Int. J. Oral Maxillofac. Surg. 2015; 44: 1423–1429
http://dx.doi.org/10.1016/j.ijom.2015.05.013, available online at http://www.sciencedirect.com

International Journal of
Oral & Maxillofacial Surgery

Research Paper
Dental Implants

Influence of the local application of sodium alendronate gel on osseointegration of titanium implants

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Abstract. The aim of this study was to perform a comparative analysis of aspects of the osseointegration of titanium implants placed with and without the local application of a bisphosphonate agent, after 28 days in vivo. The study involved the placement of 50 commercially pure titanium implants in the middle third of the tibia of 10 rabbits, with the right tibia used as the control and the left as the test site. Sodium alendronate gel was applied locally in the test group and sterile saline solution in the control group. After euthanasia, 10 implants from each group were analyzed for maximum removal torque. The remainder of the sample was processed to obtain non-decalcified slides, approximately 30 μm thick, for histomorphological and histomorphometric analyses, including bone–implant contact (%BIC). Data were analyzed at the 5% level of significance. The removal torque values of the test group were, on average, half those obtained in the control group. The test group showed a lower %BIC and notable changes in bone quality. It is concluded that the initial events in the osseointegration of titanium implants are not favoured by the local application of sodium alendronate gel in rabbits.

Key words: bisphosphonates; osseointegration; bone remodelling; dental implants.

Accepted for publication 20 May 2015
Available online 15 June 2015

Over the last few decades, there has been considerable growth in the demand for the replacement of lost teeth by means of therapy with dental implants and implant-supported dentures. Among other reasons, this is due to the fact that partial or complete edentulism affects a large proportion of persons of more advanced age, a population group that is growing steadily worldwide. The bone quality and quantity in these patients is frequently affected by systemic diseases, such as diabetes and osteoporosis, and they may also present lower potential bone regeneration, all of which may contribute to lower success rates in dental implant therapy.[2] On the other hand, the desire to attain faster osseointegration is common for both health professionals and patients. This has motivated research into the development of materials and techniques to optimize the process of bone remodelling around dental implants.

During implant placement surgery, the primary stability of the implant in bone tissue is one of the aspects used to determine whether or not to apply an immediate load. In cases in which there is no primary

0901-5027/01101423 + 07

stability during dental implant placement, it is recommended that the professional follows the protocol of two surgical stages, delaying functional loading for the period of osseointegration.[3] In this scenario it becomes important to accelerate the process of osseointegration, so that the delay between implant placement surgery and re-opening for the connection of the prosthetic abutment can be reduced.

Interest in the use of bisphosphonates as bone biomodulators in implant dentistry was aroused because of the known ability of these drugs to inhibit the activity of osteoclasts; this inhibition activity is why the drugs are used widely in the treatment of diseases characterized by excessive bone resorption, such as osteoporosis, hypercalcemia, and bone metastases.[4] Furthermore, it is known that an effect on bone formation may be expected, promoting a considerable reduction in bone turnover.[5] Studies have suggested that bisphosphonates may have a positive influence on bone formation and remodelling, and may consequently improve the fixation of titanium implants in humans.[6,7]

Because of the severe side effects caused by the systemic use of these drugs,[8–11] researchers have turned their attention to developing methods for the local delivery of these drugs to the site of interest.[12–16] The intention is that the bisphosphonate will positively influence the remodelling of bone adjacent to the implant, without causing undesirable systemic side effects. In this regard, immobilization of the bisphosphonate on the implant surface has been proposed as a way of delivering the drug locally.[17–21] However, the methodology for this immobilization is complex and requires sophisticated equipment. The direct application of bisphosphonate to the surgical alveolus immediately before implant insertion would appear to be a simpler and more practical procedure; however this has not yet been tested extensively.[13,22,23]

Therefore, the aim of this study was to propose the local application of a bisphosphonate drug (sodium alendronate) in gel form, directly to the surgical site, and to perform a comparative evaluation of aspects related to osseointegration of titanium implants inserted immediately after this application, in vivo. The hypothesis was that topically applied bisphosphonates would increase primary implant stability after 28 days.

Materials and methods

Animals and experimental groups

Ten adult male rabbits of the *Oryctolagus cuniculus* species, New Zealand lineage, with a mean body weight of 4.0 kg, were used in this research. The study was approved by the ethics committee of the university, and the animals received all the care stipulated by the institution.

A total of 50 implants were inserted in the sample. The right tibia was used as the control site and the left tibia as the test site. In the control group, sterile saline solution was applied to the surgical alveoli made in the right tibia of each animal. In the test group, a topical application of a 1 ml of sodium alendronate gel (10 mg/g) was administered to the surgical alveoli. The sodium alendronate gel was formulated specially for use in this study and the formulation was produced exactly as recommended by Reddy and Kumar.[24]

Surgical procedure

After being weighed, the animals received pre-anaesthesia medication, comprising acepromazine maleate (0.2 mg/kg) and morphine sulphate (2 mg/kg), both administered intramuscularly. After approximately 10 min, the marginal ear vein of the animal was cannulated for the administration of fluid therapy with lactated Ringer solution and enrofloxacin (10 mg/kg) 20 min before surgery. Anaesthesia was induced by means of intravenous injection of ketamine chloride (10 mg/kg) and 1 mg midazolam (1 mg/kg). Epidural anaesthesia was administered with 2% lidocaine (0.25 ml/kg). After the induction of anaesthesia, the animals were shaved and antisepsis of the region was performed, including the skin adjacent to the shaved area.

Surgery began with a linear incision, measuring approximately 2 cm in extension, on the medial diaphyseal surface of the tibia. The sites where the surgical alveoli were to be cut were demarcated, with the perforations positioned 10 mm below the tibial condyle and a distance of 10 mm between perforations. Cutting for implant insertion was performed with appropriate burs, under irrigation, to a depth of 4 mm, using first a 2-mm lance-shaped bur and then a helical bur.

After the cavities had been prepared, sterile gauze was introduced and kept in the surgical alveolus by compression for 1–2 min in order to absorb and stop the bleeding. This process guaranteed that the bisphosphonate gel would come into direct contact with the entire wall of the alveolus, without the interposition of blood.

For the test group, a 1-ml quantity of sodium alendronate was injected into the surgical alveolus immediately before implant placement[22,25] (Fig. 1a). After this, the implants were inserted (Fig. 1b). Commercially pure titanium implants with an acid-treated surface were used (Porous Nano; Conexão Sistemas de Prótese, Arujá, São Paulo, Brazil); these were 2.2 mm in diameter and 4.0 mm long, and fabricated specifically for this study.[26] The implants were inserted at a speed of 35 rpm, until they reached bone level.

To complete the surgery, the muscle and subcutaneous tissues were approximated with continuous sutures and the skin was approximated with simple, interrupted sutures, using resorbable suture thread (catgut 4–0; Johnson & Johnson/Ethicon, USA). The region was cleaned with gauze dampened with physiological solution to remove the residues of blood clots, and the wound was covered with an occlusive dressing and a gauze bandage.

During the postoperative period, all animals received analgesic medication consisting of tramadol hydrochloride (2 mg/kg) delivered subcutaneously, every 8 h, for 3 days. Antibiotic therapy consisting of enrofloxacin (10 mg/kg) was administered via intramuscular injection every 24 h for 7 days.

Euthanasia of animals

At 28 days postoperative, the rabbits were euthanized. Each animal received pre-anaesthetic medication comprising acepromazine maleate (l mg/kg), ketamine hydrochloride (15 mg/kg), and xylazine hydrochloride (2 mg/kg), all administered intramuscularly. After around 10 min, the palpebral, corneal, and pain reflexes were absent. With the animal in a plane of deep anaesthesia, 10% potassium chloride solution was administered intravenously until cardiorespiratory function ceased.

Removal torque measurement

The specimens were processed immediately after removal of the tibia for the measurement of the maximum removal torque of each implant. The tibias were first placed in 10% buffered neutral formalin solution; after 1 h, they were submitted to the torque removal test, thus they did not become dehydrated. The anatomical sample was carefully placed on the torque test equipment (CME; Técnica Industrial Oswaldo Filizola, Guarulhos, Brazil), which was controlled completely by the software programme DynaView Torque Standard/Pro M (Dyna Pro Dynamometers Ltd, United Kingdom), generating values automatically at a speed of 1 rpm and angular measurement of the