EXPERIMENTAL STUDY

The effects of carbogen and hyperbaric oxygen treatment on fracture healing in rats

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ABSTRACT

BACKGROUND: Bone fractures and fracture healing are one of the most common problems among orthopedic surgeons. In this study, we investigated the effects of hyperbaric oxygen (HBO) and carbogen (C) treatment on fracture healing in the experimental animal model.

METHODS: Twenty-four male Wistar-Albino rats were randomly divided into three groups as Group 1 (C inhalation therapy), Group 2 (HBO inhalation therapy), and Group 3 (control group), with eight rats in each group. HBO and C treatment were given to the rats in Group 1 and Group 2 1 week before the surgical procedure and 3 weeks after the surgical procedure. Following the surgical procedure, all rats were killed at the end of the 3rd week and the healing tissue in the fracture line was evaluated clinically, radiologically, and histopathologically.

RESULTS: Although there were higher histopathological, radiological, and clinical scores in the HBO and C groups in terms of fracture healing compared to the control group, there was no statistically significant difference between the groups.

CONCLUSION: There are many studies in the literature that examine the systemic and local effects of HBO and C treatments and show that they increase tissue oxygenation. Our study showed that HBO and C groups had no beneficial or harmful effects on fracture healing compared to the control group.

Keywords: Carbogen; fracture healing; hyperbaric oxygen.

INTRODUCTION

Nowadays, increasing work and traffic accidents, as well as frequent fractures due to the increase in the elderly population, have made fracture healing an important health problem. Studies on this subject focus on accelerating fracture healing. The main goals in fracture treatment in orthopedic clinics are; it is to make the patient painless by making the necessary conservative or surgical intervention as soon as possible and to mobilize the patient by helping to heal the fracture as quickly as possible.

Hyperbaric oxygen (HBO) therapy is a treatment method applied in a closed pressure chamber with a pressure higher than 1 atmosphere (1 ATA = 760 mmHg) by breathing 100% oxygen intermittently through a mask, cap, or endotracheal tube. The effect of HBO therapy on fracture and wound healing is through hyperoxygenation, neovascularization, antimicrobial activity, pressure effect, vasoconstriction, and reduction of reperfusion injury.[1] Carbogen(C) therapy is a central nervous system vasodilator and is a gas mixture of 5% CO_2 and 95% O_2. This gas, which was used in the treat-

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ment of carbon monoxide poisoning in the early 20th century, has been studied experimentally in inner ear pathologies, and it has been shown clinically to increase blood flow in perilenfatic fluid by causing vasodilation.[2,3] In our study, which we aimed to increase the oxygenation and vascularity of the inflammation site, which we consider as one of the most important dependent variables of fracture healing, we compared the effectiveness of C and HBO treatment on fracture union.

MATERIALS AND METHODS

Animal and Experimental Design

Ethical approval was obtained from the Çanakkale Onsekiz Mart University (Çanakkale) Animal Care and Ethics Committee. The Wistar-Albino rats were obtained from the Çanakkale Onsekiz Mart University Experimental Research Application and Research Center (ERARC). Rats were housed and fed at the Çanakkale Onsekiz Mart University ERARC throughout the study. All animal experiments were conducted in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the US National Institutes of Health (revised, 1985). Twenty-four Wistar-Albino male rats were utilized in the study, the average age of the rats was 4.5 months (3–6 months) and the average weight was 300 g (250–350 g). During the experimental procedure, all rats were housed under standard laboratory conditions with an artificial 12-h light/dark cycle. They were caged individually under a controlled temperature (22±1°C) and relative humidity and allowed free access to food and water in polycarbonate units. The rats were observed for 7 days in the animal care laboratory to exclude any possibility of underlying disease.

The rats were randomly divided into three independent groups, each containing eight rats. Group 1 (C inhalation therapy), Group 2 (HBO inhalation therapy), and Group 3 (control group, not received any treatment). C inhalation therapy was applied to the eight rats in the C group in the treatment room (Barotech Medical Supplies Medical Products, Istanbul, Turkey) designed for experimental animals. C treatment was performed with 5% CO_2 and 95% O_2 and discharged normal air. The pressure of the test chamber was gradually increased to 2.5 ATA within 10 min and the animals were applied 5% CO_2 and 95% O_2 oxygen under 2.5 ATA pressure for the next 40 min. At the end of this period, the room pressure was gradually decreased to 1 ATA within 10 min. Once the room pressure is at 1 ATA, the treatment is ended. This treatment protocol lasted 60 min in total. C inhalation therapy was started 1 week before the operation and was applied to eight rats in the HBO group twice a day for 4 weeks. The rats were sacrificed 3 weeks postoperatively thus they received C therapy for a total of 4 weeks. HBO treatment was performed using 100% O_2 inhalation using a similar procedure. Both treatment protocols lasted 60 min in total was applied every 12 h during the 4 weeks.

Surgical Technique

The rats were operated following an intramuscular injection of ketamine HCl 50 mg/kg, (Ketalar®, Eczacıbaşı, İstanbul, Turkey) and xylazine 10 mg/kg (Rompun®, Bayer, İstanbul, Turkey) anesthesia, as described by Bonnarens.[4] A femoral channel was prepared by means of a 1-mm Kirschner wire (Hipokrat®, Izmir, Turkey) that was inserted through the femoral condyles, and a 0.8 mm Kirschner wire (Hipokrat®, Izmir, Turkey) was inserted into this channel (Fig. 1a and b). To create a standardized fracture, the diathesis of the left femur was exposed making a small incision laterally, and the fracture was created using a hammer-osteotomy. The fascia and capsul were sutured using a sterile synthetic absorbable 3/0 suture (Atramat®, Mexico, Meksika) followed by the skin with a 2/0 nonabsorbable silk suture (Sterisilk®, Türkiye). The same antibiotic used preoperatively was also administered subcutaneously 3 days postoperatively at 45 mg/kg. Each animal was housed in its own cage and monitored daily for infection and mobility. Following surgery, rats were allowed to resume normal activity and were given unrestricted access to food. All animals survived after the surgical procedure throughout the study period. Radiological evidence of the fracture was recorded (Fig. 2).

The rats were sacrificed at the end of the 3rd week after the operation. High dose ether vapor was used as scarification method. The broken femurs of the animals sacrificed were disarticulated from the hip and knee joints not to damage the callus tissue. Following radiological examination, the soft tissues on the removed femurs were gently stripped from the bone without damaging the callus tissue and clinical examination were performed. The names of the groups to which they belong were classified and numbered for histopathological evaluation.

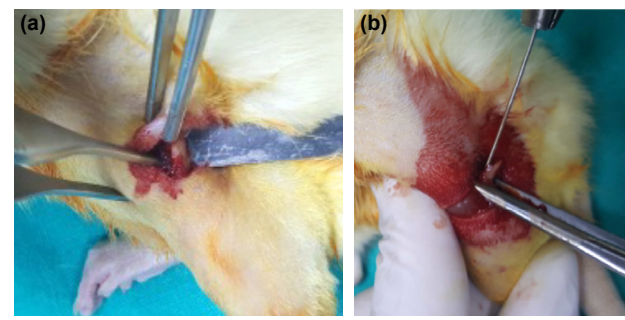

Figure 1. (a) Revealing the femur condyles and intramedullary canal preparation. **(b)** Placing the Kirschner wire as intramedullary.

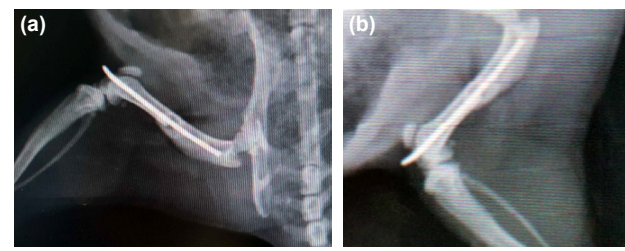

Figure 2. Radiological evidence of fracture formation.

Radiographic Evaluation

The X-rays were taken after the rats were euthanized and before the clinical evaluation. Postero-anterior plain X-rays (X-ray system; FUJIFILM Corporation, Minato-ku, Tokyo, Japan) of the femur removed from the animals sacrificed at the end of the 3rd week after the operation were commented by two ortopedic surgeons who were blinded to the content of the present study. They were asked to evaluate callus maturity according to classification of Goldberg et al.[5] In that classification, Stage 1 indicates nonunion, Stage 2 indicates possible union, and Stage 3 indicates radiographic union. The anterior–posterior radiographs of all groups were evaluated (Fig. 3). The mean radiologic scores were calculated for both groups.

Clinical Evaluation of Union

Healing was evaluated using the method described by Akman et al.[6] Pathologic movement was examined and movement was evaluated subjectively in both planes. Lack of movement in both planes (anterior-posterior and laterally) indicated full recovery (2 points), movement in one plane moderate healing (1 point), and movement in both planes indicated lack of healing (0 points).

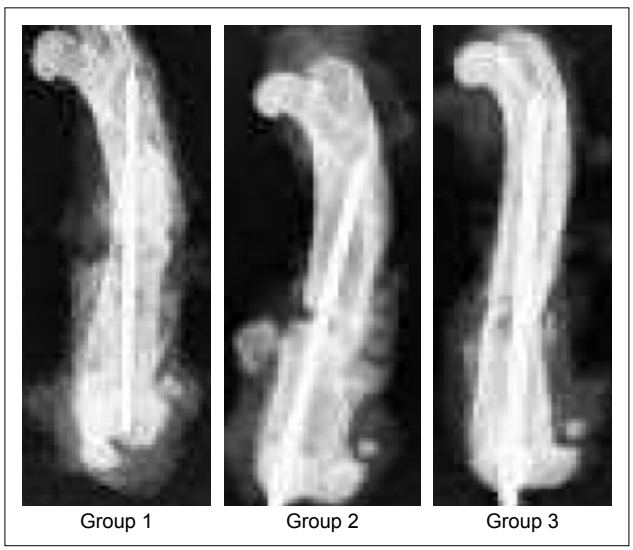

Figure 3. X-ray used in radiological evaluation.

Histopathological Analyses

Histological evaluations were conducted after clinical and radiological assessments. The bones were fixed in 10% formal solution for 2 weeks and then in Bouin's solution for 2 days. The specimens were decalcified in 10% acetic acid, 85% NaCl, and 10% formaldehyde solution for 72 h. After decalcification, longitudinal sections were taken from the fracture site, including the proximal and distal sites of the fracture. All slides were stained with standard hematoxylin and eosin methods and evaluated by a pathologist who was blinded to the groups (Fig. 4). Fracture healing was graded (1–10), as per Huo et al.[7] based on the ratios of the fibrous tissue, fibrocartilage, cartilage, and bone areas in the fracture site (Table 1).

Statistical Analysis

IBM Statistical Package for the Social Sciences Statistics 26 software (SPSS Inc., Chicago, IL, USA) was used to analyze our data. Normality of distribution for variables was tested through Shapiro–Wilk W test. Non-parametric tests were utilized for variables without normal distribution. Comparison of two groups for variables with abnormal distribution was performed with man Whitney U test and three or more groups for variables with abnormal distribution were performed with Kruskal–Wallis test. Cohen's kappa statistical analysis was used to evaluate inter-observed agreement. The results were interpreted according to Landis and Koch's guidelines[8] with 0.00–0.20 indicating very low agreement, 0.21–0.40 indicating minor agreement, 0.41–0.60 indicating moderate agreement, 0.61–0.80 indicating adequate agreement, and 0.80–1.00 indicating strong agreement. Quantitative data were expressed as mean, standard deviation, median, interquartile range as well as minimum and maximum values. Confidence interval was 95% and $p<0.05$ was considered as statistically significant.

RESULTS

Radiographic Analysis

Callus formation, remodeling, and bridging bone formation were evaluated on the radiograms of the femur removed at

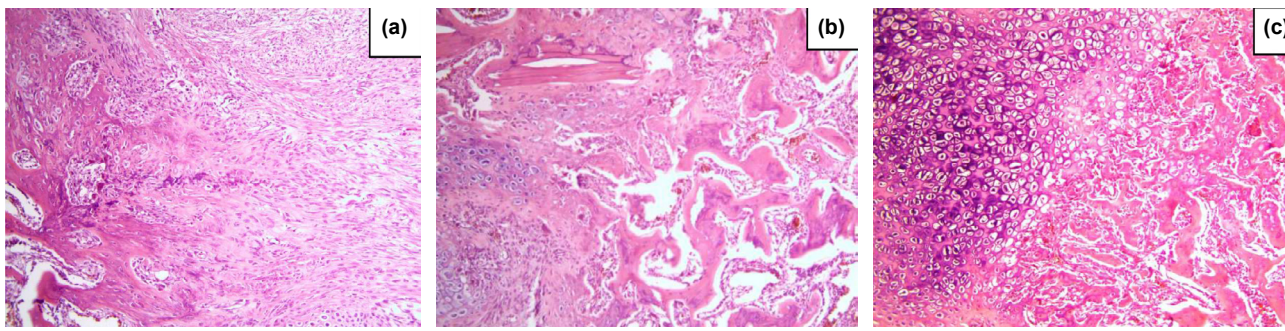

Figure 4. Histopathological appearance of femurs from groups of the rats. **(a)** Group 1, sections showing fully immature (Woven) bone in a grade 8 callus formation (H and E, 100×). **(b)** Group 2, week 1, sections showing immature bone and a small amount of chondroid tissue in a grade 7 callus formation (H and E, 40×). **(c)** Group 1, week 2, sections showing even cartilage and immature (Woven) bone in a grade 6 callus formation (H and E, 40×).

Table 1. Histological grading of callus tissue

Grade	Histological findings of callus
1	Fibrous tissue
2	More fibrous tissue
3	Equal fibrous and cartilage tissue
4	More cartilage and little fibrous tissue
5	Cartilage tissue
6	More cartilage and little immature bone
7	Equal cartilage tissue and immature bone
8	More immature bone and cartilage tissue
9	Callus with immature bone
10	Callus with mature bone

Table 2. The mean radiological stages and clinical score of three groups

	Radiologic stage of AP	Clinical score
Group 1 (n=8)	1.69	1.63
Group 2 (n=8)	1.69	1.63
Group 3 (n=8)	1.31	1.13
p-values	0.098	0.263

the end of the 3rd week after the operation. The two orthopedic surgeons demonstrated moderate inter-observer agreement for anterior-posterior radiographs (kappa = 0.41). Callus maturity and bone union increased every week according to Goldberg criteria but the comparisons of the weekly values of both groups were insignificant (Table 2). Radiological examination failed to show any beneficial or harmful effects of C and HBO treatment on fracture healing.

Clinical Evaluation and Analysis

After radiological inspection femurs were inspected for range of motion. All rats that demonstrated clinical examination agreement by the one observer were included in the study. Clinical score increased every week but the comparisons of the weekly values of both groups were insignificant (Table 2). Clinical examination failed to show any beneficial or harmful effects of HBO and C on fracture healing.

Histopathological Analysis

The progression of fracture callus in all samples taken for histopathological examination from both groups was evaluated. At the end of the 3rd week after the surgery, the fractures healed similarly in all three groups (Table 3). Histopathological scores in Group 1 and Group 2 had higher scores in the evaluation for callus progression and fracture healing, but this was not statistically significant (p=0.089). Histopathological examination was not able to exert any stimulating or inhibitory effects of C and HBO treatment on fracture healing.

Table 3. The mean histological grade of three groups

Groups	Histopatology			
	Minimum	Maximum	Median	Mean±SD
Group 1 (n=8)	6	8	7	7.1±0.83
Group 2 (n=8)	6	8	7	7±0.76
Group 3 (n=8)	5	7	6	6.25±0.71
p-values				0.089

SD: Standard deviation.

DISCUSSION

Fracture healing occurs through the mechanisms similar to wound healing, and many cytokines and mediators play a role in all stages. In addition, vascularization, mechanical factors, and free radicals in the fracture area also affect fracture healing.[9] Induction of fracture healing occurs with the complex mechanism of many local and systemic common factors, and the resulting effect is new permanent vascular formation (neovasculogenesis) and increased collagen formation, in which fracture healing is supported.[10]

When the fracture occurs, the development of arterial vasoconstriction in the fracture site causing a temporary ischemic period is followed by arterial vasodilation, and reperfusion in the fracture site. It is known that ischemia-reperfusion is one of the factors causing damage to soft tissues around the fracture. Fracture healing occurs in well-defined and successive stages. These stages are the inflammatory phase, the repair phase and the remodeling phase. The first stage is the inflammatory phase and is very important in terms of forming an early stage of fracture healing. This phase is characterized by the formation of a granulation tissue that modulates and induces cells to develop capillaries. Activation of precursor cells causes differentiation in different cell types, such as blood vessels, fibroblasts, chondroblasts, osteoblasts, and osteoclasts.[11] In the inflammatory phase (the first 5 days) inflammatory cells (leukocyte, macrophage, and mast cells) reach the fracture site. It has been shown in many studies that free oxygen radicals produced by activation of polymorphonuclear leukocytes adversely affect wound healing and granulation tissue.[12]

In studies conducted for the treatment of HBO in the current literature, despite its wide coverage in the literature, its effect has not been clearly demonstrated. Many studies have been conducted evaluating the efficacy of HBO therapy on various diseases in the field of orthopedics and traumatology but there is no indication for use in fracture healing in the current treatment guidelines.[13] In the literature, it is note-

worthy that studies related to HBO and bone tissue in recent years are mostly investigating the effect of HBO treatment on distraction osteogenesis, autogenous bone grafts, and changes in bone tissue exposed to radiation. HBO therapy is a systemic treatment method in a closed pressure chamber, by intermitting 100% oxygen intermittently under a higher pressure than an atmosphere (1 ATA = 760 mmHg), and most HBO treatments are performed at 2–3 ATA.[14] Studies in animals have shown that HBO applied increases tissue oxygen pressure in damaged bone as well as in healthy bone and increases oxygenation in damaged tissues.[15] The mechanisms of action of HBO therapy can be examined under two main titles: Primary and secondary effects. Primary oxygenation in tissue effect and increasing vascularity and events in the area shown as the regulation of cytokine balance. As a secondary effect, regulation of oxidative stress at the event site (including antimicrobial effect) is to reduce ischemia reperfusion injury and to induce wound healing. Eralp et al.[16] also looked at the effect of HBO application on bone healing in their experimental study on the boiling of autogenous bone grafts where they applied radiotherapy in rats and found that histological and radiological improvement was superior in subjects who received HBO. Clark et al.[17] measured bone density with computed tomography in the model of distraction osteogenesis in rabbit mandible and found that bone density was statistically significantly higher in the groups treated with HBO. Again Muhonen et al.[18] in their similar study, found that HBO application increased osteoblastic activity and new vessel formation. In another experimental study using distraction osteogenesis as a bone healing model, Wang et al.[19] applied HBO treatment at different times and obtained different degrees of recovery. Demirtaş et al.[20] reported that the negative effects of nicotine on fracture healing of rats disappeared with HBO treatment, but HBO alone did not cause significant changes in fracture healing. Chen et al.[21] reported that bone callus and mature osteocytes were seen in the fracture site of the tibia in rabbits without inflammatory cell infiltration in the HBO group. They reported that HBO therapy can reduce inflammatory reaction and reperfusion damage, and support osteocytic proliferation and fracture healing. The authors found that the gray value of bone callus and superoxide dismutase activity was higher in the HBO group compared to the control group, and the malondialdehyde content was significantly lower. The systematic review by Bennett et al.[22] found no relevant clinical evidence to support or refute HBO's efficacy for treating delayed union or established non-union of bony fractures. They stated that more studies are needed to examine the effect of HBO in nonunions treatment, and they think that randomized controlled trials will help provide some relevant clinical evidence to address this problem in the future. More studies of HBO therapy on fracture healing are needed. We think that HBO may increase fracture healing as a result of many effects such as decreasing the effects of cytokines and free oxygen radicals especially in the fracture line, increasing tissue oxygenation, and increasing neovascularization.

C treatment is carried out by inhaler administration of a 95% oxygen and 5% oxygen mixture in a closed pressure chamber.[23] Our study is the first experimental study on the effect of C, one of the other parameters of this experimental research, on fracture healing. Studies in the literature include studies in many diseases such as status epilepticus, sensorineural hearing loss, gastrointestinal system malignancies, and retinal artery occlusion but studies on fracture healing have not been found in the literature.[24–26] On the other hand, there are studies in the literature that show that C therapy has regulated perfusion and oxygenation in CO poisoning and in organ pathologies such as the brain and inner ear.[27] C has been used in the treatment of central retinal artery occlusion based on the assumption that carbon dioxide will prevent oxygen-induced vasoconstriction and thus preserve or even improve blood flow while maintaining oxygenation of the retina.[28] In addition, Powell et al.[29] showed that oxygenation and microcirculation in tumoral tissues have been increased with C breathing. In this context, the blood supply of tumoral tissues given C has been increased and made more radiosensitive. We think that the probable possible effect of C therapy on fracture healing is by the way of increasing the blood circulation in the fracture area secondary to systemic vasodilation, increase oxygen level in microcirculation, reducing free radical formation in the inflammation site, and supporting a good quality collagen formation.

We think that the probable possible effect of C therapy on fracture healing is increase blood circulation in the fracture area secondary to systemic vasodilation, increase oxygen level in microcirculation, reducing free radical formation in the inflammation site, and supporting a good quality collagen formation.

In our study, we examined the effects of HBO and C on the healing of fractures in rat femurs. Although radiological mean scores of Groups 1 and 2 were higher than Group 3, there was no statistically significant difference in callus formation and bone union between groups. In the evaluation made with clinical examination, the subjects in the group 1 and group 2 had higher scores than the control group, but there was no statistically significant difference. Histopathologically, the fractures healed similarly in both groups in terms of fracture healing and had higher mean histological scores than the control group. However, when both groups were compared, there was no significant difference in terms of fracture healing.

As a result in this experimental study, we conducted to determine the effects of C and HBO use on fracture healing clinically, radiologically and histopathologically, although C and HBO groups scored higher than histopathologically and clinically, no statistically significant difference was found. Therefore, in our study, we could not find any beneficial or harmful effects of HBO and C on fracture healing. In the literature studies, it has been shown that HBO and C application increases tissue oxygenation, reduces the formation of free radicals and increases tissue bleeding.

This experimental study is the first study to examine the effect of C on fracture healing, and it should be supported by further animal experiments using different protocols with different pressures and long-term application. The fact that bone and soft-tissue healing was faster and better in rats than in humans may have prevented significant differences between groups. Performing this experiment in nonunion model instead of acute fracture would have provided us with more meaningful results. The low number of subjects may have prevented us from reaching statistical significance in this study. On the other hand, taking subjects into pressure rooms for the application of C and HBO, trying to be kept in a closed area is likely to cause excessive stress to their animals, thereby causing a negative impact on fracture healing by activation of the sympathetic system. In addition, the physical movement of the animals while they are left in the confined space may cause excessive movement in the fracture area and may adversely affect the healing of the fracture. Despite all these negativities, values were found to be numerically superior in the HBO and C groups compared to the control group, but could not reach statistical significance. We think that a statistically significant difference will occur when we solve the problems such as the exposure of animals to excessive stress in the indoor environment, excessive movement inside the experimental tank in the indoor environment, and the low number of subjects.

Conclusion

As a result in this experimental study, we conducted to determine the effects of C and HBO use on fracture healing clinically, radiologically and histopathologically, although C and HBO groups scored higher than histopathologically and clinically, no statistically significant difference was found. Therefore, in our study, we could not find any beneficial or harmful effects of HBO and C on fracture healing. In the literature studies, it has been shown that HBO and C application increases tissue oxygenation, reduces the formation of free radicals and increases tissue bleeding.

This experimental study is the first study to examine the effect of C on fracture healing, and it should be supported by further animal experiments using different protocols with different pressures and long-term application.

Ethics Committee Approval: This study was approved by the Canakkale Onsekiz Mart University Animal Experiments Local Ethics Committee (Date: 02.01.2017, Decision No: 2017-01-05).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: U.M.; Design: U.M.; Supervision: U.M.; Resource: U.M., G.N.; Materials: U.M., G.N.; Data: U.M., G.N.; Analysis: O.Y., C.C.G.; Literature search: O.Y., C.C.G.; Writing: U.M., R.T.; Critical revision: G.N., B.K.

Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZ*

Sıçanlarda karbojen ve hiperbarik oksijen tedavisinin kırık iyileşmesine etkileri

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AMAÇ: Kemik kırıkları ve kırık iyileşmesi ortopedi cerrahları arasında en sık karşılaşılan sorunlardan biridir. Bu çalışmada, deneysel hayvan modelinde hiperbarik oksijen (HBO) ve karbojen (C) tedavisinin kırık iyileşmesi üzerine etkilerini araştırdık.
GEREÇ VE YÖNTEM: Yirmi dört erkek Wistar-Albino sıçanı, her grupta sekiz sıçan olacak şekilde rastgele grup 1 (C inhalasyon tedavisi), grup 2 (HBO inhalasyon tedavisi) ve grup 3 (kontrol grubu) olarak 3 gruba ayrıldı. Grup 1 ve grup 2'deki sıçanlara cerrahi işlemden bir hafta önce ve cerrahi işlemden üç hafta sonra HBO ve C tedavisi verildi. Cerrahi işlemin ardından üçüncü haftanın sonunda tüm sıçanlar sakrifiye edilerek kırık hattındaki iyileşme dokusu klinik, radyolojik ve histopatolojik olarak değerlendirildi.
BULGULAR: Hiperbarik oksijen ve C gruplarında kırık iyileşmesi açısından kontrol grubuna göre daha yüksek histopatolojik, radyolojik ve klinik skorlara sahip olmasına rağmen, gruplar arasında istatistiksel olarak anlamlı bir fark yoktu.
TARTIŞMA: Literatürde HBO ve C tedavilerinin sistemik ve lokal etkilerini inceleyen ve doku oksijenlenmesini artırdığını gösteren birçok çalışma bulunmaktadır. Çalışmamız, HBO ve C gruplarının, kontrol grubuna göre kırık iyileşmesi üzerinde faydalı yada zararlı etkilerinin olmadığını göstermiştir.
Anahtar sözcükler: Hiperbarik oksijen; karbojen; kırık iyileşmesi.

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