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ORIGINAL ARTICLE

# The evaluation of the effects of hyperbaric oxygen therapy on new bone formation obtained by distraction osteogenesis in terms of consolidation periods

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**Abstract**
*Objective* The aim of this study was to evaluate the effect of hyperbaric oxygen therapy on new bone formation obtained by distraction osteogenesis in long- or short-term consolidation periods.
*Materials and methods* Twenty-four rabbits were used. The animals were divided into two groups of 12 animals each, and vertical mandibular distraction osteogenesis was performed. Hyperbaric oxygen therapy was administered in the first group. Each group was subdivided into two subgroups according to the 30- and 60-day consolidation period. The acquired bone amounts were compared according to their radiographic density and histopathology.
*Results* Histopathologically, in the experimental group, callus formation was increased and the new bone was more mineralized. According to the radiographic densitometry analyses, there were no statistically significant differences between the 30-day consolidated subgroups of the experimental group and the 60-day consolidated subgroup of the control group ($p$=0.873).
*Conclusion* Hyperbaric oxygen therapy can be used to increase the quality and the quantity of bone and to decrease the maturation time which may shorten the consolidation period of vertical distraction osteogenesis.
*Clinical relevance* The effect of hyperbaric oxygen therapy on vertical distraction osteogenesis procedure according to consolidation periods has been determined. Hyperbaric oxygen therapy may increase the quality and the quantity of bone and shorten the consolidation period.

**Keywords** Hyperbaric oxygen therapy · Distraction osteogenesis · Bone · Collagen synthesis · Matrix deposition

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## Introduction

Distraction osteogenesis (DO) is a biological event in which new bone formation is induced by gradual separation of bony segments after an osteotomy or corticotomy. Distraction forces, applied on callus formation which connects separated bony segments, are maintained since the tissues are subject to an adequate tension. The tension of gradual forces stimulates new bone formation parallel to distraction vector [1–5]. These gradual forces develop within the fracture gap during the application of the distraction forces, activating mesenchymal cells to differentiate into osteoblasts and fibroblasts which secrete type I collagen organized into linearly arranged fibrils parallel to the vector of distraction [6]. Revascularization from the periosteal and endosteal surfaces occurs rapidly from the bony surfaces

on both sides of the gap, and woven bone rapidly extends into the collagen fibrils. This inter-zone remains relatively avascular during distraction but rapidly vascularizes and mineralizes once distraction ceases during the consolidation phase [6–8]. Research for increasing the quality of newly formed bone by DO is maintained mostly by adding supplements that provide osteogenesis. One of these supplements is hyperbaric oxygen [9–12]. It is obvious that molecular oxygen is a very important agent in wound healing. It has a critical role in collagen synthesis, matrix deposition, angiogenesis, epithelization, osteogenesis, and bacterial prevention. Augmentation of the bone by vertical DO technique, first proposed by Hidding et al., is mostly used in elder people with atrophic alveolar ridge, and in elder people there is an important decrease in immunity system, wound healing, and osteogenesis [13]. HBO therapy (HBOT) increases osteogenesis by activating osteoblasts and provides bactericidal influence, making the immunity system more effective by increasing phagocyte capacity, increases the quality and quantity of bone which is augmented by DO, and reduces the time of maturation [14–17]. Additionally, it has been shown that the distraction zone is extremely ischemic and HBOT may increase the tolerance of the tissue to ischemia and improve the survival possibility of ischemic tissue [18, 19].

The effect of DO in combination with HBOT has been investigated and shown to increase both bone mineral density and torsional strength [20]. Furthermore, Salgado et al. [21] evaluated the effects of hyperbaric oxygen therapy on an accelerated rate of mandibular DO. However, the effect of HBOT on DO procedures according to the consolidation periods has not been determined yet. The purpose of this study was to evaluate the effect of HBOT on new bone formation obtained by DO in rabbits in terms of consolidation periods.

## Materials and methods

Twenty-four New Zealand white rabbits (*Oryctolagus cuniculus*) weighing approximately 3.550±0.650 kg were used for this study. The experimental design and protocol were approved by the Department of Experimental Animals, Research and Development Center at Gulhane Military Medical Academy (GMMA). All experiments were conducted in the animal surgical laboratories of this institution. The animals were housed separately and were allowed free access to alfalfa and water and cared for under the guidelines of the institution. The animals were divided into two groups of 12 rabbits each. The first group underwent HBOT from the third postoperative day to the 10th day of consolidation. Vertical DO was applied to the second group without hyperbaric oxygen administration. Both groups were also divided into two subgroups of six rabbits each according to the consolidation periods. The first six rabbits of both groups were sacrificed on the 30th day of consolidation period and the second subgroups were sacrificed on the 60th day. The rabbits, which underwent HBOT and DO treatment and were sacrificed on the 60th day, were named as subgroup A, and the rabbits sacrificed on the 30th day were named as subgroup B. The rabbits which were only treated with DO and sacrificed on the 30th day were named as group D, and the rabbits which were sacrificed on the 60th day were named as group C (Table 1).

**Table 1** Animal groups and the millimeter equivalents of aluminum corresponding to the mean optical density of each evaluated area on radiographic images

| Observational period after surgery (days) | HBOT+DO ($n$=12) | | | | DO ($n$=12) | | | |
|---|---|---|---|---|---|---|---|---|
| | B ($n$=6) | | A ($n$=6) | | D ($n$=6) | | C ($n$=6) | |
| 30 | Sample 1 | 2.634 | | | Sample 1 | 2.319 | | |
| | Sample 2 | 3.161 | | | Sample 2 | 1.676 | | |
| | Sample 3 | 4.009 | | | Sample 3 | 1.894 | | |
| | Sample 4 | 2.722 | | | Sample 4 | 2.290 | | |
| | Sample 5 | 1.867 | | | Sample 5 | 1.911 | | |
| | Sample 6 | 2.372 | | | Sample 6 | 2.156 | | |
| 60 | | | Sample 1 | 4.379 | | | Sample 1 | 1.736 |
| | | | Sample 2 | 3.624 | | | Sample 2 | 3.048 |
| | | | Sample 3 | 3.178 | | | Sample 3 | 2.394 |
| | | | Sample 4 | 3.950 | | | Sample 4 | 2.583 |
| | | | Sample 5 | 3.351 | | | Sample 5 | 3.514 |
| | | | Sample 6 | 4.735 | | | Sample 6 | 4.352 |

*HBOT* hyperbaric oxygen therapy, *DO* distraction osteogenesis

## Anesthesia protocol

The rabbits were sedated with a combination of midazolam (2 mg/kg) and ketamin (40 mg/kg) injection before the placement of the distractors. Inhalation anesthesia with 5–6% sevoflouran was used. However, no local anesthetic agent was used so as not to influence local vascularization.

## Distraction device

A stainless steel device which was custom-made was used for distraction osteogenesis. The design of this device originated from the study conducted by Schmidt et al. [22]. The device mainly consisted of a ∩-shaped body with two legs which could be rigidly fixed to the lateral surface of the rabbit's mandible by the use of two 3-mm microscrews. The device had an activation screw that threaded into the center of the body. A flat stainless steel plaque was attached to the activation screw (Fig. 1). The devices were fixed to the lateral surface of the rabbit's mandible. Rotation of the activation screw resulted in the distraction of the flat plaque and corticocancellous bone segment away from the bone surface.

## Surgical procedure

Before the operation, the surgical field was shaved and disinfected with iodine solution. An incision was made approximately 3 cm in length below the inferior border of the mandible. After completing the fascia, muscle, and periosteal dissections, the lateral cortical surface of the mandibular corpus was exposed. Three small vertical incisions penetrating all tissue layers were made to the upper wound edge in order to appropriately place the device on the lateral cortex. Before cortical fixation, the flat plaque was fixed to the cortex and a square corticocancellous bone fragment around the plaque was separated from corpus. Afterwards, the activation screw attached to the separated bone fragment was fixed to the device. Consequently, the device was secured to the cortical surface of the corpus mandible. The operational areas were primarily closed with 3/0 silk sutures. The single side of the mandible was used in order not to alter the nutritional needs of the animals (Fig. 2). The devices were used only once to avoid causing any cellular reaction.

## Distraction protocol

Occlusal radiographs were taken to determine the beginning position of the device and the cortical bone. The distraction process was initiated after 7 days of latent phase in both groups. The activation screw was turned 0.25 mm twice a day during the 10 days of distraction period. Totally, 5 mm of distraction was obtained in every animal at the end of the distraction period and occlusal radiographs were taken. None of the animals was lost during the study.

## Application protocol of hyperbaric oxygen

HBOT was performed at GMMA Undersea Research Center. The animals in the experimental group were exposed to hyperbaric oxygen from the third postoperative day to the 10th day of consolidation. They were taken into hyperbaric oxygen tanks for a total of 25 days each under 2.4 ATA pressure for 90 min.

## Sacrification protocol

The animals were sacrificed on the 30th and 60th day, respectively, of the consolidation period. Following the application of a combination of intramuscular ketamine and xylazine (Alfamine + Alfazine) to the animals for sedation purposes, the rabbits were sacrificed with intracardiac pentobarbital injections. Dissections of soft tissues were made excluding the distraction application area. The soft tissues in these areas were preserved for histopathological examination.

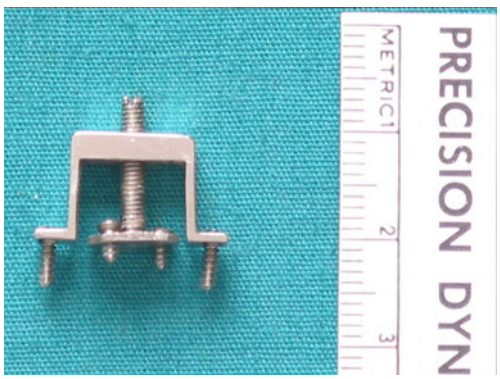


**Fig. 1** Photo of a self-assembled, custom-made, stainless steel DO device

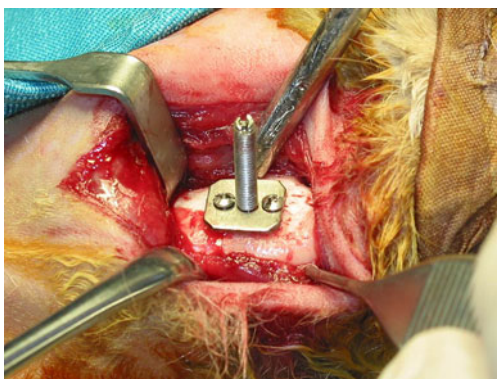

**Fig. 2** Application of the DO device

### Standardization of occlusal radiographs

At the end of the consolidation period, occlusal radiographic images were obtained with a Trophy Trex 70 kVp 8 ma (Croissy Beaburg/ France) X-ray tube, Novelix type 2.5 aluminum total filtration and 0.80 s of exposure time. Ultraspeed D size-4 (Eastman Kodak Company, Rochester, NY, USA) radiographs were used. Occlusal radiographs were put parallel under the mandibular border and exposed from a 10-cm distance. Densitometry analyses of occlusal radiographs and of bony structures from radiographs were based on photodensitometry. To minimize the variations in the density of the radiographs, after exposure and bathing procedures, these radiographs were exposed with testing objects which were stable and known in the amount of density (step-wedge technique) (Fig. 3). Densitometry analyses of radiographic images were made with a transmission densitometer (DT 1105 RY Parry Limited, Chatham, Kent, England). Optic density of researched areas from different points for a total of three times and the averages of these measurements were taken. The amount of mineralization in the evaluated area in every radiograph was clarified by the appearance of a difference in the equivalent aluminum thickness (Al eq. mm) and the obtained results were statistically evaluated.

### Histopathological examination

All of the resection materials were left in a 10% neutral buffered formalin solution for 3 days. After that, each distraction device was removed and the surrounding soft tissues, except the periosteum, were skinned and decalcified in formic acid solution for 4 days. When sufficiently soft, tissue samples were processed and embedded in paraffin for histopathologic examination. Standard 4–5-μm sections were prepared and transferred onto slides for each block of tissue. All slides were stained with haematoxylin and eosin and evaluated using a light microscope (Fig. 4).

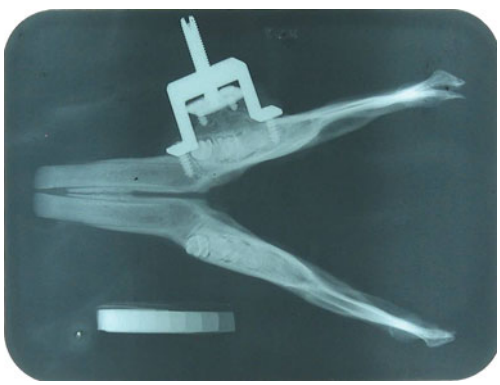

**Fig. 3** An occlusal radiograph after consolidation period

### Statistical analyses

Descriptive statistics were calculated for the specimens of both groups. SPSS 10.5 for Microsoft Excel was used for data processing and analysis. Descriptive statistics were shown as mean ± standard deviation. For comparing the differences of DO and DO+HBOT groups on the 30th and 60th days, Mann–Whitney *U*-test was used. The *p* values equal or less than 0.05 ($p<0.05$) were accepted as statistically significant.

## Results

### Radiological measurements

The millimeter equivalents of aluminum (Al eq. mm) corresponding to the mean optical density of each evaluated area on radiographic images are shown in Table 2. In the comparison of the mean optical densities of the newly formed bone areas between subgroups within each group, there were statistically significant differences ($p=0.025$, $p=0.037$). Densitometry analyses of radiographs showed that there was no statistically significant difference between the subgroup B (30 days consolidated subgroup of the experimental group) and the subgroup C (60 days consolidated subgroup of the control group) ($p=0.873$). Additionally, there were statistically significant differences between the subgroup A (60 days consolidated) in the experimental group and subgroup D (30 days consolidated) in the control group ($p=0.004$) (Table 2).

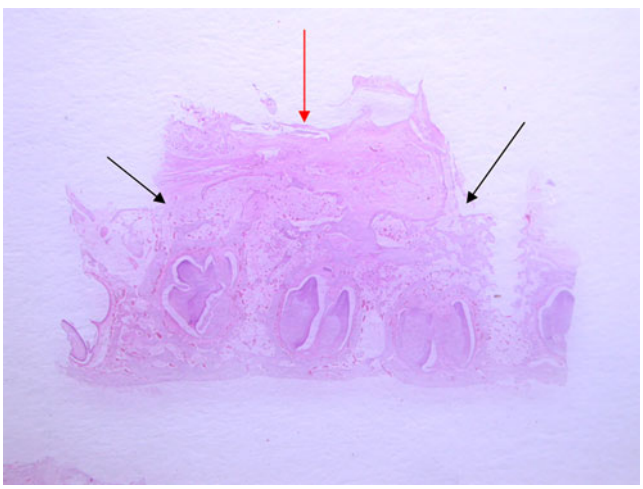

**Fig. 4** In a macroscopic image (×2.5) of 60-days consolidated subgroup of HBOT-applied group, outer cortex of mandible (marked by *black arrows*), periosteal thickness, and newly formed bone tissue line (marked by a *red arrow*) are observed

**Table 2** Descriptive statistics of the optical density of each evaluated area on radiographic images and comparison between subgroups within each and between groups

| Main groups | HBOT+DO | | DO | | Comparison between subgroups | |
|---|---|---|---|---|---|---|
| Subgroups | A (60 days) | B (30 days) | C (60 days) | D (30 days) | *u* | *p* |
| Mean ± SD | 3.869±0.603 | 2.794±0.731 | 2.937±0.917 | 2.041±0.254 | | |
| A and B | | | | | 4,000 | 0.025[a] |
| C and D | | | | | 5,000 | 0.037[a] |
| A and C | | | | | 6,000 | 0.055 |
| A and D | | | | | 0.000 | 0.004[a] |
| B and C | | | | | 17.000 | 0.873 |
| B and D | | | | | 5,000 | 0.037 |

*HBOT* hyperbaric oxygen therapy, *DO* distraction osteogenesis, *SD* standart deviation

[a] Significant differences between subgroups within each group. Significant at $p<0.05$

## Histopathological evaluations

Histopathological evaluations were performed by the Department of Pathology at Gulhane Military Medical Academy. According to findings, more new bone tissue formation and a more mature trabecullar structure were observed in 60 days consolidated subgroups of the main groups than the 30 days consolidated subgroups of the main groups. Moreover, in the cross-sections obtained from the 30 days consolidated subgroup of the experimental group, an approximately equal trabecullar bone body formation was observed compared to 60 days consolidated subgroup

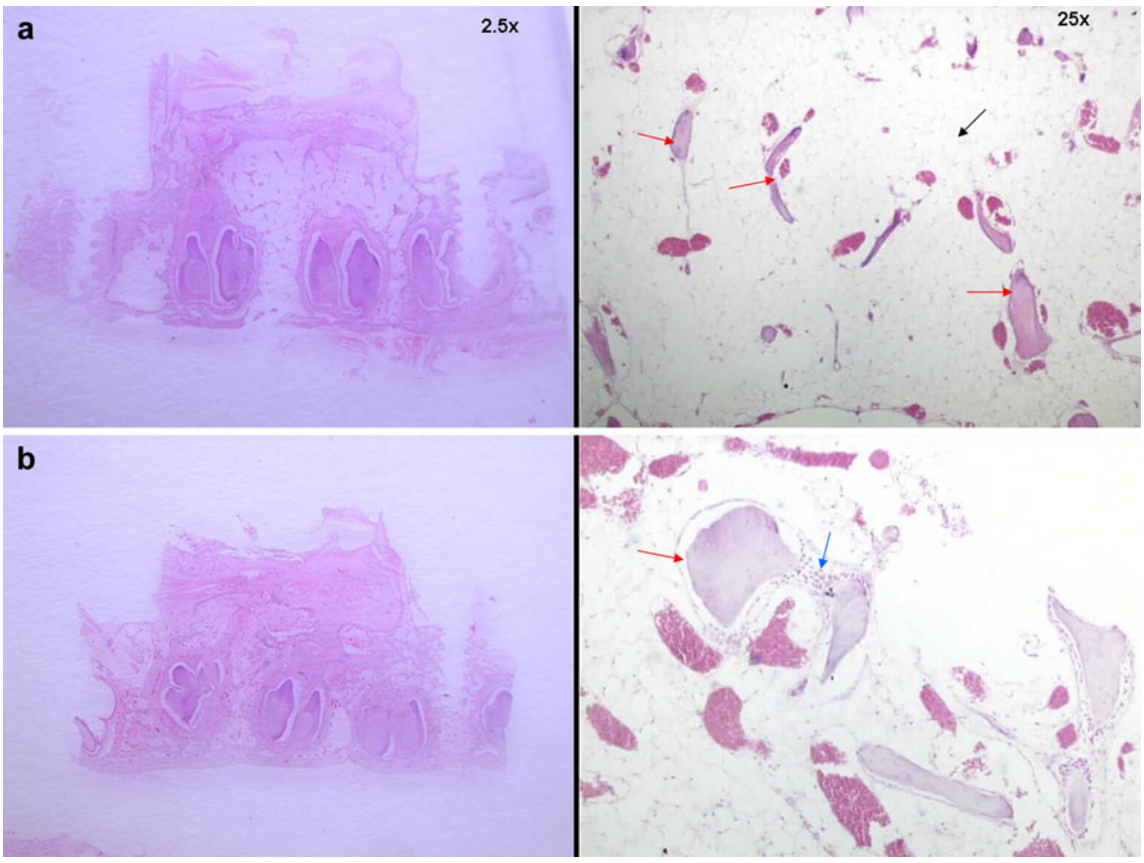


**Fig. 5** Macroscopic histopathological images (×2.5) of experimental **a** 30-day and **b** 60-day consolidation periods awaited rabbit mandibles. In microscopic images (×25), occasionally one of the bone tissues (marked by *red arrows*) and fat tissue in the newly formed bone tissue (marked by a *black arrow*) are observed. Increased osteoblasts (marked by a *blue arrow*) and newly formed, dense bone tissue (marked by a *red arrow*) are observed in distraction area on postoperative day 60

of the control group. Histopathological examinations showed that the distraction areas of specimens which have HBOT were full of newly formed bone which was strong and dense and could provide support to the forces. In distraction sites without HBOT, the newly formed bone was adipose bone tissue richly full of interstitial fat tissue in small amounts of dense bone tissue and connective tissue collagens integrated with osteoblasts (Figs. 5 and 6).

## Discussion

According to the tension–stress theory of Ilizarov, which exists as the pioneer of DO, the duration of tension forces produce tension stress which stimulates active improvement in the tissues. Moreover, slowly frequenting tension increases proliferation and biosynthesis and metabolic activity of the tissues. The essential reason of this procedure is the increase of blood flow to the tissues [23–25].

Research for increasing the quality of newly formed bone by DO is maintained mostly by changing distraction rhythms, latency and consolidation periods and adding supplements that provide osteogenesis. The affirmative influence of hyperbaric oxygen on bony and soft tissues is well known for a long time [5, 9, 16, 26, 27]. A study performed by Sawai et al. [28] has evaluated the effect of HBOT on autogenous free bone grafts transplanted from the iliac crest to the mandibles of rabbits. The results indicate that hyperbaric oxygen accelerates the union of autogenous free bone grafts. Okubo et al. [26] examined the effect of HBOT on the osteoinductive activity of recombinant human bone morphogenetic protein-2 (rhBMP-2), 5 mg of which was implanted into the calf muscle of rats using atelopeptide type I collagen as a carrier, and they observed that the local tissue alkaline phosphatase activity and calcium content in the HBOT group were significantly greater than in the control group. These results suggest that hyperbaric oxygen accelerates the activity and rate of osteoinduction by rhBMP-2. Muhonen et al. [9] evaluated the effects of irradiation and hyperbaric oxygen on osteoblastic activity and angiogenesis in rabbit mandibular DO. Hyperbaric oxygen changed the osteogenic pattern towards that of non-irradiated bone and it has been concluded that radiotherapy disturbs bone formation and neovascularization related to DO.

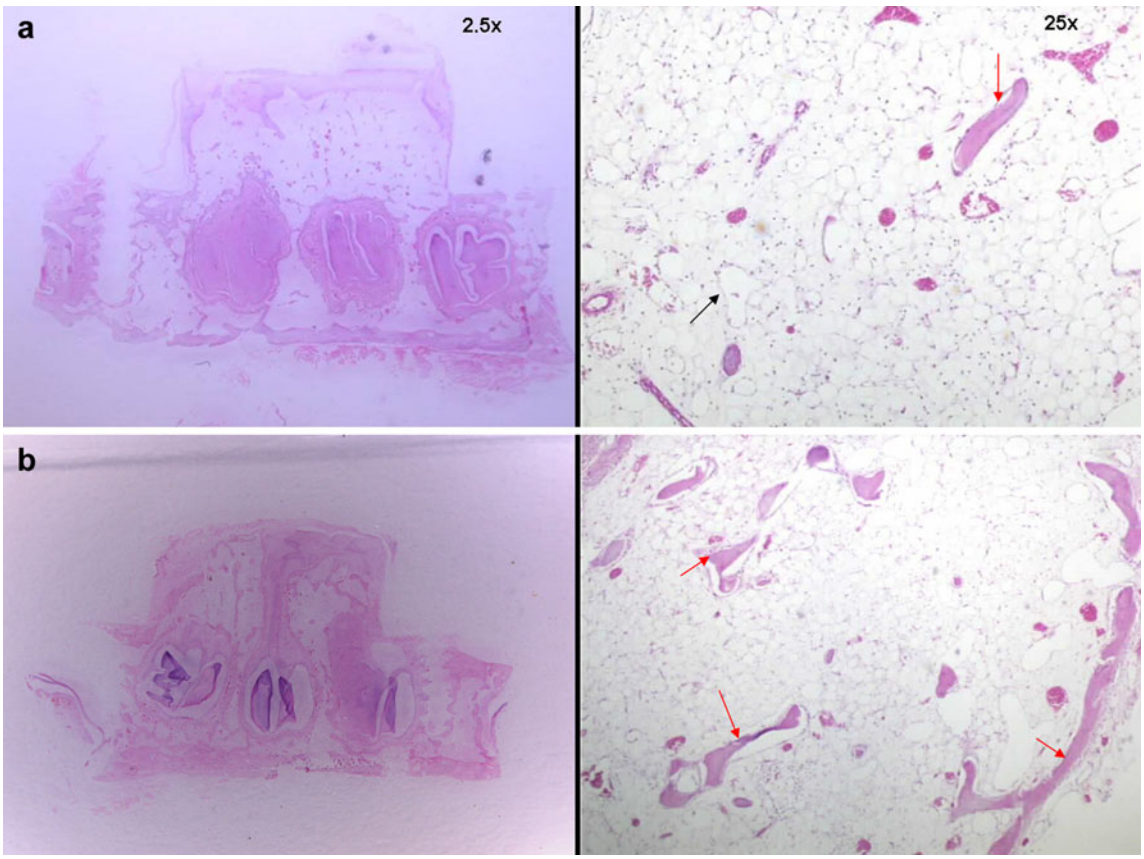


**Fig. 6** Macroscopic histopathological images (×2.5) of control **a** 30-day and **b** 60-day consolidation periods awaited rabbit mandibles. In microscopic images (×25), less bone tissue (marked by a *red arrow*) and more fat tissues (marked by a *black arrow*) are observed in the newly formed bone tissue on postoperative day 30. On postoperative day 60, an approximately equal trabecullar bone body formation (marked by *red arrows*) was observed compared to the 30-day consolidated subgroup of the experimental group

In a rabbit limb-lengthening modeled study of Eralp et al. [29], it has been suggested that there was a significant increase in bone mineral density in the HBOT group compared with that in the non-HBOT group, but no statistically significant differences were observed between the biomechanical parameters of the two groups. Parallel to the findings of the previous studies, in the present study, the bone which was maintained in the HBOT group was more superior in trabeculation and interstitial tissue formation. These results suggest that hyperbaric oxygen accelerates the activity and rate of osteoinduction in DO. From a clinical point of view, it is important to determine when the regenerated bone is strong enough for the distraction device to be removed and to allow unrestrained functional loading of the distracted complex. Therefore, there are still controversies regarding the rhythm of distraction and the duration of latency and consolidation periods [30].

According to Swennen et al. [31], a 6–8-week consolidation period was best for all mandibular lengthening and expansion distraction osteogenesis procedures and for the reconstruction of segmental defects by bone transport or compression distraction osteogenesis. Salgado et al. [20] suggested that hyperbaric oxygen application during DO procedures served to augment the healing process in distraction osteogenesis, allowing for more rapid distraction in order to decrease the overall treatment time. Kudoh [32] stated that HBOT could be useful for the early removal of the distraction device in distraction osteogenesis.

According to the radiological and histopathological results of the current study, no difference was detected between 30 days consolidated subgroup with HBOT and 60 days consolidated subgroup without HBOT. This showed us hyperbaric oxygen increases osteogenesis and may result in a decrease of the consolidation period. In the current study, both in experimental and control groups, the density of bone which existed in 60 days of consolidation period is more dense than that in 30 days of consolidation period according to densitometry analyses ($p=0.025$, $p=0.037$). These findings verify the studies made for the identification of an ideal consolidation period [14, 33–38]. It means that waiting for longer consolidation period can form radiologically more dense bony structures than shorter consolidation period. If we evaluate the subgroups with the same consolidation period radiologically, between subgroups B (DO and HBOT applied) and D (DO applied), there is a statistically significant difference in favor of subgroup B ($p=0.037$). According to this, it can be concluded that HBOT can be useful in reducing the consolidation period of vertical DO.

The vertical DO technique used in this study was first proposed by Hidding et al. in 1999 [13] as a new technique for the treatment of alveolar ridge atrophy. They have developed to move dentolous and edentolous segments of the alveolar process vertically with a device in microplate design and reported good stability and predicted the movement of the segments. In the literature, the main advantages of vertical DO were stated as: 1—no bone harvesting, 2—decreased resorption tendency, 3—lower morbidity compared with conventional techniques, 4—lower infection rate, 5—feasibility to insert dental implants 12 weeks after a distraction procedure, and 6—gain of soft tissue [21, 39, 40].

In this study, inclusion of the image of an aluminum step-wedge transformed the readings of light transmission in the radiograph into an equivalent thickness of aluminum 34. Therefore, all radiographic images were assessed under the same conditions. Radiographically, according to the result of densitometry analyses, it was observed that HBOT has increased the new bone density in the short term. Furthermore, the same result has been observed in the histopathological examinations.

## Conclusion

With the knowledge of the current study, it can be concluded that HBOT can be used to increase the quality and the quantity of bone and to decrease the maturation time which shortens the consolidation period of vertical DO. Moreover, for obtaining better results, further studies with bigger experimental animals and different consolidation periods can be performed to evaluate the effect of HBOT on new bone formation obtained by DO. The vertical DO model used in this study is widely used to increase the alveolar bone height, which is especially a challenging problem in dental implant surgery [41, 42]. Therefore, HBOT combined with DO could also be useful in daily dental practice.

**Conflict of interest** None

**Funding source** None

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