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Osteoneogenesis due to periosteal elevation with degradable and nondegradable devices in Göttingen Minipigs

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ABSTRACT

Introduction: Periosteal distraction or elevation has been known as an experimental method to induce new bone formation. Although it uses the principles of distraction osteogenesis no further osteotomy is necessary. The purpose of this study was to test devices of different materials and to evaluate the point of origin of the new bone formation.
Material & methods: On each calvaria of twelve male adult Göttingen Minipigs three devices were implanted. The materials used were degradable PDLLA (poly-DL-lactide), PGA (polyglycolic acid) and nondegradable Ti (titanium). After a consolidation time of 2, 4 and 6 weeks days a total of 36 specimens were harvested. To identify the total amount of newly created bone, micro-CT and histological analysis were performed.
Results: All degradable devices collapsed to a certain extent within the observation time but osteoneogenesis took place in all materials after a consolidation time of 2, 4 and 6 weeks after implantation above and under the devices. No statistical significant differences between the materials were found. However, most bone formation took place in the space under the periosteum and above the devices ($p < 0.001$).
Conclusion: Periosteal elevation can produce new bone formation with degradable devices, which derives from the periosteum and the underlying bone. In this interaction the periosteum seems to contain the larger share.

1. Introduction

Bone deficiency of the alveolar ridge remains one of the primary obstacles to the long-term success of dental implants (Clementini et al., 2012). Autogenous bone grafting and distraction osteogenesis are well-established procedures for bone augmentation. However, they are invasive procedures requiring osteotomy and corticotomy, with a risk of donor site morbidity or complications (Dahlin et al., 1988; Esposito et al., 2006; Saulacic et al., 2009). A different method that is not yet in clinical use, called "periosteal distraction osteogenesis" (PDO), has been described previously (Kostopoulos and Karring, 1995; Schmidt et al., 2002). Although this technique is based on the principles of osteodistraction, osteotomy is not necessary. New bone formation is initiated by creating a

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space between the periosteum and the local bone (Shimizu et al., 2001). The periosteum is known to play an important role in bone healing and osteoneogenesis. It has been shown that in long bones, up to 90% of woven bone in early fracture callus is derived from the periosteum (Zhang et al., 2005). The periosteum consists of two layers, an outer fibrous layer and an inner cambium layer, which contain osteoblast progenitor cells. When influenced by growth factors, these progenitor cells are able to migrate into their surroundings, where they proliferate and differentiate into osteoblasts (Matsushima et al., 2011). Moreover, the periosteum itself is able to promote osteoblast differentiation and osteogenesis by sensing mechanical stretching and regulating the expression levels of genes involved in BMP signaling pathways, which is the basic principle of PDO (Ito et al., 2014).

Other authors have demonstrated that sufficient bone can be produced by this technique (Schmidt et al., 2002; Yamauchi et al., 2013). In earlier animal studies, we showed de novo bone formation of 5 mm or more with this method (Kessler et al., 2007). In a different study, we evaluated the difference between dynamic and static elevation (Tudor et al., 2010). The elevation was performed either intermittently, by raising the device with a distraction screw, or immediately, by inserting a convex device between the periosteum and the cortical bone, which can be called static PDO. The latter method follows strongly the technique of “guided bone regeneration” (GBR) first described by Dahlin et al. 1988. Its basic principle is that bone regeneration is enhanced by inserting a shielding material between bone and the overlying soft tissue. These two procedures seem to offer the possibility to create similar amounts of new bone (Lethaus et al., 2010). However, in contrast to GBR, static PDO aims to create bone through expanding the periosteum.

To perform PDO, many authors have used titanium (Ti) as the device material, which has to be removed in a second operation to enable implantation into the newly formed bone (Oda et al., 2009; Rompen et al., 1999; Tudor et al., 2010; Zakaria et al., 2012). This feature must be considered as a drawback because it presents additional risks. With the use of degradable devices, further operations could be avoided, with static PDO and implantation of dental implants performed simultaneously.

One aim of the present study was to determine whether bone generation rates in static PDO are similar around degradable devices compared with nondegradable devices. Degradable polymers such as poly-DL-lactide (PDLLA) and polyglycolic acid (PGA) show good mechanical stability and biocompatibility (Vert et al., 1992; Wildemann et al., 2005). In this study, we performed immediate PDO on the calvaria of minipigs using PDLLA or PGA as a degradable material or Ti as a nondegradable material, and compared the materials' bone generation rates.

The factors influencing bone growth in the space created by PDO have not been sufficiently characterized so far. There are indications that the stimulus can come from both the periosteum and the cortical bone (Saulacic et al., 2013a,b), which might have an influence on the location of new bone formation (Saulacic et al., 2012). Therefore, the second aim of the current study was to evaluate the precise origin and location of osteoneogenesis in the area of static PDO.

2. Material and methods

We performed static PDO on the calvaria of 12 male adult Göttingen Minipigs. This animal model was chosen due to the similarity of its metabolic rate and bone healing to those of humans (Pearce et al., 2007). The experiments were conducted with the approval of the Government States Animal Ethical Committee (84-02.04.2013). Adequate measures were taken to minimize pain and animal discomfort.

Three groups (groups I, II, and III) were randomly created, with four animals in each group (weight range 38.0–56.9, mean 43.6 kg). The groups were defined by time allowed for healing after implant insertion: 14 (group I), 28 (group II), or 42 (group III) days. Every animal received three subperiosteal devices, each composed of a different material: one nonbiodegradable Ti device and two biodegradable devices consisting of a polylactic acid (PDLLA or PGA). Altogether, we implanted 36 subperiosteal devices.

General anesthesia was induced by ketamine (Ketaminol, CEVA, Düsseldorf, Germany) (15 mg/kg) and pentobarbital (Narcoren, Merial, Hallbergmoos, Germany) (15 mg/kg) and maintained via inhalation of isoflurane (1.0–1.5 vol.%) (Forane, Abbott, Wiesbaden, Germany). Prior to surgery, a single shot of the antibiotic cephalexin (Zinacef, GSK, Munich, Germany) (750 mg i.v.) was given. During the whole procedure, tracheal intubation was maintained for ventilation. The operation was performed under standardized sterile conditions. After shaving and disinfection of each animal's head, a U-shaped incision was performed and a full-thickness skin-periosteal flap was carefully elevated to expose the calvarial bone. Each custom-made periosteal distraction device (height 10 mm, diameter 15 mm) was placed on the bone surface of every animal (Fig. 1). All devices were minimally perforated on the top and side faces to allow blood filling postoperatively. The Ti devices (KLS Martin, Tuttlingen, Germany) were fixated with Ti screws, and the other two devices (PDLLA/PGA, KLS Martin, Tuttlingen, Germany) were attached with resorbable pins. The skin-periosteal flap was repositioned to cover the three devices and readapted into two layers using resorbable sutures. No periosteal releasing incisions were made.

After a consolidation time of 12, 28, or 42 days, the animals were euthanized with an overdose of barbiturate under general gas anesthesia. A total of 36 specimens, consisting of scalp tissue, device material, and underlying bone, were harvested.

To identify the total amount of newly created bone, micro-computed tomography (micro-CT) and histological analysis were performed on all 36 specimens.

The specimens were harvested and fixed in 4% paraformaldehyde for 24 h, followed by dehydration using an ethanol gradient (70–100%). Embedding was performed with Technovit 9100 NEW (Heraeus Kulzer GmbH, Germany) following the manufacturer's specifications. The probes were initially imaged using dual-energy micro-CT (TomoScope Duo; CT Imaging, Erlangen, Germany). The two tubes of the flat-panel micro-CT were operated at 40 kV and 1.0 mA and at 65 kV and 0.5 mA (Gremse et al., 2011), and 2880 projections with 1032 × 1012 pixels were acquired over 6 min. Reconstructions were performed using a Feldkamp-type

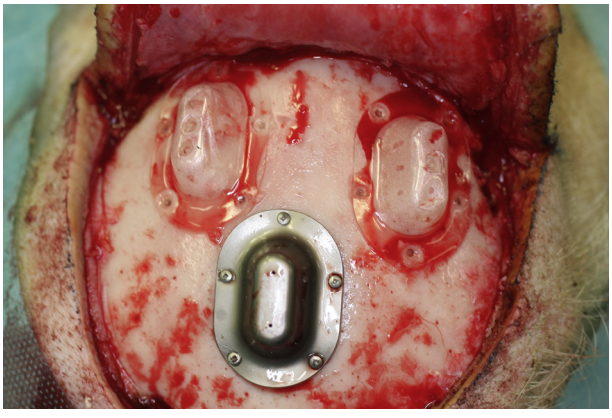

Fig. 1. Intraoperative view of all three devices (Ti, PGA, PDLLA) implanted on the Minipig calvaria.