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Therapeutic Effects of Boric Acid in a Septic Arthritis Model Induced by *Escherichia coli* in Rats

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Abstract

The study aimed to evaluate the therapeutic effect of boric acid (BA) in experimentally induced septic arthritis. A total of 30 rats, 6 rats in each group (5 groups), were used in the study. No treatment was applied to the rats in the control group. Only BA was administered intraperitoneally (IP) to the rats in the bor group. *Escherichia coli* was administered at a single dose of 25 µL, 1×10^{10} cfu/rat from the right foot pad of the rats, via intra-articular route, to the mice in the arthritis, arthritis-bor, and arthritis-antb groups. Then, BA at a dose of 50 mg/kg and cefazolin at a dose of 25 mg/kg were administered to the rats in the arthritis-bor and arthritis-antb groups, respectively, for 7 days via the IP route. At the end of the study, all animals were euthanized following the ethical rules. Blood and tissue samples were taken from the rats for biochemical and histopathological analyses. The levels of GSH, MDA, Endoglin, Endocan, and TNF-β markers were measured in the blood samples taken. A significant decrease was observed in MDA and Endoglin levels in the boric acid–administered group compared with the arthritis group, while a significant increase was observed at the GSH level. Histopathologically, it was determined that the reactive surrounding tissue response in the bor group was significantly reduced. As a result, a significant decrease in inflammation was found biochemically and histopathologically in the groups treated with BA.

Keywords Boric acid · Endocan · Endoglin · GSH · MDA · Septic arthritis · TNF-β

Introduction

Septic arthritis (SA) is a disease that develops due to a bacterial, mycobacterial, or fungal pathogen attack and can show serious mortality (10–15%) and morbidity (25–50%) with an incidence of 2–6/100,000 per year [1–3]. SA process by pathological invasion of a joint and subsequent inflammation. *Staphylococcus aureus* is the most common cause of septic arthritis in children [4]. The sequelaes of SA may be listed as cartilage damage, growth disturbance and avascular necrosis of the femoral head, and osteomyelitis (8%) in patients. Because of these complications, SA in children is orthopedic and surgical emergency [5, 6]. The epidemiologic and microbiologic features of SA differ significantly between developed and developing regions and age groups [7]. Recently, MRI has become more useful clinical medical device to define SA in pediatric patients with SA [8]. Beside, SA in adults can show higher morbidity and mortality. The prosthetic hip or knee is a potential clinical condition for SA in adults [9]. The clinical appearance of SA is different in adults, children, and neonatal patients. In adults, gonococcal arthritis can be diagnosed as differently than children type [10].

The order of causative frequency of the cases is methicillin-susceptible *S. aureus* (53%), *Escherichia coli* (18%), and *Klebsiella pneumoniae* (13%) [1]. Although Newman criteria are used in the diagnosis of SA, the reactivation of latent infections (including Tbc) should not be ignored in the age of biological agents we live in [11]. The international prevalence of multidrug-resistant enterobacteria, which are now

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positive for extended-spectrum β-lactamases, has increased greatly over the past decade. This situation has increased the number of extraintestinal pathogenic *E. coli* (ExPEC) infections (e.g., osteoarticular infections due to *E. coli*) [12, 13]. A variety of studies explored ExPEC [14–19].

SA caused by *E. coli* from broiler chickens also poses a risk to humans [20]. Multidrug resistance associated with *E. coli* has become an increasingly important problem, especially in the field of public health. This drug resistance is associated with extended-spectrum β-lactamases that increase the resistance to third-generation cephalosporins (e.g., ceftriaxone) and is associated with the mechanisms of resistance to other classes of antibiotics often used to treat Gram-negative infections [21].

Boric acid (BA), also known as hydrogen borate, boracic acid, or orthoboric acid, is evaluated as a weak monobasic acid derivative (Lewis acid rating). It has the chemical formula H3BO3 and exists as white colorless solid crystals or a white powder soluble in water. Its molecular mass is 61.83 g/mol, its density is 1.435 g/cm3, and its melting point is 170.9 °C. BA and its salts are found in seawater, fruits, and plants. It is often used as an antiseptic, pesticide, flame retardant, neutron absorber, or precursor to other chemical compounds.

The neurotoxic, genotoxic, and carcinogenic effects of acrylamide (ACR) were detected associated with the accumulation of excessive reactive oxygen species and causes oxidative stress. Acaroz et al. showed that boron effectively ameliorated ACR-caused oxidative stress, inflammation [22]. Another study presented the protective and ameliorative effects of BA against formaldehyde-induced oxidative stress in A549 cell lines that formaldehyde (HCHO) is a reactive agent and the most essential common carcinogenic environmental pollutant. BA exhibited a protective effect in A549 cell line against formaldehyde-induced lipid peroxidation. Furthermore, it ameliorated the antioxidant status and mRNA expression levels of proinflammatory cytokines [23].

BA, which is used as a supplement in the industry, is currently used in medicine as an antiseptic and eyewash solution for minor burns or cuts due to its antibacterial effects. In medicine, boron compounds are used for treating arthritis, osteoporosis, and coronary heart disease. The most pivotal application of boron is neutron capture therapy which has been extensively applied for treating different types of cancer should be added in this part. Arsenic caused changes in biochemical parameters, total oxidant/antioxidant status, and DNA damage in mononuclear leukocytes. Moreover, it increased IFN-γ, IL-1β, TNF-α, and NFκB mRNA expression levels in rat tissue. In their study, Ince et al. showed that boron treatment improved arsenic-induced alterations in biochemical parameters and increases in DNA damage and proinflammatory cytokine gene expressions [24]. By the human and animal experimentally studies, the effects of boron are listed as follows: (i) positively affecting bone growth and central nervous system function, (ii) alleviating arthritic symptoms, (iii) showing properties of a bioactive element. These effects are thought to occur through the formation of boroesters in biomolecules containing cis-hydroxyl groups. It shows that an intake of less than 1.0 mg for boron inhibits the health benefits of boron [25].

It is also used against bacterial vaginosis associated with excessive alkalinity in treating candidiasis due to non-*Candida albicans* (vaginal douche), in the prevention of athlete's foot, in treating otitis externa (ear infection), and as a preservative in urine sample bottles. Turkey holds the majority of BA reserves. Hence, BA capacity is vital for our country. Some studies have reported the antimicrobial and strong antiseptic properties of BA [26, 27].

The present study aimed to investigate the therapeutic effects of BA in the *E. coli*-induced rat SA model. The biochemical analysis with GSH, MDA, Endoglin, Endocan, and TNF-β markers, and histopathological investigations were performed to reveal the effect of BA in the SA model created with *E. coli* in rats.

Material and Methods

The study started after the document numbered KAÜ-HADYEK 2020/115 was obtained from the Kafkas University Animal Experiments Local Ethics Committee. The experiment was conducted with female Wistar rats (250–300 g) kept under a 12–12-h light/dark cycle (lights on between 06:00 and 18:00 h) with free access to water and food at controlled ambient temperature (22 ± 2 °C). All experiments were performed in light of the ethical guidelines of the International Association for the Study of Pain (IASP, 1983). A total of 35 female Wistar Albino rats were used in the study. By monitoring the 15-day adaptation period, food and drinking water were given ad libitum to five groups, each consisting of seven rats. The cages and the room they were placed in were cleaned daily. Food and drinking water containers were cleaned regularly. The rats were monitored according to the 3R principle (replacement, reduction, refinement). In the study, a dose of 25 µL, 1×10^{10} cfu/rat, of *E. coli* was administered to the rats as a single dose intra-articularly from the right footpad to establish an experimental rat SA model. Intraperitoneal BA was administered at a dose of 50 mg/kg daily to rats detected to have SA. The studied groups were as follows:

- Group I (Control): No treatment was performed on the rats.
- Group II (Bor): BA was administered by intraperitoneal (IP) injection to rats at a dose of 50 mg/kg for 7 days.

- Group III (Arthritis (Art)): To create an SA model, *E. coli* was administered at a single dose of 25 µL, 1×10^{10} cfu/rat, to the rats intra-articularly from the right footpad.
- Group IV (Art-Bor): To create an SA model, *E. coli* was administered at a single dose of 25 µL, 1×10^{10} cfu/rat, to the rats from the right foot pad via the intra-articular route. Then, 50 mg/kg dose of BA was administered via the IP route for 7 days from the third day of the study.
- Group V (Art-Antibiotic (Antb)): To create an SA model, *E. coli* was administered at a single dose of 25 µL, 1×10^{10} cfu/rat, to the rats from the right foot pad via the intra-articular route. Then, 25 mg/kg dose of cefazolin was administered via IP injection for 7 days from the third day of the study.

BA is toxic at a dose of 2660 mg/kg for the mammalian mean lethal dose (LD50) rating (5.14 g/kg is toxic for oral dosages of the LD50 to rats). At the end of the study, the rats were euthanized under anesthesia (xylazine (15 mg/kg) (Rompun), i.m.) and ketamine hydrochloride ((75 mg/kg) (Ketalar)) by the cervical dislocation method. Then, blood and tissue samples were taken from the rats. In the final stage, biochemical and histopathological measurements were made on the blood and tissue material taken from the rats. The blood samples were centrifuged at 3000 rpm for 3 min, and their plasma was separated and stored at –20 °C until analysis.

Biochemical Analysis

The GSH analysis of plasma samples was performed by the method of Beuter et al. [28], and the MDA analysis was performed by the method of Yoshioka et al. [29]. Endoglin, Endocan, and TNF-β assays were performed with a commercial enzyme-linked immunoassay (ELISA, TX/USA) kit following the kit procedure.

Histopathological Analysis

Tissues taken for the study were first kept in 10% buffered formalin solution for 24 h and then placed in decalcification solution (Facepath) for 12 h for the decalcification process. Then, paraffin blocks were prepared from the tissues taken for routine tissue follow-up, and 4-µ thick sections were taken. The sections were stained with hematoxylin & eosin (H&E) and evaluated under a light microscope (Olympus BX46, UK). Three serial sections were examined for each tissue, and inflammation, proliferative synovial changes, and reactive surrounding tissue response were examined as existing or absent.

Statistical Analysis

One-way analysis of variance was used to determine the differences in the obtained biochemical results. The results were interpreted using Tukey's honestly significance difference (HSD) test. Histopathological results were analyzed with the Mann–Whitney *U* test (Graphpad Prism 8, CA, USA). The results were expressed as mean ± standard deviation.

Results

Biochemical Findings

Figure 1A shows the GSH parameter results of the biochemical analyses. Accordingly, a significant increase was found in the control ($P < 0.001$), boron ($P < 0.0001$), art + bor ($P < 0.05$), and art + antb ($P < 0.05$) groups compared with the art group. In addition, a significant increase was observed in the bor group compared with the art + bor ($P < 0.0001$) and art + antb ($P < 0.0001$) groups.

A significant decrease in MDA level was observed in the control ($P < 0.0001$), boron ($P < 0.0001$), art + boron ($P < 0.001$), and art + antb ($P < 0.01$) groups compared with the arthritis group (Fig. 1B).

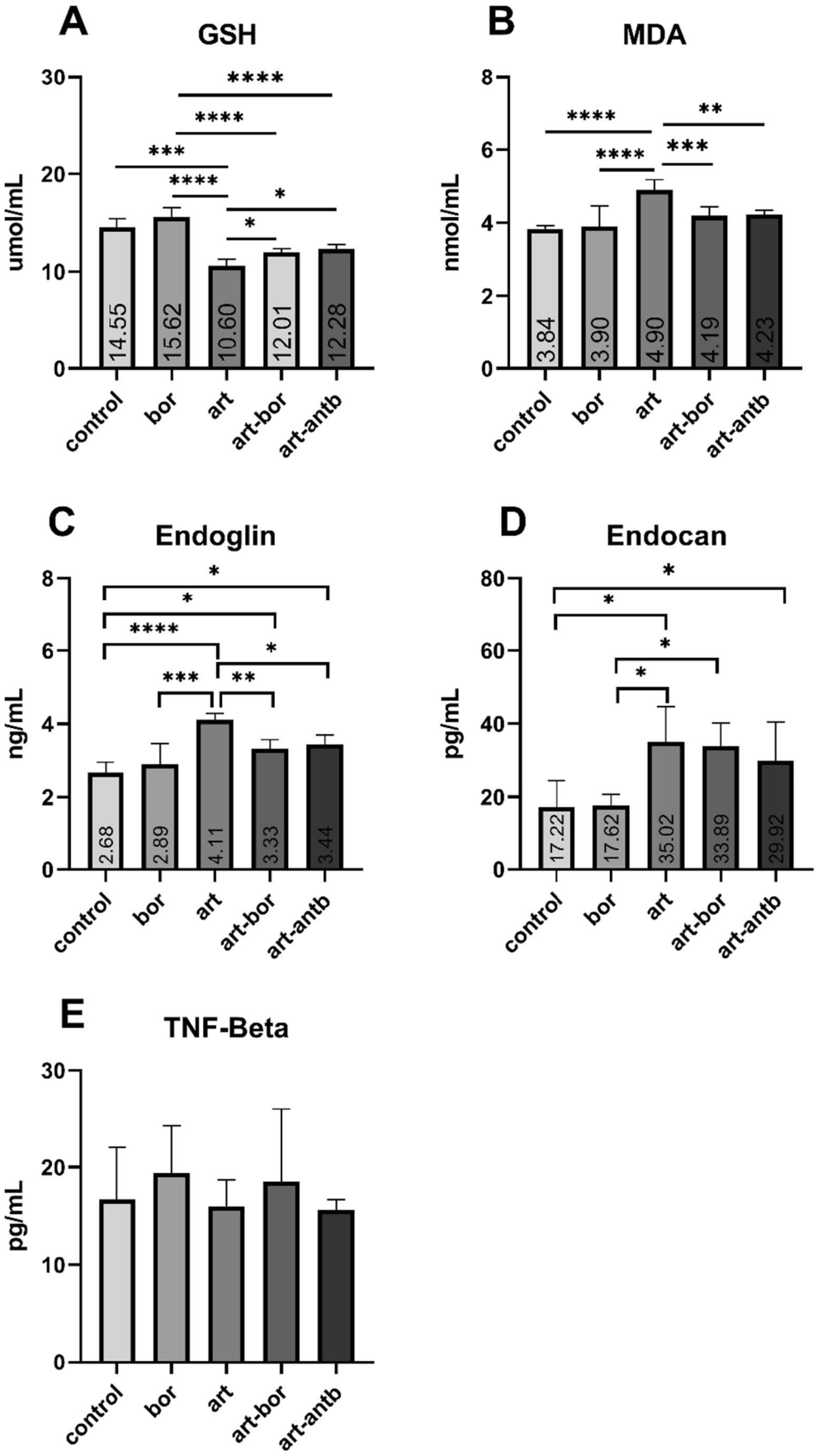
As shown in Fig. 1C, endoglin (CD105) analysis demonstrated significantly high levels in the art group ($P < 0.0001$) and significantly moderate levels in the art + bor and art + antbt groups ($P < 0.05$) compared with the control group. A highly significant difference was observed between the bor and art groups ($P < 0.001$); however, the comparison between the art and art + bor groups indicated moderately significant difference ($P < 0.01$). Also, a relatively weakly significant difference was observed between the art and art + antbt groups ($P < 0.05$).

Figure 1D shows the results of endocan analysis. Significant increases were found in the art and art + antbt groups compared with the control group ($P < 0.05$); however, significant increases were noted in the art and art + bor groups compared with the bor group.

No statistically significant difference in TNF-β level was found between the groups ($P > 0.05$), as shown in Fig. 1E.

Histopathological Findings

Light microscopic examination revealed no inflammation, proliferative synovial changes, and reactive surrounding tissue response in the control group (Fig. 2A and F) and bor group (Fig. 2B and G). However, variable degrees of inflammation, proliferative synovial changes, and reactive surrounding tissue response were observed in all rats in the arthritis group (Fig. 2C and H). Statistical analyses showed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◂**Fig. 1** Means and standard deviation. Errors in the five groups (**A**, **B**, **C**, **D**, **E**) for biochemical parameters. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$

significant differences in all parameters in the arthritis group compared with the control ($P=0.003$ for all parameters) and bor groups ($P=0.003$ for all parameters). In the antibiotic group, inflammation and reactive surrounding tissue changes were observed in two rats, while proliferative synovial changes were observed in three rats (Fig. 2D and I). Inflammation and proliferative synovial changes were found in all rats, while reactive surrounding tissue changes were observed in two rats (Fig. 2E and J). Statistical evaluations performed in the control and antibiotic groups showed no significant difference in inflammation ($P=0.134$) and reactive surrounding tissue response ($P=0.134$), but proliferative synovial changes were significantly more in the antibiotic group ($P=0.050$). The analyses performed in the control and boron groups showed significantly more inflammation ($P=0.003$) and proliferative synovial changes ($P=0.003$) in the boron group; however, no change was observed in the reactive surrounding tissue response ($P=0.134$). Inflammation ($P=0.050$) and reactive surrounding tissue response ($P=0.050$) were significantly less in the antibiotic group compared with the arthritis group, but proliferative synovial changes did not decrease at the same level ($P=0.134$). The analyses performed in the arthritis and bor groups revealed that bor treatment had no effect on inflammation ($P=1.000$) and proliferative synovial changes ($P=1.000$); however, it decreased the reactive surrounding tissue response significantly ($P=0.050$).

Discussion

SA is an infection that occurs more often in the elderly and children. It can affect any age. However, the risk factors for the development of AA include rheumatoid arthritis (RA) or osteoarthritis (OA), joint prosthesis, low socioeconomic status, intravenous drug use, alcoholism, diabetes mellitus (DM), previous intra-articular corticosteroid injection, and cutaneous ulcers [20]. Other important causes in adults are the time after intra-articular corticosteroid injections or arthrocentesis with an estimated risk of less than 1 in 1000. Patient age, DM, kidney and liver diseases, pre-existing joint disease, and methicillin-resistant *S. aureus* (MRSA) infection are factors that accelerate these conditions [2].

Pediatric osteo-articular infections frequently remind of the infection coupling, as both SA and osteomyelitis (OM), with the increasing number and resistance rate to antibiotic therapy worldwide [30]. The ideal duration of IV and oral antibiotics and the indicators of the need for surgical intervention have not been adequately defined [31]. Arthritis (or osteoarthritis) and OM developing in the background of synovitis can be associated with different etiologic agents. *Staphylococcus* sp. (mainly *S. aureus*) is the most frequently isolated bacteria. However, an increase in the incidence of SA and OM due to *E. coli* has also been reported. Between 15 and 50% of osteoarticular infections involve both the joint and the bone. OM and SA have different pathogen profile, affected age group, and duration of treatment. Early diagnosis and treatment of osteoarticular infections is important to minimize complications [31]. The immune response and colonization pattern in vitamin A–deficient rats colonized with *E. coli* O6 K13 pOmp 21 strain were examined in a study. This was the first report showing that vitamin A deficiency led to increased bacterial translocation and increased risk of infections such as SA. ExPEC has been identified as the leading cause of infections in both humans and poultry [32]. A study by Ergönül et al. [33] showed an increase in *E. coli* resistance day by day in hospitals in Turkey, but also the development of resistance to some antibiotics.

BA exhibits antimicrobial properties and has actually been used as an antimicrobial for many years. Therefore, it may be a useful treatment for BA, SA, and OM [34, 35]. The efficacy of BA was supported by the fact that the total antioxidant levels were low in the treatment groups. This showed that an antibiotic was the cornerstone in treating OM and local BA administration was a good adjunct to surgery and/or further antibiotic therapy. BA is a good adjunctive alternative to surgery and ongoing antibiotic therapy of resistant OM. The same study investigated whether local and systemic applications of BA reduced the number of MRSA in a rat OM model; BA was compared with vancomycin (V). Total antioxidant levels were found to be significantly different in all treatment groups compared with the control group. Microbiological and histopathological evaluation showed that the systemic or local application of BA was effective in treating rat OM [36]. In another study, which used BA-containing borate bioactive glass, chitosan-linked gentamicin and borate glass pellets also healed bone infection in a rabbit model of tibial osteomyelitis caused by Gram-negative bacillus *E. coli* and repaired bone defects within 6 weeks after implantation. This study showed that BA could be used as a gentamicin carrier not only to destroy osteomyelitis caused by Gram-negative bacteria but also to repair bone defect caused by infection through the degradation of borate glass [19]. In our study, BA was found to provide an equivalent treatment to today's conventional SA antibiotic therapy.

Endoglin (alias CD105, END, FLJ41744, HHT1, ORW, and ORW1) is a type I membrane glycoprotein found on cell surfaces and is part of the TGF-β receptor complex. It has a very important role in angiogenesis. The human endoglin gene is located on human chromosome 9 with its cytogenic position at 9q34.11. Endoglin glycoprotein is encoded by 39,757 bp and translated into 658 amino acids

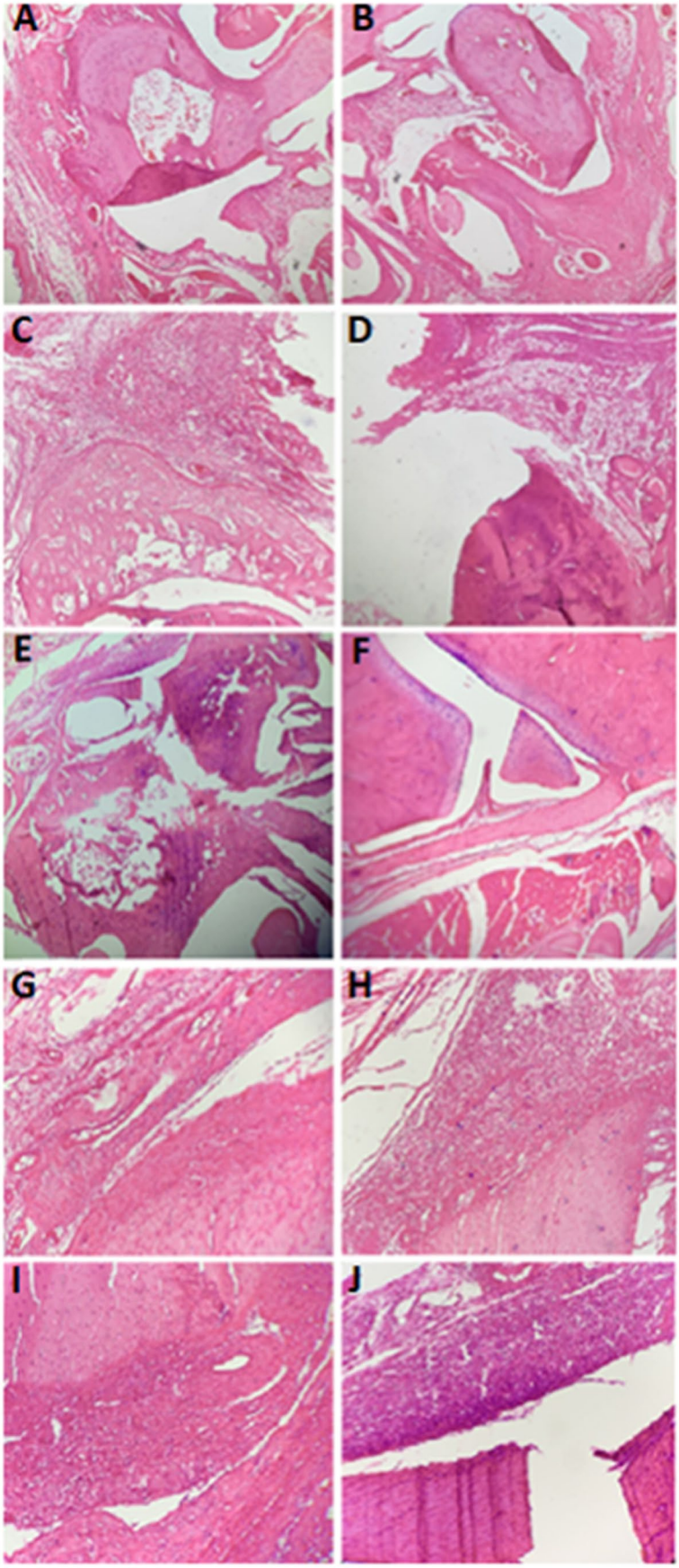

Fig. 2 It showed pathological findings of all groups under the light microscopic images. **A** Joint and surrounding tissues at morphological limits in the control group (H&E, 100×). **B** Joint and surrounding tissues at morphological limits in the Bor control group (H&E, 100×). **C** Inflammation and surrounding tissue response in the positive control group (H&E, 100×). **D** Inflammation and surrounding tissue response in the antibiotic group (H&E, 100×). **E** Inflammation and surrounding tissue response in the boron group (H&E, 100×). **F** Joint and surrounding tissues at morphological limits in the control group (H&E, 200×). **G** Joint and surrounding tissues at morphological limits in the Bor control group (H&E, 200×). **H** Inflammation and surrounding tissue response in the positive control group (H&E, 200×). **I** Inflammation and surrounding tissue response in the antibiotic group (H&E, 200×). **J** Inflammation and surrounding tissue response in the Bor group (H&E, 200×)

[37]. The expression of the endoglin gene is activated in inflamed tissues, in sites such as vascular damage, and during embryogenesis. Endoglin was first identified using monoclonal antibody (mAb) 44G4. Endoglin can mediate F-actin dynamics, focal adhesions, microtubular structures, and endocytic vesicular transport. In a study conducted with mouse fibroblasts, the overexpression of endoglin caused a reduction of some extracellular matrix (ECM) components, decreased cellular migration, a change in cellular morphology, and intercellular cluster formation. Endoglin has been suggested to play a role in cytoskeletal organization that affects cell morphology and migration [38, 39]. The endoglin levels detected in the SA rat model we created with *E. coli* showed that BA was quite effective in treating SA.

Endocan, a proteoglycan (dermatan sulfate proteoglycan) found in circulation, is a novel blood- and tissue-based biomarker. In 1996, Lassalle et al. first identified a novel human endothelial cell–specific molecule (ESM) cloned from a human umbilical vein endothelial cell cDNA [40]. The gene (ESM) on the fifth chromosome encodes endocan. Endocan with other mediators may have a vital role in cell proliferation and thus wound repair. It is associated with endothelial dysfunction ranging from sepsis and inflammation, vasodilation, edema to coagulopathy, ischemia, and organ failure. Inflammatory mediators [interleukin (IL)-1 and TNF-α] induce endocan expression, and hence the blood levels of this soluble proteoglycan (PG) may closely reflect the presence and severity of inflammation as well as response to therapy. Scherpereel et al. observed that the level of circulating endocan in the blood was related to the severity of sepsis and also reflected the outcome of the patient [41]. Endocan has been detected in endothelial cells of lung tissue, skin, adipose tissue, and coronary and pulmonary arteries. Endocan may have an important role as a prognostic marker in sepsis, inflammation, and acute lung disorders. Compared with the larger PG molecules of ECM, endocan has essentially different biological functions. Both the protein core and glycosaminoglycan of endocan are involved in interactions with ECM components, cell surface proteins, intracellular molecules, and soluble mediators that regulate cell differentiation, migration, and adhesion. Endocan plays a role in inflammation, regeneration, and tumorigenesis [42]. In the SA rat model we created, the endocan levels measured to monitor the course of sepsis also showed that BA was effective in SA antibiotherapy and provided quite adequate results.

TNF-β (TNFbeta, lymphotoxin alpha, TNFSF1B, LTA) plays a role in the induction of inflammation and antiviral response, development of secondary lymphoid organs, and tumor formation. It can be measured by ELISA. TNF-β is produced by activated lymphocytes. Soluble TNF-β is a 25-kDa T cell–derived glycoprotein. TNF-β is induced in a limited way by restricted T-cells to class I and class II antigen-specific MHC. TNF-β has various effects on target cells, such as killing, growth stimulation, induction of adhesion molecule expression, and differentiation [36, 43]. The mechanisms of TNF-β effects include receptor binding, internalization, changes in prostaglandins, and chromosome integrity. Recent studies have shown that both TNF-α and TNF-β can activate neutrophils in vitro. The exposure of neutrophils to TNF-α or TNF-β causes the production of superoxide radicals, induces the phagocytic response, and increases antibody-dependent cell cytotoxicity. The release of IL-1 from human endothelial cells is also induced by TNF-α and TNF-β. All in vitro studies indicated that TNF-β might play an important role in immunoregulation. In fibroblasts, TNF-β induces the synthesis of colony-stimulating factors, IL-1, collagenase, and prostaglandin-E2. Monocytes are stimulated for terminal differentiation. In B cells, TNF-β acts as a mitogen. Since TNF-β exerts proliferative effect on fibroblasts, it can participate in the wound-healing process. The assay developed by Adolf and Lamche has provided a simple and rapid method for determining serum TNF-β levels with a minimum detectable dose as low as 7 pg/mL serum. This test helps to clarify the possible diagnostic and prognostic value of circulating TNF-β in various neoplastic and inflammatory diseases [44, 45]. TNF-β is 35% identical and 50% homologous to TNF-α. TNF-α, which appeared as an anticancer agent in the first place, plays a key role in the course of infection and the inflammatory response that leads to synovial proliferation due to RA [46]. However, some studies have shown that TNF-β levels are also elevated in the serum and synovial tissue of patients with RA and OA [47, 48]. TNF-β was reported to stimulate proliferation and inflammatory cascade signaling in fibroblast-like synoviocytes, the trigger and starting point of RA [39]. Interestingly, in an in vivo collagen-induced arthritis mouse model, anti-TNF-therapy dramatically improved the disease course compared with anti-TNF-α therapy. [49]. Desch et al. showed that TNF-β had a very early and similar but less potent inflammatory potential compared with TNF-α. However, the signal transduction pathway of TNF-β has not been investigated in chondrocytes. Various studies also supported an important role of ethnicity in the relationship of TNF-α and TNF-β polymorphism with RA [50–52]. In conclusion, evidence indicated that TNF-β was associated with autoimmune and inflammatory diseases and patients with RA had elevated synovial TNF-levels. Yet, the results of our study indicated that BA did not stimulate chronic inflammation in terms of TNF-β levels, but led to desired targets in treating SA.

Oxidative stress can be evidenced by increased levels of MDA and decreased levels of GSH. The lipid peroxidation, MDA formation, and oxidative stress are closely related concepts. The significant increased levels of tissue MDA can be used as an indicator of tissue damage. The levels of

MDA increased significantly can be used bio-marker of oxidative stress. Upon this, GSH acts an active role to prevent of oxidative damage. GSH is an electron donor in protecting toxic substances from oxidative damage. The depletion of intracellular GSH causes oxidation and damage of lipids, proteins, and DNA by ROS. The oxidative stress and lipid peroxidation can play a role in the pathophysiology of SA [53]. By checking Fig. A and B, we can find that BA administration in rats cures SA, decreases tissue MDA levels, and increases GSH levels. This study showed that BA provided the necessary antioxidant effect in the SA model, as shown by the glutathione (GSH) and malondialdehyde (MDA) values. In addition, the results were consistent with the strong antioxidant effect levels of BA mentioned in the literature.

The measurement of serum endoglin, which is a marker of inflammatory damage, level showed that BA had anti-inflammatory damage–inhibitory properties. Endocan levels, which were measured in terms of observing the inflammation in the infectious environment and the destructive effect of this inflammation in treating SA and OM, emphasized that BA positively had changed the course of inflammation in the environment in favor of treatment. Yet, tumor necrosis factor-β (TNF-β) levels measured for the follow-up of chronic inflammation, an undesirable situation after the infectious process, also showed that BA did not cause chronic inflammation. BA showed satisfactory results in treating SA with its strong antioxidant, strong angio-genetic, and strong anti-inflammatory (especially chronic inflammation) effects.

Conclusions

The biochemical and histo-pathological analyses in this study indicated that BA provided an adequate response against arthritis. BA has serious antioxidant and anti-inflammatory effects on SA model. This effect has been found to be as effective as that of cefazolin. BA can serve as a new alternative in treating SA both in the medical world and in Turkey due to its strong antioxidant, strong angiogenic, and strong anti-inflammatory effects. Hence, we think that BA may be an alternative treatment option to cefazolin. However, more experimental studies are needed in this regard.

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