EXPERIMENTAL STUDY

Effect of boric acid on cartilage formation of osteochondral defects in rabbit knee: An experimental study

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ABSTRACT

BACKGROUND: The present study aimed to investigate the healing of articular cartilage with boric acid (BA) injection in an experimental cartilage defect model of rabbit knee.

METHODS: Nine skeletally mature female New Zealand White rabbits were used. The right knees of the rabbits were assigned as the study group and injected with the BA solution and the left knees of the rabbits as the control group. Under anesthesia, a cylindrical full-thickness osteochondral defect (4 mm in diameter and 3 mm in depth) was formed using a drill on the anterior side of the articular surface of the medial femur condyle. The BA solution was administered to the right knees of rabbits in the form of an intra-articular injection (8 mg/kg) for 6 weeks, at the same day and hours each week. The animals were euthanized at the end of the 2nd month.

RESULTS: In both macroscopic evaluation and microscopic evaluation, statistically significant differences were observed in the BA injection group compared with the control group ($p<0.05$). In the macroscopic examination of the defect area, statistically significant differences were observed between the groups in terms of degree of defect repair, integration to border zone, and macroscopic appearance ($p<0.05$). The averaged results of all evaluated parameters of the International Cartilage Repair Society visual histological assessment score were better for the BA group.

CONCLUSION: The healing process of the cartilage injury could be improved by BA injection administration. In future, BA may safely be used as an additional treatment modality in clinical practice to enhance the healing process of cartilage injuries, which are commonly observed orthopedic problem.

Keywords: Articular cartilage; boric acid; cartilage repair; intra-articular injection; osteochondral defect.

INTRODUCTION

Articular cartilage consists of chondrocytes surrounded by an extracellular matrix, and its avascular character results in the limited ability of articular cartilage to repair itself.[1–4] Given its specific structure, articular cartilage further complicates the regeneration process.[1,2] Injury of the articular cartilage may lead to progressive degeneration.[2–5] Therefore, the treatment of damaged articular cartilage is a major clinical problem.[2–4]

Different treatment methods have been developed of cartilage damage.[1–5] However, no definite treatment method is available. Defined surgical treatment methods include open-surgery procedures, arthroscopic debridement, bone marrow stimulation, tissue engineering, osteochondral autografting, autologous chondrocyte implantation, and matrix-induced autologous chondrocyte implantation.[2–5] In addition to these surgical methods, well-known intra-articular agents, such as platelet-rich plasma, hyaluronic acid, and ozone are used in treatment methods.[3–5]

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Despite the available treatment methods, full restoration of articular cartilage is not possible.[1,3–5] In general, good results are reported, regardless of the used; however, the search for new treatment methods continues.[1,3–6]

Boron is a mineral that is found in nature; boric acid (BA) is a boron compound.[6–9] This element is widely used in industries, agriculture, and cosmetic applications.[6–12] The major source of boron is diet.[6–10] Dietary boron supplementation may have important effects on various metabolic and physiological systems.[10,11] Boron does not accumulate in the human body.[6–11] BA is nontoxic at extremely high doses, and it can be safely used in clinical practice.[6–11] BA is also an inexpensive agent and easily available.[10,11] The beneficial effects of BA have been reported in various experimental and clinical studies.[6–12] However, only two studies reported the effectiveness of BA on the cartilage tissue.[6,12]

The present study aimed to evaluate the healing of osteochondral injuries of the articular cartilage with BA injection using an experimental cartilage defect model of rabbit knee.

MATERIALS AND METHODS

Animals

All experimental protocols conducted on the animals were consistent with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Animal Experiments Local Ethics Committee of Erciyes University (approval number: 19/005; date: January 18, 2019). Nine skeletally mature female New Zealand White rabbits weighing between 2.0 and 2.5 kg were used. The animals were kept at 22–25°C with 40%–70% humidity under a 12 h light/dark cycle with free access to food and water. The animals were observed for 7 days in the animal care laboratory to exclude any possibility of underlying disease.

Surgical Technique

Each rabbit was anesthetized with an intramuscular injection of ketamine HCl (50 mg/kg, Ketalar; ParkeDavis, Eczacıbaşı, İstanbul, Turkey) and xylazine anesthesia (6 mg/kg, Rompun; Bayer, Istanbul, Turkey). The rabbit was placed in the supine position, and a medial para-patellar approach was used to operate on the knee joint. Then, the patella was dislocated laterally to expose the articular surface. After the confirmation that the intra-articular structures were normal, a full-thickness osteochondral defect (4 mm in diameter and 3 mm in depth) was made in the center of the medial femoral condyle by using a drill (Fig. 1). Surgery was performed in the bilateral knee joints of the rabbits. Finally, all the incisions were closed in accordance with the anatomical layers. After surgery, the rabbits were allowed free movement in their cages, their limbs were allowed to bear the entire body weight, and their general health status was monitored.

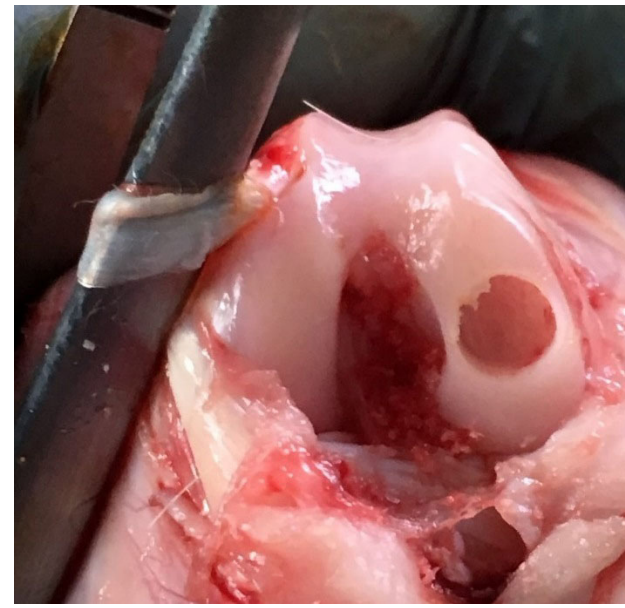

Figure 1. Osteochondral defect view of the medial femoral condyle of a rabbit knee.

The right knees of the rabbits were designated as the study group and injected with BA solution and the left knees of the rabbits as the control group.

BA Administration

For intra-articular injection, 99% powder boron form was dissolved in distilled water to obtain a 10% BA solution. The BA solution was administered to the right knees of rabbits in the form of an intra-articular injection of 8 mg/kg for 6 weeks, at the same day and hours each week. After injection, the rabbits were allowed free movement in their cages. After the 6-week injection period, 2 weeks were waited, and the animals were observed. At the end of 8th week, the rabbits were euthanized using intramuscular high-dose pentobarbital.

Macroscopic Evaluation

After 8 weeks from the day of surgery, the animals were sacrificed, and both distal femoral condyles of the rabbits were removed. The defect sites of distal femoral condyles of the rabbits were photographed and blindly scored by two different investigators by using the International Cartilage Repair Society (ICRS) macroscopic assessment score.[13,14]

Histopathological Evaluation

After macroscopic evaluation, the specimens were fixed in 10% formalin for 7 days and decalcified in 10% ethylenediaminetetraacetate-buffered saline solution for approximately 3 weeks. The specimens were dehydrated with serial ethanol, embedded in paraffin and cut into 5 µm sections. The histological preparations were stained with hematoxylin and eosin. The histological results were blindly evaluated by pathologist using a light microscope (×50). The samples were evaluated in accordance with the ICRS visual histological assessment score.[14]

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics 21.0 (IBM, Armonk, NY, USA). All the results are expressed as the mean ± standard deviation (SD). Numerical data were analyzed using the Shapiro–Wilk test to assess whether they were parametric. The differences in macroscopic and histologic scores between the groups were analyzed with the Mann–Whitney U-test. A 95% confidence interval and P value less than 0.05 were considered statistically significant for all analyses.

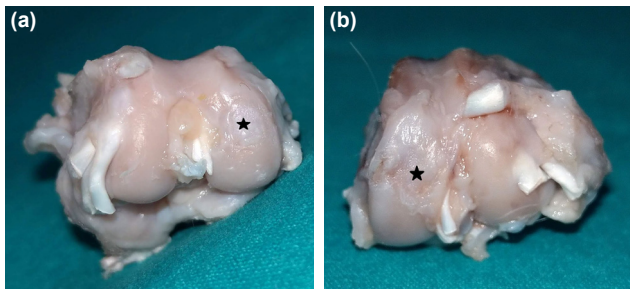

Figure 2. Macroscopic view of osteochondral healing (asterisk) in the boric acid group **(a)** and control group **(b)**.

RESULTS

Macroscopic Evaluation

No infection was detected in the knees of the animals after sacrification. The medial femoral condyle defects in both groups were usually repaired with a more whitish and definitive healing tissue than the surrounding normal cartilage (Fig. 2). According to the ICRS macroscopic assessment score, eight of the samples in the BA group were Grade II (nearly normal) and one was Grade I (normal). In the control group, two samples were Grade IV (severely abnormal), the other six samples were Grade III (abnormal), and one sample was Grade II. The mean total ICRS macroscopic assessment score was 10.1±1.36 in the BA group and 5.66±2.59 in the control group (p=0.001).

In the macroscopic examination of the defect area, statistically significant differences were observed between the groups in terms of degree of defect repair, integration to border zone, and macroscopic appearance. The mean degree of defect repair score in the BA group was 3.77±0.44, whereas it was 2.44±0.88 in the control group (p=0.001). The mean

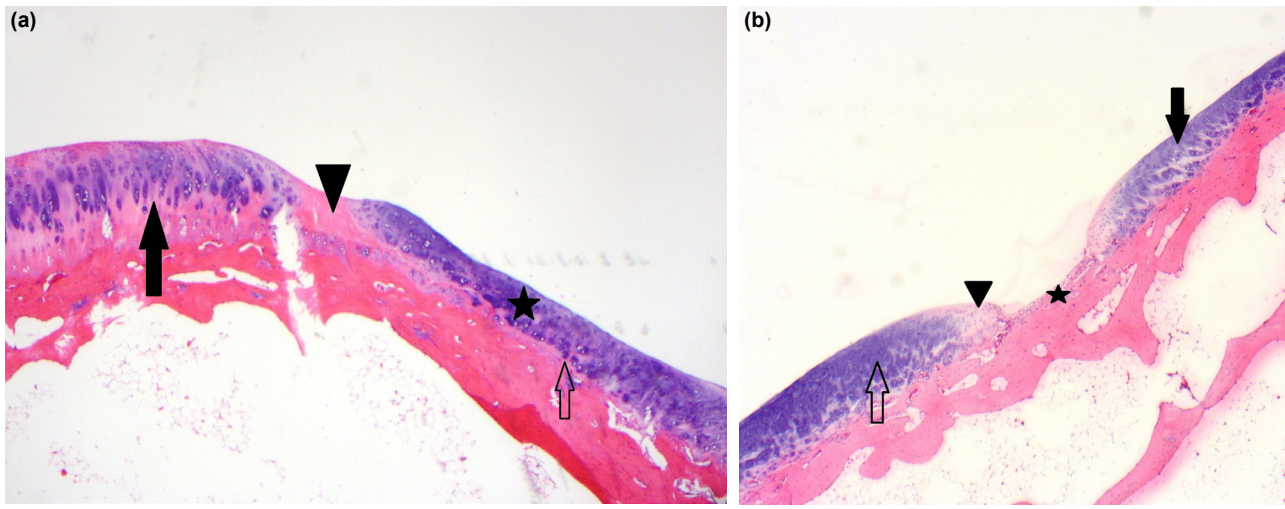

Figure 3. Histopathological appearance of cartilage formed in the boric acid group **(a)**. Appearance of intact cartilage tissue adjacent to the defect showing a columnar array (arrow). Appearance of fibrous connective tissue (arrowhead). Columnar array and clustering cells observed together (asterisk). Formation of tidemark (hollow arrow) (hematoxylin and eosin staining; magnification, ×50). Histopathological appearance of cartilage formed in the control group **(b)**. Hyaline and fibrous cartilage was observed together (hollow arrow). Appearance of fibrous tissue (arrowhead). Appearance of inflammation (asterisk). Columnar array and clustering cells were examined together (arrow) (haematoxylin and eosin staining; magnification, ×50).

Table 1. Total International Cartilage Repair Society macroscopic assessment score results of both groups

	Degree of defect repair		Integration to border zone		Macroscopic appearance		Overall repair assessment	
	Boric acid group	Control group	Boric acid group	Control group	Boric acid group	Control group	Boric acid group	Control group
Mean±SD	3.77±0.4	2.44±0.8	3.33±0.50	1.88±1.2	2.55±0.8	1.33±0.8	10.1±1.3	5.66±2.5
P-value	0.001		0.012		0.013		0.001	

ICRS: International Cartilage Repair Society; SD: Standard deviation.

Table 2. Total International Cartilage Repair Society histological assessment score results of both group

	Surface		Matrix		Cell distribution		Cell population viability		Subchondral bone		Cartilage mineralization (Calcified cartilage)		Overall repair assessment	
	Boric acid group	Control group	Boric acid group	Control group	Boric acid group	Control group	Boric acid group	Control group	Boric acid group	Control group	Boric acid group	Control group	Boric acid group	Control group
Mean±SD	1±1.5	0	2±0.5	1.22±1.0	1.77±0.4	0.88±0.7	2.88±0.3	1.77±1.2	2.77±0.4	1.88±0.6	3±0	1.30±1.5	13.4±2.2	7.1±4.4
P-value	0.065		0.088		0.014		0.030		0.005		0.013		0.003	

ICRS: International Cartilage Repair Society; SD: Standard deviation.

score of the integration to border zone was 3.33±0.50 in the BA group and 1.88±1.26 in the control group (p=0.012). Based on the macroscopic appearance score, the mean value was 2.55±0.88 in the BA group and 1.33±0.86 in the control group (p=0.013) (Table 1).

Histopathological Evaluation

Table 2 shows the characteristics of the groups based on the ICRS visual histological assessment score. The averaged results of all evaluated parameters were better for the BA group. The mean ICRS histological assessment scores were 13.4±2.29 in the BA group and 7.1±4.48 in the control group (p=0.003). The histological evaluation revealed significantly better results in the BA group in terms of the cell distribution (p=0.014), cell population viability (p=0.03), subchondral bone (p=0.005) and cartilage mineralization (p=0.013). The scores of the BA group in terms of the surface and matrix higher greater than those of the control groups but showed no significance (p=0.065, p=0.088, respectively) (Fig. 3).

DISCUSSION

In this study, we examined the effect of weekly intra-articular BA injection on healing in the osteochondral defect model created in the rabbit knee. In macroscopic and microscopic evaluation, we observed significant differences in the BA group compared with the control group.

Boron compounds have beneficial effects on various metabolic and physiological systems.[6–11,15] BA exhibited the effects on reactive oxygen species, the metabolism of calcium, potassium, and Vitamin.[9,10,15–18] BA affects the synthesis of the extracellular matrix, and this effect plays an important role in the tissue repair process by increasing the release of proteoglycans, collagen, and proteins.[12,19]

BA may be effective in tendon healing, osteoporosis, bone fractures, osteoarthritis, nervous system functions, wound healing, and cancer therapies.[7–11,19–22] In such studies, boron plays an important role in treatment and preventing various diseases with its possible mechanisms of action.[7–11,19–22]

Two studies presented the effect of BA on the chondral structure. The first study was conducted on the pelvic cartilage in the chick embryo by Benderdour et al.[12] They investigated the in vitro the effect of BA on connective tissue metabolism in culture. At the end of the study, they detected that the presence of boron in culture medium decreased the synthesis of proteoglycans, collagen, and total proteins but increased the release of these macromolecules. In addition, this study demonstrated that cartilage cells release tumor necrosis factor (TNF)-α when treated with boric solution. The findings suggest that the release of TNF-α may affect BA during cartilage metabolism in vitro and wound healing in vivo. TNF-α stimulates angiogenesis, regulates the activity of fibroblasts and activates the expressions of genes encoding-specific in-

flammatory mediators.[12,18] Korkmaz et al.[6] studied the osteochondral defect and oxidative stress of BA in rats. In this study, the boron group yielded better osteochondral defect repair scores compared with the control group. Boron has also been reported to have antioxidant properties.

No consensus exists in the literature on the administration dose of BA. BA is nontoxic at extremely high doses; therefore, it can safely be used in the clinical practice.[6–11] Concentration doses of BA solution in studies reported in the literature range from 0.1% to 10%.[6–11,18] In our study, we applied a 10% (8 mg/kg) concentration into the joint, given the toxic doses specified in the literature, the doses in previous animal studies and the concentrations used in clinical practice.

Given that reported lesions larger than 3.0 mm in diameter rarely heal in rabbits without specific treatment, in this study, we selected a 4 mm diameter osteochondral injury because of its repair difficulty and to demonstrate the potential of BA.[1,23]

Osteochondral repair was completed within 6 weeks, and remodeling of the osteochondral structure was continued afterward.[2] Therefore, the minimum time until investigation of repair of the osteochondral tissue should range from 4 weeks to 6 weeks.[2] In our study, we waited another 2 weeks at the end of the 6-week injection application and performed the sacrification process after 8 weeks.

In this study, although the use of BA solution showed positive effects on healing injuries of the articular cartilage, several limitations were encountered. First, different doses of BA were not injected at varied time points. Second, the effective dose of BA was selected based on studies in the literature. Third, this study is an experimental research performed on rabbits. Thus, we cannot ensure the same beneficial effect of BA on human cartilage. Therefore, further clinical studies should be performed. These limitations may be overcome in future studies.

Conclusion

The effect of BA on cartilage injury was investigated in this study, and the results showed that the healing process of cartilage injury could be improved by BA injection administration on the knee joint of rabbits. In future, BA may safely be used as an additional treatment modality in clinical practice to enhance the healing process of cartilage injuries, which are commonly observed orthopedic problem.

Ethics Committee Approval: This study was approved by the Erciyes University Animal Experiments Local Ethics Committee (Date: 18.01.2019, Decision No: 19/005).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: F.O., S.G.; Design: F.O., S.G., E.A., K.Y., C.K., T.A.; Supervision: F.O., C.K., T.A.; Resource: F.O., S.G., E.A., K.Y.; Materials: F.O., S.G., E.A.; Data: F.O., S.G., E.A.; Analysis: F.O., S.G., E.A., K.Y., C.K., T.A.; Literature search: F.O., S.G., E.A., K.Y., C.K., T.A.; Writing: F.O., S.G., E.A.; Critical revision: F.O., S.G., E.A., K.Y., C.K., T.A.

Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZET*

Tavşan diz eklemi osteokondral defekt modelinde borik asitin kıkırdak iyileşmesi üzerine etkisi: Deneysel çalışma

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AMAÇ: Bu çalışmada, tavşan diz eklemi deneysel kıkırdak defekti modelinde eklem kıkırdağının borik asit (BA) enjeksiyonuyla kıkırdak iyileşmesi üzerine etkisi araştırıldı.
GEREÇ VE YÖNTEM: Dokuz adet iskelet gelişimi olgun, dişi, Yeni Zelanda beyaz tavşanı kullanıldı. Tavşanların sağ dizleri çalışma grubu olarak atandı ve BA çözeltisi eklem içine enjekte edildi. Tavşanların sol dizleri ise kontrol grubu olarak belirlendi. Tavşanlara anestezi altında, medial femur kondilinin eklem yüzeyinin ön tarafında matkap ucu kullanılarak, silindirik tam kalınlıkta bir osteokondral defekt (4 mm çapında ve 3 mm derinliğinde) oluşturuldu. BA çözeltisi tavşanların sağ dizlerine altı hafta boyunca, her hafta aynı gün ve saatte eklem içi enjeksiyonu (8 mg/kg) şeklinde uygulandı. İkinci ayın sonunda hayvanlara ötenazi uygulandı.
BULGULAR: Makroskopik ve mikroskobik değerlendirmede, BA enjeksiyon grubunda kontrol grubuna göre anlamlı farklılıklar gözlendi ($p<0.05$). Defekt bölgesinin makroskopik değerlendirmesinde defekt onarım derecesi, sınır bölgesi integrasyonu ve makroskopik görünüm açısından gruplar arasında BA grubu lehine anlamlı farklılıklar tespit edildi ($p<0.05$). ICRS görsel histolojik değerlendirme skoruna gore değerlendirilen tüm parametrelerin ortalama sonuçları BA grubu için daha iyi olarak tespit edildi.
TARTIŞMA: Kıkırdak yaralanmasının iyileşme süreci BA enjeksiyon uygulaması ile geliştirilebilir. Gelecekte BA, yaygın olarak görülen bir sorun olan kıkırdak yaralanmalarının iyileşme sürecini arttırmak için klinik uygulamalarda ek bir tedavi yöntemi olarak kullanılabilir.
Anahtar sözcükler: Borik asit; eklem içi enjeksiyon; eklem kıkırdağı; kıkırdak onarımı; osteokondral defekt.

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