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The influence of cortical bone perforation on guided bone regeneration in humans

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Abstract. The purpose of this study was to evaluate the effect of cortical bone perforation on angiogenesis and osteogenesis of the augmented ridge in guided bone regeneration. Eighteen patients who had osseous defects in the mandible were selected. In the test group ($n = 9$), alveolar cortical bone in the area of regeneration was perforated. No decortication was performed in the control group ($n = 9$). Subsequently, defects were augmented by guided bone regeneration using resorbable membrane and bovine bone. After a healing period of 7 months, trephine cores were harvested for histological and histomorphometric analysis of the grafted areas. Histomorphometry demonstrated that the amount of newly formed bone in the test group (27.8%) was greater than that in the control group (25.3%), but the difference was not statistically significant ($P = 0.13$). However, the mean number of microvessels in the test group was significantly higher than that in the control group ($P = 0.01$). This study found that cortical bone perforation favourably affects the amount of new bone formation in the grafted sites after 7 months of healing. Cortical bone perforation significantly increase number of new vessels (angiogenesis) of the regenerated bone. Further randomized clinical trials are required to confirm these results.

Key words: guided bone regeneration; GBR; decortication; bone perforation; angiogenesis; osteogenesis; histomorphometric; histology.

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A sufficient amount of bone surrounding implants is essential to obtain a satisfactory treatment outcome in the long term.[1] A deficiency of the alveolar ridge resulting from a trauma, pathology, or congenital defect, may impede implant placement.[2] The principles of guided bone regeneration (GBR) have been used for many years to augment the bone height and/or width and provide clinicians with an adequate amount of bone for implant placement.[3,4] Various clinical studies have shown bone regeneration within or beyond the confines of the original skeletal boundary by creating space for new bone formation and excluding soft tissue from invasion into the space.[5,6]

The intramarrow penetration of cortical bone may affect the quality of regenerated bone by facilitating the migration of osteoprogenitor cells from the bone marrow into the isolated space created.[7] Previous studies have used cortical bone decortication in different clinical conditions, such as periodontal osseous defects and alveolar ridge augmentation.[8–10] However, perforation of the cortical bone prior to GBR is a controversial subject. Lee et al. showed that intramarrow perforation may improve the amount of newly formed bone and accelerate angiogenesis.[11] In contrast, there are some studies that have shown no beneficial effect for

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perforation of the cortical bone prior to GBR.[12–14]

The question of whether such perforations would have any effect on the quality of regenerated bone histologically in humans has not been addressed. This study evaluated the effect of intramarrow penetration on regenerated bone histologically in humans. The purpose of this study was to evaluate the effect of cortical bone decortication on the angiogenesis and osteogenesis of the augmented ridge in GBR.

Materials and methods

Eighteen patients (eight men and 10 women) who required dental implants in areas with mandibular osseous defects were selected. The patients had a median age of 52 years (age range 25–72 years) and were in good general health. All of the patients presented a partially edentulous mandible with either an extended or single tooth gap. Subjects were assigned to one of two groups: test patients ($n = 9$) received perforation of the recipient bed; control patients ($n = 9$) had no perforation of the recipient bed prior to GBR.

The inclusion criterion was the presence of an atrophic mandibular ridge with a buccolingual width of between 2 mm and 5 mm, as measured on serial sections of an axial computed tomography scan. Patients with diabetes, osteoporosis, or other metabolic disorders, smokers, pregnant patients, and patients who had any systemic or local factors that would inhibit a normal wound healing process were excluded. All of the patients volunteered to participate in the study and informed consent was obtained from each of them. The patients were informed that a biopsy specimen would be taken from the grafted site at the time of implant placement with no untoward effect on implant osseointegration. All procedures and materials were approved by the local ethics committee and the institutional board of research. The principles of the Declaration of Helsinki were followed in this study.

Surgical procedure

The patients were prescribed antibiotic prophylaxis (1 g of amoxicillin given orally 1 h preoperatively and then every 8 h after the procedure for 7 days). Intrasulcular and crestal incisions were used to elevate a full thickness periosteal flap and expose the recipient bone. In the areas with an existing tooth adjacent to the osseous defect, the intrasulcular incision was extended two teeth mesial or distal to the defect.

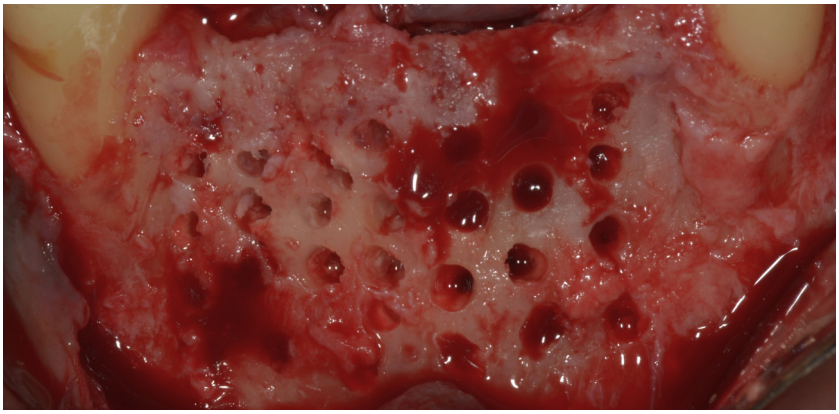

Fig. 1. Cortical bone perforations were carried out inside the area of the bone augmentation.

Following flap elevation, the alveolar bone ridge was examined carefully and the implant site was identified using a stent. All of the cases had a sufficient amount of vertical bone height and only the orofacial bone width at the prospective implant site needed to be augmented.

In the test group patients, the alveolar cortical bone in the area of regeneration was perforated using a number 2 high-speed round bur, under generous irrigation with 0.9% saline solution, to allow access of the cells from the bone marrow to the augmented site (Fig. 1). No decortication of the cortical bone was performed in the control group patients. Subsequently, a resorbable collagen membrane was placed and stabilized with fixation pins (Ace Surgical, Brockton, MA, USA) at the apical part of the defect. Particles (particle size 250–1000 μm) of cancellous deproteinized bovine bone mineral (Bio-Oss; Geistlich AG, Wolhusen, Switzerland) were placed in the defect area and covered by the membrane. The ridge was augmented to a size sufficient for standard implant placement. A periosteal releasing incision was performed at the apical portion of the flap; tension-free primary closure was achieved and the flap was sutured with resorbable suture material (Vicryl, Ethicon, Somerville, NJ, USA).

Postoperatively, the patients received analgesic and anti-inflammatory medication (ibuprofen 600 mg) for 3 days and were instructed to rinse with 0.12% chlorhexidine digluconate oral rinse twice daily for 2 weeks. Postoperative examination and suture removal were performed after 14 days. If needed, the temporary partial dentures were adjusted to avoid trauma to the surgical area.

After a 7-month healing period (mean 7.4 months), prior to implant placement, the alveolar ridge was exposed and the augmented site visualized. Bone core samples (3.5 mm in diameter and 10 mm in length) were obtained from within the boundaries of the augmented site using a trephine drill, under copious irrigation, without compromising implant placement. Dental implants (Straumann AG, Waldenburg, Switzerland) were placed according to standard protocols in a prosthetically ideal position and the flap repositioned and sutured; 29 implants were placed in the 18 patients. All biopsy specimens were placed in 10% neutral buffered formalin for 10 days to fix the dissected block sections.

Histological preparation

The bone specimens were cleared with xylene and embedded in paraffin. Sections 4 μm thick were cut longitudinally using a Jung K microtome (Leica microtome type sm2500s; Leica, Wetzlar, Germany). The prepared slices were stained with haematoxylin and eosin (H&E) and observed in normal transmitted light under a microscope (Carl Zeiss, Oberkochen, Germany). Bone vitality, foreign body reaction, and the number of microvessels were assessed.

Histomorphometry

The histomorphometric analysis was performed by digitizing the images from the microscope with a camera (Olympus BX50; Olympus Optical Co., Tokyo, Japan) and a frame grabber. The images from each area of the biopsy core were obtained and analysed using image analysis software (ImageLab 2000; Softium, Sao Paulo, Brazil) to calculate the thickness of the bone trabeculae (μm) and the percentages of residual graft particles (RG), newly formed bone (NB), and soft

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tissue components (ST) (i.e., bone marrow and/or connective tissue) in each specimen. In order to calculate the number of microvessels and to avoid errors in counting the vessels, each vessel was demarcated. For each biopsy, 10 high-power fields corresponding to 1.1 mm^2 were evaluated. Values were expressed as the number of microvessels per square millimetre.

Statistical analysis

The averages and ranges for the percentage of newly formed bone, soft tissue components, residual graft particles, thickness of the bone trabeculae, and number of microvessels were calculated. Paired *t*-tests were used to determine possible differences between the test and control groups for variables of interest. All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). A *P*-value of 0.05 was set as the significance level.

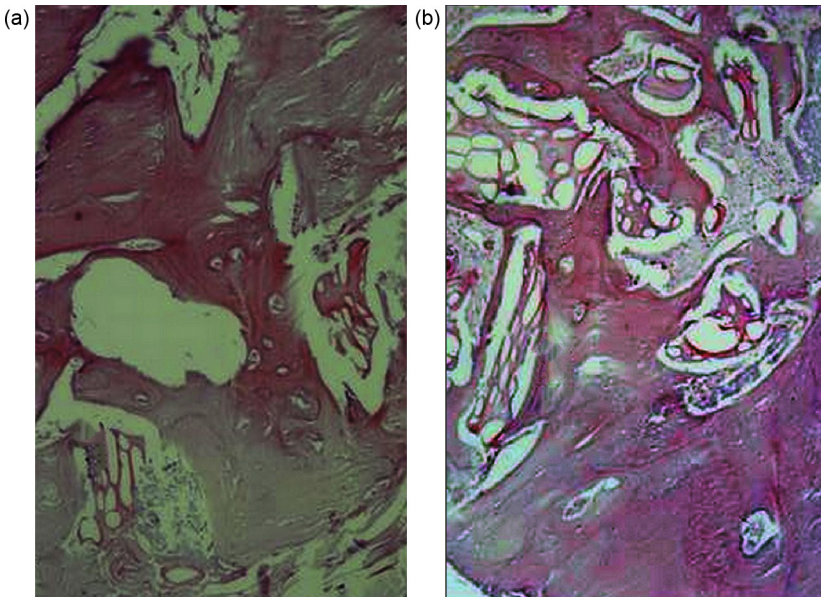

Fig. 2. Graft particles interconnected by bridges of newly formed bone and close contact between the residual graft particles and newly formed bone was observed (haematoxylin and eosin; original magnification 100×): (a) with decortication; (b) without decortication.

Results

All grafted sites healed uneventfully. No flap dehiscence and no exposure of membranes were noted. All implants were placed with good primary stability and after 4 months of healing were subsequently restored. No residual parts of the collagen membrane could be detected at re-entry surgery and the regenerated tissue appeared as mineralized bone tissue and adequate to place implants without further grafting.

Histological findings

The remaining graft particles were surrounded by newly formed vital bone and soft tissue. Histological examination of the biopsies showed graft particles interconnected by bridges of newly formed bone, and close contact between the residual graft particles and newly formed bone was observed in both the test and control groups (Fig. 2). The histological appearance of the graft material showed that it had osteoconductive properties. Many viable cells were noticed in the newly formed bone matrix. In both groups, the amount of bone formation was higher in the area close to the native alveolar bone. Signs of remodelling within the bone matrix, including the presence of osteocytes in the bone trabeculae, incremental appositional lines, and angiogenesis, were observed in the control group as well as the test group (Fig. 3).

Histomorphometric findings

Histomorphometric data related to the different groups are presented in Table 1. The average percentage of newly formed bone was 27.77 ± 11.32 for the test group and 25.33 ± 11.5 for the control group. There was no significant difference between the test and control groups for the various histomorphometric variables (NB, RG, ST) (Table 2).

Bone trabeculae showed a lamellar structure with different thicknesses. The average thickness of the bone trabeculae measured was 96.11 ± 12.86 μm in the test group and 100.33 ± 27.32 μm in the control group (Table 3). There was no significant difference between the test and control groups with regard to thickness of the bone trabeculae ($P = 0.42$).

The numbers of microvessels found in the two groups are presented in Table 4. The mean number of microvessels in the test group (10.11 ± 2.86) was significantly higher than that in the control group (5.44 ± 3.54) ($P = 0.01$).

Discussion

Many clinical studies have performed decortication of the recipient bone as part of a guided bone regeneration protocol and have reported successful results.[15–17] In contrast, some animal studies have

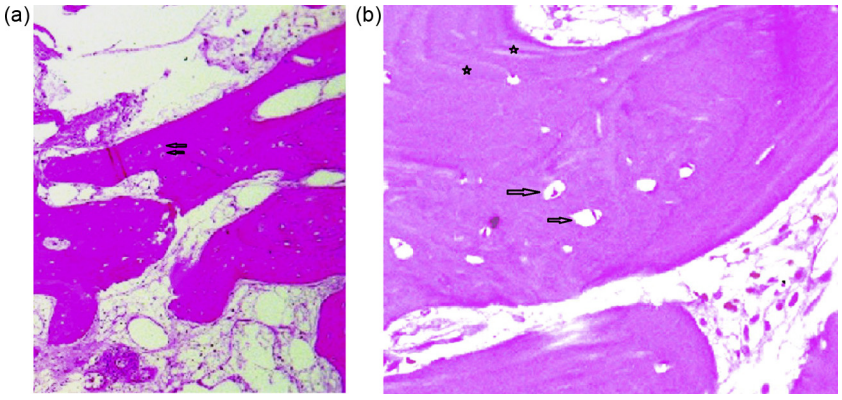

Fig. 3. Incremental appositional lines (*) and osteocytes (arrows) in mineralized matrix showing signs of remodelling at the augmented site without decortication: (a) haematoxylin and eosin, original magnification 100×; (b) haematoxylin and eosin, original magnification 400×.

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Table 1. Histomorphometric results of core samples taken from grafted sites with decortication and without decortication.

Patient	Healing time (months)	Newly formed bone (%)	Soft tissue components (%)	Residual particles (%)
Decortication				
A	8	23	52	25
B	8	29	31	40
C	7.5	28	29	43
D	6	23	42	35
E	7	28	43	29
F	8	37	27	36
G	6	26	40	34
H	8.5	27	38	35
I	7	29	35	36
Mean	7.3	27.8	37.4	34.8
Without decortication				
J	7	19	56	25
K	8	31	54	15
L	7.5	29	46	25
M	6.5	16	52	32
N	7	22	48	30
O	9	24	44	32
P	8	36	31	33
Q	7.5	24	49	27
R	7	27	43	30
Mean	7.5	25.3	47	27.7

Table 2. Analysis to determine possible differences between test (decortication) and control (without decortication) groups for variables of interest.

	Decortication ($n = 9$) Mean ± SD	Without decortication ($n = 9$) Mean ± SD	*P*-value[a]
Newly formed bone (%)	27.77 ± 11.32	25.33 ± 11.5	0.13
Soft tissue components (%)	37.44 ± 14.93	47 ± 15	0.24
Residual particles (%)	34.78 ± 16.24	27.67 ± 10	0.09

SD, standard deviation.
[a] Paired *t*-test; $P < 0.05$ considered significant.

demonstrated that bone formation can occur without decortication.[18–20] Therefore, whether perforation of the recipient bone has a beneficial effect on bone regeneration or not remains controversial.

Previous studies have investigated the histomorphometric effects of cortical bone perforation on grafted sites in cranial defects of animals.[11,21,22] Histomorphometric analysis has the capability of precisely assessing the inter-phase between the newly formed bone, residual graft particles, and soft tissue and is considered the gold standard method to estimate the amount of newly formed bone, residual graft particles, and soft tissue at grafted sites.[23]

Majzoub et al. showed a significant increase in the amount of new bone formation in the groups that had intramarrow penetration at 10, 21, 42, and 60 days.[21] Lee et al. evaluated the effect of cortical perforation on osteogenesis and angiogenesis following GBR using beta-tricalcium phosphate in rabbit calvaria.[11] They reported that the amount of newly formed bone was significantly greater at 2 weeks after surgery in the group that had received decortication. However, there was no significant difference between the groups after 4 or 8 weeks. Based on their study, the effect of recipient cortical bone decortication is more prominent in the osteogenesis occurring in the early phase of bone healing.[11] Slotte and Lundgren showed no significant difference between a test group with cortical perforations of contiguous donor bone and a control group regarding augmented bone tissue volume or bone density.[22] The current study found no significant difference in the amount of new bone formation or trabecular bone thickness between the experimental and control groups after a healing period of 7 months.

In agreement with the present study, Norton et al. observed similar amounts of newly formed bone and residual graft particles at augmented sites with bovine bone after a healing period of 26 weeks.[9] However, they used decortication in all of the cases and did not have a control group to compare the effect of decortication on bone regeneration.

Conti et al. showed that decortication resulted in better integration of bone graft into the recipient vertebral bone in dogs, within 1 to 3 months.[12] However, by 6 months there was no benefit with respect to the non-decorticated areas. Ishikawa et al. evaluated the effect of spinal decortication and instrumentation in rabbits and could not find a beneficial effect of decortication on spinal fusion rates.[13] Adeyemo et al. found that, after 4 months, decortication of the recipient bed offered no advantage over a non-decorticated bed with respect to healing and the incorporation of an onlay bone graft.[24]

Min et al. observed no significant difference in osteogenesis after 1 month of healing; however, after 3 months, the experimental group with decortication showed a significant increase in the percentage of new bone.[25]

Table 3. Thickness of trabeculae in the test (decortication) and control (without decortication) groups.

Thickness of trabeculae (μm)	
Decortication	Without decortication
77	126
96	110
112	96
92	98
105	75
108	113
83	102
99	104
93	79
Mean ± SD	Mean ± SD
96.11 ± 12.86	100.33 ± 27.32

SD, standard deviation.

Table 4. Numbers of blood vessels in the test (decortication) and control (without decortication) groups.

Number of microvessels per square millimetre	
Decortication	Without decortication
9	5
13	3
8	8
12	4
10	5
7	9
12	3
13	8
7	4
Mean ± SD	Mean ± SD
10.11 ± 2.86	5.44 ± 3.54

SD, standard deviation.

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Angiogenesis is a multistep process and is considered one of the main steps required prior to bone formation. The presence of new blood vessels is critical since they nourish the grafted site with osteoprogenitor cells and provide the required minerals for bone maturation.[7]

Angiogenesis usually proceeds from the existing blood vessels that may become exposed to the grafted site after reflection of the flap, which results in injury of the vessels continuing from the flap into the bone surface.[26] Tearing of the vasculature may be sufficient to initiate the biological cascade of bone regeneration.[21] There are different hypotheses that may explain the beneficial effect of bone decortication on bone formation, including (1) improved angiogenesis; previous studies have shown that an opening through the medullary bone facilitates the sprouting of new vasculature into the regenerated bone and enhances angiogenesis.[7,21] (2) Decortication of the recipient bone provides a pathway to a vessel-rich cancellous bone that irrigates the grafted site with blood. This brings more progenitor cells and cytokines to the area.[7] (3) Cortical bone penetration is considered a noxious stimulus that initiates the regional acceleratory phenomenon thereby facilitating normal bone healing.[27,28] (4) Perforation of the recipient bed may improve the mechanical interlocking of the bone graft and the recipient native bone. This becomes more valuable in monocortical bone block grafting, where the stability and fusion of the block graft to the recipient bed is critical.[29,30]

The blood supply and angiogenesis play important roles in GBR.[31] The positive effect of cortical bone perforation on angiogenesis has been shown in previous studies.[32] Mesenchymal stem cells have been shown to induce angiogenesis by differentiating into vascular endothelial cells.[7,33] Marat et al. found an increase in vessels following bone marrow transplantation into the subcutaneous tissues of dogs.[32] Shimoji et al. investigated the efficacy of bone perforation and collagen sponge onlay placement in the rat femur and noticed frequent angiogenesis into the collagen sponge.[33] They also showed significantly greater newly formed bone in the group with perforation of the cortical bone compared to the other groups on days 14 and 28.

Numerous studies have reported the intimate dynamic interplay between angiogenesis and bone formation.[7,26,34] Previous studies on cortical bone perforation have demonstrated the induction of new vessels in connective tissue and rapid revascularization into the grafted site, which eventually promotes osteogenesis.[31,35] In agreement with previous investigations, the present study showed significantly higher numbers of blood vessels in the test group in comparison to the control group after 7 months of healing.

Cortical perforation could act as an additional surgical trauma, resulting in the loss of donor site bone volume. However, improved angiogenesis and accelerated bone formation may compensate for the early volumetric loss associated with decortication.[7,21,34] Cha et al. noticed numerous blood clots and granulation tissue at the interface of the donor site and the grafted bone.[34] They showed that by creating a physiological pathway for blood vessel penetration through the cortical bone, capillary ingrowth was enhanced, which in turn advanced bone formation.[34]

All of the previous studies were performed on animals. The present investigation was a clinical study to evaluate the effect of intramarrow penetration on regenerated bone histologically in humans. Of note, most of the animal studies that assessed the efficacy of decortication used the calvarium as the recipient bed, which is not comparable to the mandible and maxilla due to the presence of several natural foramina in the calvaria of rabbits and rats.[22] This could favour revascularization and improve osteogenesis and hence bias the assessment of the efficacy of cortical bone perforation. In the present study, only osseous defects in the mandible were included, thus mandibular bone was the recipient bed for all augmented sites.

Another confounding factor that may affect the results from animal studies is the use of small animal species such as rats and rabbits, which have a high potential for osteogenesis and faster metabolism.[7] It would be more appropriate to use larger animal species such as monkeys or dogs to perform such studies.[34,36] Although the principles of osteogenesis are similar in humans and animals, caution must be exercised when extrapolating experimental findings relative to the rate and amount of new bone formation from animal models to humans.

Another factor that may influence the quality of the regenerated bone is the size of the perforations made in the recipient bone. Nishimura et al. evaluated the effect of two different perforation sizes on the amount of bone formation and found that larger perforation sizes were associated with a faster and greater amount of new bone formation in the early phases of healing.[31] However, no difference was found in the amount of regenerated bone at 3 months after therapy.

This study has several limitations that should be acknowledged. First, a split-mouth study design would have been ideal since it would have provided the opportunity to compare the influence of decortication on bone regeneration and eliminate the host as a variable. Second, it is recommended that biopsies be taken at various time points so that the effect of decortication on osteogenesis at different healing times can be assessed. Finally, randomized clinical trials with larger sample sizes are required to confirm the present findings and improve on the scientific data obtained and the statistical power.

In conclusion, within the limitations of the present investigation, this study found that cortical bone perforation favourably affects the amount of new bone formation in the grafted sites after 7 months of healing. Cortical bone perforation significantly increase number of new vessels (angiogenesis) of the regenerated bone and may provide some advantages without any serious negative effect. Further randomized clinical trials with larger sample sizes are required to confirm these findings.

Funding

None.

Competing interests

No external funding, apart from the support of the authors' institution, was available for this study.

Ethical approval

All procedures and materials were approved by the local ethics committee and the Institutional Board of Research of Mashhad University of Medical Sciences (protocol 347293). The principles of the Declaration of Helsinki were followed in this study.

Patient consent

Written consent was obtained from the patients to publish the clinical photographs.

Conflicts of interest

None.

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