



## Comparison of the Behavioral Changes in Pain Patterns in Brucellosis Patients under Oral Gabapentin and Naproxen Treatment: A Randomized Clinical Trial

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### Abstract

**Background:** Brucellosis is a common disease between humans and animals which can cause various types of organ involvement. Of the most common and important disorders, it is a skeletal disorder that causes severe pain. The aim of this study was done to compare the behavioral changes in pain patterns in brucellosis patients under oral gabapentin and naproxen treatment.

**Methods:** This study was a paralleled randomized controlled clinical trial on 86 patients with brucellosis disease. All 15-65-year-old patients with diagnosed brucellosis and no history of other systemic diseases were included. Patients with a history of using corticosteroids were excluded. After receiving their informed consent, the eligible patients were randomly divided into two equal groups of intervention (gabapentin) and control group (naproxen) using a block randomization method. Then, the pain severity was assessed using visual analog scale (VAS) before, as well as 4, 7, and 10 days post-intervention. In this study, the patients, data collector (pain intensity assessment), and analyzer were blinded. The data were analyzed using repeated measure ANOVA. Significance level was set at 0.05.

**Results:** Among the participants, 56 patients (65.1%) were male and the mean age of the patients was  $46.85 \pm 19.15$  years, which was not significantly different between the two groups. In the case of painful and involved joints, sacroiliac joint with 34 cases (39.5%) was the most commonly involved joint in both groups. There was a significant difference between the two groups regarding the mean pain intensity on the fourth day ( $P$ value = 0.021) and seventh day ( $P$ value = 0.001), while there was no difference at other times.

**Conclusions:** The results of this study revealed that gabapentin significantly and rapidly decreased skeletal pain in brucellosis patients. Therefore, it can be used as an appropriate drug for the control of bone and joint pain in brucellosis patients, though at least it should be used for a few day period.

**Keywords:** Brucellosis, Gabapentin, Naproxen, Skeletal pain.

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## Introduction

Brucellosis is one of the most common diseases in Iran. This disease is a global economic and health problem. Thirty-five percent of the patients are children under the age of 15 years.<sup>1</sup> This condition is one of the most commonly transmitted diseases that can be transmitted between humans and animals through direct contact with blood, placenta, fetal and uterine secretions of infected animals (cattle, sheep, goats, pigs, camels and buffalos), while consumption of contaminated raw animal

products (especially milk and its products) can be an indirect route of transmission to humans.<sup>2</sup> Brucellosis bacteria are Gram-negative and aerobic coccobacilli that are separated from each other by serological and biochemical techniques.<sup>1,2</sup> There are six main species of brucella which include: Melitansis, Suis, Abortis, Canis, Ovis, and Neotome, among which the first four species have pathogenic potentials for humans.

Human brucellosis caused by brucella melitansis (which is the most invasive and pathogenic species among the species of brucella) occurs in places where infected sheep and goats are a serious public health problem. However, due to the extensive establishment of pasteurization, brucellosis in many countries has changed to a scattered occupational disease among those involved in the transport of livestock, such as the veterinarians, the staff of laboratories, employees and workers dealing with the production and packaging plants of the meat and slaughterhouses.<sup>1,2</sup> The ways to control of disease are predominantly based on disease prevention, and care is a key tool for managing the prevention and control of the disease.<sup>3</sup> Most patients with brucellosis show nonspecific symptoms of a nervous system disorder such as headache, lethargy, and depression. Generally, acute or chronic illness begins with continuous or regular fever with varying periods of chills, sweating, especially at night, tiredness, loss of appetite and hunger, weight loss, headache, and general pain in the body.

Brucellosis can cause damage to all systems and organs in the body, but most of all, the skeletal system, the urinary tract, the liver, the heart, the lungs, and the spleen are affected. Bone and joint pain is common in brucellosis which are heavily persistent. Muscle and skeletal pain occurs in over 85% of patients with brucellosis. These pains are present in almost all joints of the body, but are more common in the lumbosacral, knee, and shoulder belt.<sup>4,5</sup> The intensity of the pain is very diverse and varies from mild to severe pain and prolonged pain where most patients need analgesics to control their pain.<sup>4</sup> Various drugs are used to control arthritis and osteomyelitis pain with the most commonly used NSAIDs being diclofenac, ibuprofen, indomethacin, Piroxicam, and Naproxen.<sup>5,6</sup> Naproxen is a good anti-inflammatory medicine for bone pain. This drug is a potent inhibitor of cyclooxygenase enzyme, which converts arachidonic acid into prostaglandins.<sup>7,8</sup> This medication reduces the production of prostaglandins by inhibiting cyclooxygenase and thus has an analgesic and anti-inflammatory effect.<sup>9</sup> The effect of each of these drugs varies from person to person, and sometimes does not provide satisfactory results in some people.<sup>10</sup> Thus, newer drugs should

be found to control bone pain in patients with this condition. Gabapentin is one of the new drugs used in this field. This medication with its central effect mitigates and controls the bone pain in brucellosis patients.<sup>6</sup> Gabapentin, given its analgesic properties, has been able to largely replace other drugs in controlling bone and joint pain. It is a gamma amino butyric acid (GABA) analogue initially produced for the treatment of epilepsy, but is currently used for various uses, including pain relief, especially pain with a neurological origin (such as headache and back pain) and inflammation (arthritis and osteomyelitis).<sup>11</sup> Since the extent of this effect is not yet clear and due to the high prevalence of brucellosis in this area, the aim of this study was to compare the behavioral changes in pain patterns in brucellosis patients under oral gabapentin and naproxen treatment, admitted to Imam Hossain hospital of Shahroud during 2017.

### Materials and Methods

This study was conducted on all brucellosis patients who had severe or fairly severe joint and bone pain and referred to Imam Hossain hospital of Shahroud, in north east of Iran from March 2017 to August 2017.

After explaining the purpose of the study and obtaining the informed consent, all patients (86 subjects) were randomized. Then, the pain intensity of the patients was recorded based on Visual Analog scale (VAS) at the beginning of the study on a 10 cm ruler, with painlessness on the number 0 and the most severe pain on the number 10.

Inclusion criteria: age 15 to 65 years, a definitive diagnosis of brucellosis, no history of other systemic diseases (such as diabetes or thyroid disease), vascular diseases, coagulation problems (such as hemophilia), and history of gastrointestinal bleeding and structural disorders (scoliosis and spondylolisthesis, etc.), absence of neurological symptoms such as straight leg raise (SLR) and positive cross-SLR, decreased tendon reflexes and diminished sensation in examination, no use of oral or injectable painkillers in the past 10 days, as well as willingness to enter the study.

Exclusion criteria: injection of corticosteroids in the waist or other areas of the body in a month before and during the study, a positive record of opium use, history of the use of hypnotic, anti-epileptic, and relaxant drugs in the last two weeks, severe hypersensitivity to either of the two drugs (gabapentin and naproxen), and lack of consent to continuing the cooperation. The flow-diagram of study is shown in figure 1.

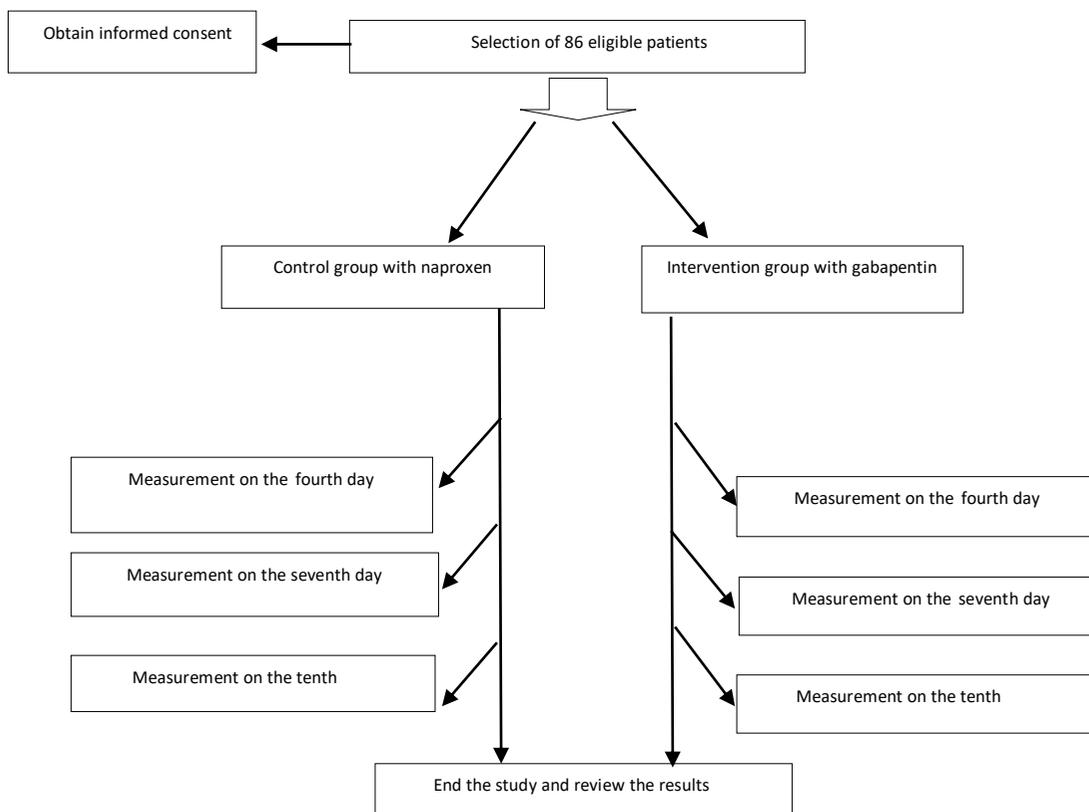


Figure 1. The flow-diagram of study

This randomized, parallel clinical trial was approved by the institutional review board of Shahroud University of medical sciences (with ethics code: IR. SHMU.REC.1395.72 from the ethics committee of Shahroud university of medical sciences and research project code: p93/073 from research deputy of Shahroud university of medical sciences) and registered in Iranian registry of clinical trial. (IRCT registration number: IRCT20171124037609N1).

A questionnaire including demographic and clinical information was filled for each eligible patient (n = 86). They were randomly allocated into intervention (use of gabapentin) and control group (use of naproxen) using blocked randomization with size of 4. To conceal the randomization sequence, we used sequentially numbered, opaque envelopes. In this study, patients, data collector, (pain intensity assessment), and analyzer were blinded.

In the intervention group, 200 mg of gabapentin tablets twice daily (400 mg daily) and the control group, 250 mg of naproxen tablets twice daily (500 mg daily) were administered. Then, the severity of pain was determined using a Visual Analog Scale (VAS) on one day before, as well as days 4, 7, and 10 post-administrations.

The variables studied included sex, age, duration of brucellosis at the beginning of the study and post-treatment, bone pain reduction using VAS, complications following treatment by the two drugs, and severe post-treatment pain.

The sample size was estimated based on various research objectives and according to numerous studies such as Kasimcan and Levin,<sup>12,13</sup> and via the G-Power software version 3.0.10.

Data analysis was performed based on intention to treat analysis by statistical software SPSS version 16. For describing the findings, descriptive statistics such as mean, standard deviation, and frequency were used. In order to compare the two groups at different times, we used repeated measure ANOVA. Significance level was set at 0.05.

## Results

In this study, 86 brucellosis patients participated, where 56 patients (65.1%) were male and 30 patients (34.9%) were female, and the mean age of patients was  $46.4 \pm 18.8$  years. There was no significant difference in sex and age between the two groups. The clinical and demographic characteristics of the patients in the two groups are reported in table 1. The results of repeated ANOVA showed that there was an interaction between time and group. Thus, we added a Bonferroni post hoc test to compare the mean scores between the two groups in terms of time intervals. The results of this study revealed that the severity of pain at the beginning of the visit and the end of the third day post treatment had no significant difference between the two groups. However, on the fifth (Pvalue = 0.021) and seventh days (Pvalue = 0.001), pain severity was significantly lower in the intervention group. The results of the pain intensity at different times in the two groups are shown in tables 2 and 3.

**Table 1. Comparison of demographic data and clinical variables in intervention and control groups**

Variables	Intervention group(N = 43)	Control group (N = 43)	Pvalue
Mean age (years)	47.4± 19.7	45.9± 18.8	0.078
Sex			
– Male	29 (67.4%)	27 (62.8%)	0.093
– Female	14 (32.6%)	16 (37.2%)	
BMI (kg/m <sup>2</sup> )	24.2± 3.9	24.9± 4.1	0.143
History of diabetic			
– Yes	10 (23.3%)	11 (25.6%)	0.121
– No	33 (76.7%)	32 (74.4%)	
History of skeletal disorders			
– Yes	7 (16.3%)	5 (11.6%)	0.107
– No	36 (83.7%)	38 (88.4%)	
History of analgesic using			
– Yes	43 (100.0%)	43 (100.0%)	0.451
– No	0 (100.0%)	0 (0.0%)	
History of corticosteroid using			
– Yes	27 (62.8%)	29 (67.4%)	0.081
– No	16 (37.2%)	14 (32.6%)	
History of smoking			
– Yes	28 (64.4%)	30 (68.9%)	0.083
– No	15 (35.6%)	13 (31.1%)	
History of addiction			
– Yes	14 (33.3%)	13 (31.1%)	0.108
– No	29 (66.7%)	30 (68.9%)	
Mean duration of pain (days)	25.2± 19.7	23.6± 20.9	0.128
Place of pain			
– Sacroiliac	16 (37.2%)	18 (41.9%)	0.083
– Lumbosacral	12 (27.9%)	11 (25.6%)	
– Shoulder belt	7 (16.4%)	6 (13.9%)	
– knee	3 (6.9%)	4 (9.3%)	
– Others	5 (11.6%)	4 (9.3%)	
Number of joints involved			
– One	5 (11.6%)	4 (9.3%)	0.067
– Two	17 (39.5%)	15 (34.9%)	
– Three and more	21 (48.8%)	24 (55.8%)	

**Table 2. Comparison of mean of pain intensity in two groups at different times of intervention using repeated measure ANOVA**

	Intervention group Mean $\pm$ SD	Control group Mean $\pm$ SD	Group	Time	Interaction of group and time
Before treatment	8.2 $\pm$ 0.6	8.1 $\pm$ 0.3			
Fourth day after treatment	7.4 $\pm$ 0.3	7.8 $\pm$ 0.3	F = 10.3	F = 15.3	F = 21.2
Seventh day after treatment	4.9 $\pm$ 0.2	6.4 $\pm$ 0.2	Pvalue = 0.03	Pvalue = 0.01	Pvalue = 0.0.001
Tenth day after treatment	3.8 $\pm$ 0.4	5.7 $\pm$ 0.3			

**Table 3. Frequency distribution of patients in two groups based on the mean of pain intensity at different times**

Time	Intervention group Mean (95% CI) VAS	Control group Mean (95% CI) VAS	Pvalue
Before intervention	8.2 (7.8-8.4)	8.1 (7.8-8.3)	0.128
At the end of the fourth day	7.4 (7.1-7.6)	7.8 (7.5-8.1)	0.062
At the end of the seventh day	4.9 (4.7-5.2)	6.4 (6.2-6.7)	0.021
At the end of the tenth day	3.8 (3.6-4.0)	5.7 (5.5-5.9)	0.001

## Discussion

In the present study, the patients in the gabapentin group received more effective pain control on the seventh and tenth days' post-treatment, but on the fourth day after treatment, the pain control did not differ significantly between the two groups. Although the exact mechanism for gabapentin in reducing bone pain is still unclear, according to studies, it has a repressive effect on the central nervous system and can control pain centers in the brain through controlling the pain and analgesia Induced.<sup>12,13</sup>

In a study by Mamalis et al., gabapentin was able to effectively control bone pain among 62 patients with different degrees of brucellosis.<sup>14</sup> Also, the use of gabapentin has also been effective in controlling chronic bone pain due to other infectious diseases. This, as with the present study, suggests the positive effect of this drug on controlling skeletal pain.<sup>15,16</sup>

In the study by Mete et al., various types of analgesics, especially non-steroidal drugs, were used to reduce skeletal pain, such as pain in the lumbosacral joints and pelvic bundle in brucellosis, all of which were the same, while gabapentin was able to reduce the pain at a greater speed and with a better effect. This finding is consistent with the results of our study.<sup>17</sup>

In a study by Mehanic et al. on 62 patients with severe infectious brucellosis, oral gabapentin administration showed a significant decline in skeletal pain and reduced the need for other analgesics, especially opium drugs. Eighty percent of the patients responded well to gabapentin. There was also a reduction in the duration of stay in the department due to severe skeletal pain, while also improving the patient function and contributing to a faster process for the discharge of patients when using this drug. In the present study, less pain was observed in the gabapentin group on the fifth and seventh days' post-treatment, which is consistent with the results of the Mehanic study.<sup>18</sup>

Gabapentin (and Pregabalin), in addition to controlling arthritis and bone pain, can also control pain associated with soft tissue damage around the joints, as well as ligaments and muscles. It is also useful in controlling pain caused by sports injury.<sup>19</sup>

In the study by Andrabi et al., the analgesic effects of gabapentin in patients undergoing joint surgery due to the underlying condition of brucellosis and its associated damage were investigated. They confirmed the role of gabapentin in the rapid and effective reduction of postoperative pain.<sup>20</sup>

In a study by Mrabet et al., who intended to control pain in 676 patients with various types of skeletal disorders, including brucellosis, gabapentin and several non-steroidal anti-inflammatory drugs (naproxen, indomethacin and diclofenac sodium) were used comparatively. The results showed that gabapentin more effectively reduced the pain of these patients and it was more effective than the other drugs used, which is consistent with the results of the present study.<sup>21</sup>

In a study by Yilmaz and Cerit, the administration of injected gabapentin was effective in relieving skeletal pain in patients with brucellosis with involvement of more than three major joints.<sup>22,23</sup>

In the present study, it was found that there was a significant difference on the fourth day post-treatment between gabapentin and naproxen. the reason can be attributed to the fact that for initiating effective analgesic therapy by gabapentin, it is necessary that the serum level of the drug reach a satisfactory level so that it can exert its analgesic effect.

The results of this study revealed that gabapentin effectively and more rapidly reduced the skeletal pain in brucellosis patients and caused more satisfaction among patients. Thus, it can be used as an appropriate analgesic for the control of bone and joint pain in brucellosis patients. However, since the onset of its effects requires a proper level of the drug, it is necessary to use it for at least several days.

The limitations of this research included the lack of cooperation of patients in determining the severity of pain due to impatience. This problem was largely overcome through the patience of the executives and changing the timing. Also, in case the patients felt that despite the explanation and justification of the presenters, they did not have the proper cooperation to express their pain severity, the patient would be excluded from the study and replaced with another patient.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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