recurrence rate of monotherapy) and the long duration of treatment (7). In one study, it was found that among the various treatment regimens for brucellosis, the combination of doxycycline, rifampicin, and gentamicin was more effective than other treatment regimens (8). The rate of treatment failure in using these treatment regimens is 3.1 to 26% and the recurrence rate is 2.4 to 26% (9, 10).

Because brucellosis is an intracellular bacterium, the cellular immune system is the body's main defense mechanism against this bacterium (11). As a result, strengthening the cellular immune system, especially increasing interleukin 10, can improve the treatment status of patients with brucellosis (12). Studies have shown that deficiencies in some elements and vitamins, including vitamin A, have long-term effects on the cellular immune system (13). Recent research has identified it as an anti-inflammatory vitamin because of its positive effect on the immune system. These studies have shown that vitamin A has therapeutic effects on infectious diseases (14).

In previous studies, the effects of vitamins E (15) and D (16) on brucellosis have been studied. Kurtaran et al. showed that vitamin D and vitamin D receptor levels were lower in people with brucellosis (16). Although no research has been done on the effectiveness of vitamin A on the symptoms of brucellosis, recent research has identified vitamin A deficiency as one of the risk factors for brucellosis (17). Some early trials have also shown the effectiveness of vitamin A in the treatment of brucellosis (18, 19). In a study conducted by Salehi et al., it was observed that the duration of symptom improvement between the control and intervention groups was statistically the same, but the incidence of recurrence in patients in the intervention group was significantly lower than patients in the control group (19). In another study by Kurmanova et al., it was found that the use of vitamin A at a dose of 33,000 units three times a day for 10 to 12 days, during the treatment of patients with acute and subacute brucellosis, reduced the duration in the period of symptoms in these patients (18).

Considering the cases of failure and recurrence of the disease in using different treatment regimens of brucellosis (20) and considering the growing trend of this disease (21), it seems that the use of complementary therapies is of great importance and necessity. On the other hand, due to the strengthening effects of vitamin A on the immune system, it seems necessary to use vitamin A as an adjunct treatment in this disease. Therefore, the aim of this study was to evaluate the effectiveness of vitamin A on clinical symptoms and treatment outcome in patients with brucellosis.

## Methods

This experimental study was performed according to the instructions approved by the ethics committee of Arak University of Medical Sciences with ethics code IR.ARAKMU.REC.1397.106 and clinical trial registration number IRCT20180815040807N1 in Vali-e-Asr Hospital in Arak.

A total of 110 patients with brucellosis were divided into control and intervention groups based on Wright serology test and clinical interview. Patients were enrolled in the study despite the symptoms of Brucella and a positive serological test, and were excluded from the study if there were focal complications including Brucella spondylitis, Brucella endocarditis, Noro Brucellosis, Sacroiliitis, and Epididymo-orchitis or any immunodeficiency.

The two groups were examined in terms of age, gender, absence of underlying immunodeficiency and use of interfering drug, place of residence (city or village), contact with livestock, history of consumption of unpasteurized local dairy products. Furthermore, each of the ESR, CRP, Wright's serologic test, Coombs Wright test and 2ME, CBC diff and LFT tests were performed at the beginning of the study and, if necessary, according to the history and paraclinical

examinations of the patient (MRI, echocardiography, etc.) to rule out possible focal cases. Patients in both groups received rifampin at a dose of 600 mg once a day for 6 weeks and doxycycline at a dose of 100 mg twice a day for 6 weeks, except that the patients in the intervention group received vitamin A orally at a dose of 25,000 units per day for 6 weeks. Criteria for measuring the effectiveness of treatment were considered based on the symptoms of the disease (number of days of fever, number of days of chills, number of days of sweating, number of days of myalgia and number of days of anorexia), chronicity, death and recurrence of the disease. These cases were obtained through a checklist of symptoms of brucellosis. Patients' symptoms were compared after the intervention. The general framework of the present research design can be seen in the table below. Research data were analyzed using SPSS software version 22 and t-student and Chi-square tests and $p<0.05$ was considered significant.

**Table 1. Research outline**

| Steps / Group | Selection | Sample size | Pre-test | Intervention | Post-test |
|---|---|---|---|---|---|
| Intervention group | RE | 55 | $T_1$ | X | $T_2$ |
| Control group | RC | 55 | $T_1$ | - | $T_2$ |

## Results

The mean age in the intervention group was 18.31±42.67 and in the control group was 15.36±43. There were no significant differences between the two groups in terms of gender, absence of underlying immunodeficiency and use of interfering drug, place of residence (city or village), contact with livestock, history of consumption of unpasteurized local dairy products (Table 2).

**Table 2. Demographic characteristics of control and intervention groups**

| Characteristics | Control group | Intervention groups |
|---|---|---|
| **Gender** | | |
| male | 32 | 36 |
| female | 23 | 19 |
| Age (Mean±SD) | 42.87±18.31 | 43±15.36 |
| **Contact with livestock** | | |
| yes | 50 | 47 |
| no | 5 | 8 |
| **History of consumption of unpasteurized local dairy products** | | |
| yes | 49 | 46 |
| no | 6 | 7 |
| **Place of residence** | | |
| city | 3 | 8 |
| village | 52 | 47 |

The results showed a significant difference in the symptom of fever in the post-treatment phase between the two group, indicating a significant decrease in the intervention group with a mean of (14.72±27.61) compared to the control group with a mean of (53.45±141.14) (t=1.99, p=0.048). However, there was no significant difference in chills symptom between control groups with a mean of (26.63±103.02) and intervention with a mean of (3.27±10.55). The results showed a significant difference in the symptom of sweating in the post-treatment phase between the two groups, indicating a significant decrease in the intervention group with a mean of (19.27±28.98) compared to the control group with a mean of (61.9±142.35) (t=2.135, p=0.035). Furthermore, in the intervention group, arthralgia symptom with a mean of (56±96.83) showed a significant decrease compared to the control group with a mean of (107.45±158.18) (t=2.057, p=0.042). Symptoms of myalgia in the intervention group with a mean of (13.45±27.23) compared to the control group with a mean of (52.36±141.44) showed a significant decrease after the intervention (t=2, p=0.048). After the intervention, significant decrease was observed in symptom of anorexia in the intervention group with a mean of (13.3±47.39) compared to the control group with a mean of (51.81±129.80) (t=2.06, p=0.041) (Table 3). Results of Chi-squared to determine the difference between the two groups in terms of complete recovery ($x^2=19.52$, $p<0.01$), recurrence ($x^2=18.15$, $p<0.01$) and chronicity ($x^2=23.62$, $p<0.01$) indicated a significant difference between the intervention and control groups. Thus, the rate of recurrence and chronicity in the intervention group was less than the control group and the rate of complete recovery in the intervention group was higher than the control group (Table 4).

**Table 3. Differences in clinical and laboratory characteristics before and after treatment of patients in the two groups**

| Symptom | Control group Mean±SD | Intervention group Mean±SD | t-value | p-value |
|---|---|---|---|---|
| **Fever** | | | | |
| Before treatment | 17.72±28.72 | 2.34±40.85 | -0.834 | 0.406 |
| After treatment | 53.45±141.14 | 14.72±27.61 | 1.99 | 0.048 |
| **Chills** | | | | |
| Before treatment | 17.30±28.92 | 23.34±40.85 | 0.202 | 0.841 |
| After treatment | 26.63±103.02 | 3.27±10.55 | 0.160 | 0.112 |
| **Sweating** | | | | |
| Before treatment | 11.61±13.05 | 23.27±21.67 | -3.46 | 0.001 |
| After treatment | 61.09±142.35 | 19.27±28.98 | 2.135 | 0.035 |
| **Arthralgia** | | | | |
| Before treatment | 23.25±32.68 | 28.87± 27.92 | -0.953 | 0.343 |
| After treatment | 107.45±158.18 | 56± 96.83 | 2.057 | 0.042 |
| **Myalgia** | | | | |
| Before treatment | 11.14±15.91 | 15.90±24.26 | -1.21 | 0.226 |
| After treatment | 52.36±141.44 | 13.45±27.23 | 2 | 0.048 |
| **Anorexia** | | | | |
| Before treatment | 19.50±26.08 | 22.60±35.36 | -0.522 | 0.603 |
| After treatment | 51.81±129.80 | 13.3±47.39 | 2.06 | 0.041 |

**Table 4. Table of values related to recurrence and chronicity of symptoms and Chi-square test to compare intervention and control groups after intervention**

| Group | Complete recovery | | | Recurrence | | | Chronicity | | |
|---|---|---|---|---|---|---|---|---|---|
| | number(%) | $x^2$ | p-value | number(%) | $x^2$ | p-value | number(%) | $x^2$ | p-value |
| Control | 39(70.9) | 19.52 | 0.01 | 14(25.5) | 18.15 | 0.01 | 2(3.6) | 23.62 | 0.01 |
| Intervention | 51(92.7) | 19.52 | 0.01 | 4(7.3) | 18.15 | 0.01 | 0(0) | 23.62 | 0.01 |

## Discussion

The results of this study show that the administration of 25,000 units of vitamin A per day for 6 weeks is effective on the symptoms of fever, sweating, arthralgia, myalgia and anorexia in people with brucellosis. However, vitamin A did not reduce the symptoms of chills in patients. The results also show that taking vitamin A reduces the recurrence and chronicity of brucellosis and improves complete recovery. Kurmanova et al. showed that the use of 33,000 units of vitamin A three times a day for 10 to 12 days in the treatment of patients with acute and subacute brucellosis reduces the duration of symptoms in these patients (18). In the present study, it was also shown that administration of vitamin A for 6 weeks reduces the symptoms of brucellosis. Cash-Goldwasser et al. also showed in their study that vitamin A can have therapeutic effects on infectious diseases by improving the immune system (17). Although the immune system was not directly studied in our study, since brucellosis is also an infectious disease, it can be said that the effectiveness of this vitamin is based on improving the immune system. That's because vitamin A is involved in both the production of antibodies and the activation of immune T cells. Since cell-mediated immune system is the body's main defense mechanism against this disease (11), it seems that people who have a weaker immune system or are malnourished are more susceptible to this disease and its symptoms (12). In a study by Yingst et al., it was found that deficiency of iron, zinc, vitamin B6, vitamin A, copper, sodium, and vitamin D affected cell-mediated immune systems in the long term (11). In another study conducted by Salehi et al., the results showed that the duration of symptom improvement between the control and intervention groups was statistically the same, but the incidence of recurrence in patients in the intervention group was

significantly lower than patients in the control group (19). However, in our study, vitamin A also reduced the recovery time of symptoms. This discrepancy between the results of the present study and Salehi may be due to the duration of vitamin A consumption, which was 3 weeks or less in the study of Salehi et al. In another study, it was found that taking vitamin A for 4 weeks improved both symptoms and recurrence rate in patients (19), which was consistent with the results of the present study.

In the present study, with increasing the duration of vitamin A consumption for 6 weeks compared to previous studies, the process of improving patients' symptoms and treatment outcome (reducing recurrences and not causing chronic cases) has been associated with better results than previous studies and it seems that the effects of vitamin A on cellular immunity are more pronounced over a longer period of time, and since patients do not show signs of hypervitaminosis during treatment and follow-up, it seems that this dose and duration of treatment can be combined with standard and common treatments for brucellosis in an uncomplicated and safe way.

However, the results of the present study showed that the effect of vitamin A on the symptoms of chills is no different from the use of standard drugs. This may be due to the effectiveness of common treatments for acute symptoms such as chills, or the fact that the symptoms of chills remain spontaneously less than other symptoms in a person.

Based on the results of the present study and its comparison with previous studies, it is concluded that the use of vitamin A supplementation with a dose of 25,000 units for 6 weeks with appropriate antibiotic therapy in the treatment of patients with brucellosis may improve therapeutic outcome in these patients and reduces both the duration of symptoms and the rate of recurrence and chronicity of the disease, which can be achieved through the effect of vitamin A on increasing the body’s immune system and thus patient’s resistance to the disease.

In conducting this study, we faced limitations such as patients not visiting on time and lack of full cooperation, which is recommended to be removed in future studies with more detailed follow-up and the establishment of specialized clinics for brucellosis. Moreover, due to technical and time limitations, the effect of vitamin A on the immune system was not studied. Therefore, it is suggested that in future studies, the effectiveness of vitamin A in other doses on the symptoms of the disease and on the immune system be investigated.

## Acknowledgment

We would like to thank the Vice Chancellor of Research and Technology of Arak University of Medical Sciences and all the staff of Vali-e-Asr Hospital and the patients who cooperated in conducting the research.

## References

1.Centers for Disease Control and Prevention. Brucellosis reference guide: exposures, testing, and prevention. Centers for Disease Control and Prevention. Atlanta: Centers for Disease Control and Prevention; 2017. Available from: https://www cdc gov/brucellosis/pdf/brucellosi-reference-guide pdf

2.Franc KA, Krecek RC, Häsler BN, Arenas-Gamboa AM. Brucellosis remains a neglected disease in the developing world: a call for interdisciplinary action. BMC public health. 2018;18(1):125.

3.Rostami H, Tavana AM, Tavakoli HR, Tutunchian M. Prevalence study of brucellosis in Iranian military forces during 2001-2009. J health polic sust health. 2015;2(2):191-5.

4.Yagupsky P, Morata P, Colmenero JD. Laboratory diagnosis of human brucellosis. Clin Microbiol Rev. 2019;33(1):e00073-19.

5.Galinska EM, Zagórski J. Brucellosis in humans-etiology, diagnostics, clinical forms. Ann Agric Environ Med. 2013;20(2):233-8.

6.Centers for Disease Control and Prevention. Third Case of Rifampin/penicillin-resistant strain of RB51 Brucella from consuming raw milk. 2019. Available from: https://www.vdh.virginia.gov/blog/2019/01/23/third-case-of-rifampin-penicillin-resistant-strain-of-rb51-brucella-from-consuming-raw-milk/

7.Bosilkovski M. Brucellosis: treatment and prevention. UpToDate. 2021. Available from: https://www.uptodate.com/contents/brucellosis-treatment-and-prevention/print

8.Skalsky K, Yahav D, Bishara J, Pitlik S, Leibovici L, Paul M. Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. Bmj. 2008;336(7646):701-4.

9.Bayindir Y, Sonmez E, Aladag A, Buyukberber N. Comparison of five antimicrobial regimens for the treatment of brucellar spondylitis: a prospective, randomized study. J Chemother. 2003;15(5):466-71.

10.Hasanjani Roushan MR, Soleimani Amiri MJ, Janmohammadi N, Sadeghi Hadad M, Javanian M, Baiani M, et al. 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. J Antimicrob Chemother. 2010;65(5):1028-35.

11.Yingst S, Hoover DL. T cell immunity to brucellosis. Crit Rev Microbiol. 2003;29(4):313-31.

12.Maliji GH, Sadeghi M, Haji Ahmadi M, Karimi AK, Mosavi Kani E. Comparison of serum level of interleukin (il)-10 and interleukin (il)-12 human brucellosis in cattle owners and health controls (babol). J Babol Univ Med Sci. 2008;10(3):30-4. [In Persian]

13.Qadir MI, Rozi M. Overview of university students about causes and treatment of bacterial disease Brucellosis. Glob J Rare Dis. 2019;4(1):001-2.

14.Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. J Clin Med. 2018;7(9):258.

15.Nemec M, Hidiroglou M, Nielsen K, Proulx J. Effect of vitamin E and selenium supplementation on some immune parameters following vaccination against brucellosis in cattle. J Anim Sci. 1990;68(12):4303-9.

16.Kurtaran B, Akyildiz O, Ulu AC, Inal SA, Komur S, Seydaoglu G, et al. The relationship between brucellosis and vitamin D. J Infect Dev Ctries. 2016;10(2):176-82.

17.Cash-Goldwasser S, Maze MJ, Rubach MP, Biggs HM, Stoddard RA, Sharples KJ, et al. Risk factors for human brucellosis in northern Tanzania. Am J Trop Med Hyg. 2018;98(2):598-606.

18.Kurmanova KB, Ishchanova RZh, Sakhisheva SSh, Studentsova VK, Tsirel'son LE, Alshinbaeva GU. Increasing the effectiveness of antibiotic therapy by correcting immunologic disorders with vitamin A in patients with brucellosis. Antibiot Khimioter. 1990;35(7):35-8.

19.Salehi M, Salehi H, Salehi MM, Salehi M. Comparison between antibiotic therapy of Brucellosis with and without vitamin A. Adv Biomed Res. 2014;3:245.

20.Golshani M, Buozari S. A review of brucellosis in Iran: epidemiology, risk factors, diagnosis, control, and prevention. Iran Biomed J. 2017;21(6):349-59.
21.Enkelmann J, Stark K, Faber M. Epidemiological trends of notified human brucellosis in Germany, 2006-2018. Int J Infect Dis. 2020;93:353-8.