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Effects of local simvastatin on periosteal distraction osteogenesis in rabbits☆

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Abstract

Our aim was to evaluate the effect of local simvastatin on the formation of new bone using a new design of periosteal distractor. The distractors were placed between the periosteum and bone at the inferior border of the mandible of 20 New Zealand rabbits. In the first group ($n = 10$) simvastatin was applied locally to the distraction zone. The other 10 rabbits served as controls. The formation of new bone was evaluated with digital direct radiography, computed tomography (CT), and histomorphometric analyses. New bone formed in all rabbits, but more formed in the experimental group according to histomorphometric variables. However, other measurements did not differ significantly between the groups. The new design of the periosteal distraction device was successful in causing new bone to form. Local simvastatin made no significant contribution to the procedure.

Keywords: Periosteal distraction; Simvastatin; Bone augmentation; Osteogenesis

Introduction

The "gold standard" for the reconstruction of bony defects remains autogenous grafting,[1] but morbidity at the donor site and the limited quantity of bone available are the main disadvantages.[2–7] Distraction osteogenesis has the potential to overcome these disadvantages, and in addition can provide lengthening of soft tissue together with new bone.[5–7] Various techniques of distraction osteogenesis have been described with reasonable success rates, and in recent years the idea of osteogenesis by periosteal distraction for the treatment of bone deficiencies has also been suggested.[1,2,8,9]

The highly vascularised internal osteoblastic layer of periosteum plays a part in distraction osteogenesis. It is composed of mesencymal stem cells,[5] and it has therefore been suggested that it is more important than endosteum in distraction osteogenesis.[9,10]

Statins are effective lipid-lowering drugs that are widely used to reduce the risk of cardiovascular disease given their ability to inhibit the 3-hydroxy-3-methylglutaryl-coenzyme.[11] They are extensively bound to plasma proteins and predominantly metabolised by the cytochrome P450 family of enzymes, and their main route of elimination is through bile after being metabolised by the liver.[12] Several studies have shown that both systemic and local simvastatin contribute to bony regeneration.[11–15] Although the exact mechanism is not known some hypotheses have been

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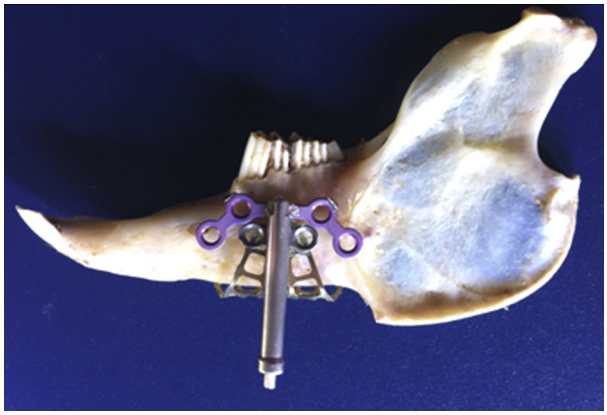

Fig. 1. Photograph of the orientation of the device to the rabbit mandible; lateral view.

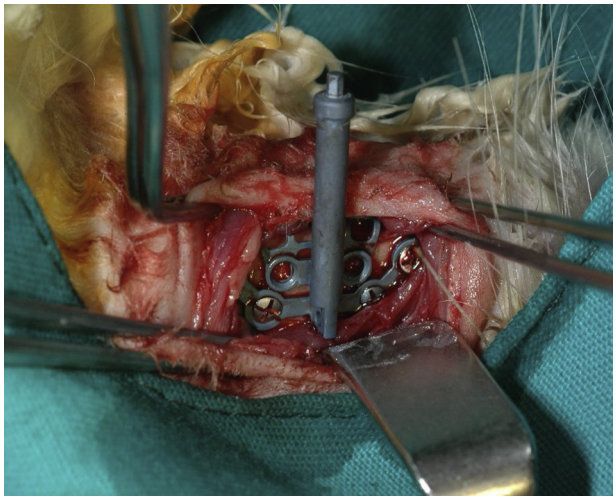

Fig. 2. Intraoperative photographs showing fixation of the device with screws laterally.

proposed, which are mostly based on the increased expression of the bone morphogenetic protein-2 (BMP-2) gene in bony cells after statins have been given.[12–15] It has also been shown that statins (including simvastatin) stimulate the expression of vascular endothelial growth factor in osteoblasts through reduced protein prenylation and the phosphatidylinositide-3 kinase pathway, which promotes osteoblastic differentiation.[16]

In this study we have evaluated the effects of local simvastatin on the formation of new bone through a periosteal distractor that was designed and manufactured particularly for this study in rabbits' mandibles.

Material and methods

The study was reviewed and approved by the ethics review committee of Cukurova University Medical Scientific Research Centre. Twenty skeletally mature New Zealand rabbits weighing 2.8–3.2 kg (mean (SD) 3.05 (0.15) kg) were divided into two groups of 10 each. The same periosteal distractor and distraction procedure were used in both. Simvastatin-soaked gelatin sponges were placed on the distraction zone during the operation in the study group, and dry gelatin sponges were used in the control group.

A new periosteal distraction device was designed and manufactured for this study (Synthes, Solothurn, Switzerland). The distraction device is made of pure titanium and there are three components; mesh (the easily bendable part of the device), the distractor, and the fixation plate. It was designed to be adjustable to the inferior border of the rabbit mandible. It raises the periosteum and other soft tissue layers in a superior direction, and allows a distraction gap to be created between the periosteum and the cortex (Fig. 1).

Surgical technique

After the general anesthesia had been maintained with IM 35 mg/kg ketamine (Alfamyne, Egevet, Izmir, Turkey) and 5 mg/kg xylazine (Rompun, Bayer, Istanbul, Turkey) the animal was placed supine and the distractors put in place. A skin incision about 2 cm long was made parallel to the inferolateral surface of the mandible. Care was taken to make the incision as far as possible from the distraction site (1–2 cm lateral to the inferior border) to keep the periosteum intact. The dissection continued through the subcutaneous and muscle layers. The periosteum was carefully raised to expose the inferior border of the mandibular bone. When the surface of the bone was exposed, the cortex was perforated with a thin, round bur. The distractor was fixed to the lateral aspect of the mandible with 4 titanium screws (Fig. 2). Before the distractor was finally placed, the adjustment was checked, the gelatin sponge was inserted, and the wound closed.

In all animals, a gelatin sponge was placed between the mesh and the surface of the cortical bones. In the study group, the sponge was soaked with simvastatin, while in the control group it was not. Commercially available simvastatin tablets (Zocor 10 mg, Merck Sharp & Dohme, Istanbul, Turkey) were used. A concentration of simvastatin of 2.5 mg/ml was prepared by dissolving a quarter of each tablet in saline. The dose of simvastatin was the same as that used in a previous study in rabbits.[15] The solution was soaked in 0.02 g of gelatin sponge. After the distractor had been secured in its final position it was filled with gelatin sponges. The soft tissue layers were sutured primarily with 4/0 resorbable sutures (Vicryl, Ethicon, Brussels, Belgium).

Postoperative care

Tramadol 1 mg/kg and cefazolin 25 mg/kg were given intramuscularly preoperatively and twice a day for 4 days postoperatively. The rabbits were housed in separate cages and fed soft food for a week. After the first week, normal