The Topical Administration of Bisphosphonates in Implant Surgery: A Randomized Split-Mouth Prospective Study with a Follow-Up Up to 5 Years

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ABSTRACT

Objective: To evaluate the efficacy of the topical administration of bisphosphonates in implant therapy.

Materials and Methods: Thirty-nine consecutive patients were selected for a split-mouth study. Inclusion criteria were: presence of a bilateral or total edentulism, ability to tolerate conventional implant procedures, older than 18 years. Ten patients were smokers. Ten patients were fully edentulous in both maxilla and mandible, 12 patients had fully edentulous maxilla or mandible, and 17 were bilaterally partially edentulous (9 in the mandible and 8 in the maxilla). A one-stage procedure was adopted in all cases. The prosthetic phase started 10 weeks after implant insertion. Each patient received implants on the control side and the test side, with insertion performed in the conventional way on the control side; on the test side, a 3% clodronate solution mixed with a surfactant (Tween-20) at a 1:3 ratio was topically administered both at the implant surface and at the implant site.

Results: One hundred fifty-five implants were inserted. The test and control groups included 75 and 80 implants, respectively. The implant insertion torque was no less than 30 Ncm. A total of 7 implants failed in the control group (6 before loading and one after 12 months of loading). No failure occurred on the test side. By the 5-year follow-up, no further implant failure had been recorded. Overall, implant survival rates at 5 years for the test and control groups were, respectively, 100% and 91.3%, the difference being significant ($p < .01$). Mean marginal bone loss was 0.85 ± 0.71 mm in the test group and 1.12 ± 0.85 mm in the control group after 1 year of loading and stable thereafter. The difference was not significant.

Conclusions: The topical administration of bisphosphonates may positively affect implant survival in the preloading and postloading phases in partially and fully edentulous patients. However, a larger study population is needed to verify these promising clinical results.

KEY WORDS: bisphosphonates, dental implants, edentulism

INTRODUCTION

In periodontal and implant surgery, clinical research has addressed the issue of how to enhance bone healing and prevent bone destruction. Various types of implant surfaces with different features, aiming at improving implant osseointegration, have been developed in the past decades.[1–8] A stable osseointegration over time is a requisite for the long-term success of implant-supported prostheses.

A number of biological and pharmacological substances have been introduced in order to enhance osseointegration through stimulation of physiological processes. The use of autogenous platelet concentrates rich in growth factors,[9–12] recombinant growth and

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differentiation factors,[13–19] statins,[20–22] parathyroid hormone,[23,24] different types of surface-bound substance,[25–29] and bisphosphonates[30–42] has been proposed. These mediators may be delivered locally at the intended site or systemically, producing a general metabolic improvement.

Bisphosphonates are chemical compounds used in many clinical settings, such as for the prevention and treatment of primary and secondary osteoporosis, Paget's disease, multiple myeloma, and other solid malignant tumors characterized by bone metastasis and osteolysis.[43,44]

Bisphosphonates have a high bone tissue tropism and basically act as inhibitors of osteoclast resorption activity, maintaining bone density and strength. These compounds can be divided into two main categories: the first-generation bisphosphonates (such as etidronate, clodronate, and tiludronate) and the second-generation or aminobisphosphonates (such as pamidronate, alendronate, zoledronate, and risedronate). The latter category of bisphosphonates is characterized by the presence of an amino group, which provides a far greater potency and a longer half-life than the first-generation compounds.[35,36]

A recent review of the literature on osseointegration of dental implants in patients under bisphosphonate therapy showed that such drugs in general did not have a negative influence on implant success.[45] Of the 12 studies included in that review, only two (one retrospective study and one outdated case report) showed a negative impact of bisphosphonates on implant osseointegration.

Given their antiresorptive action, it can be assumed that the topical administration of bisphosphonates in adjunct to conventional implant treatment might be beneficial for limiting the peri-implant bone resorption occurring after implant placement and loading.[46,47] Bisphosphonates could therefore be used to slow down the physiological decrease in primary stability of the implants during the initial phase of osseointegration, thus improving bone fixation and reducing the implant failure rate. This might be particularly useful for immediate and early loading procedures, as it has been shown that with such protocols, most failures occur in the first few months after implant placement.[48]

Early experimental evidence has demonstrated that the topical use of bisphosphonates at implant surface might improve osseous fixation of the implants.[30]

Previous clinical research showed that bisphosphonate coating might be beneficial for dental implant fixation in edentulous patients, producing an improvement in the implant stability quotient.[33,34] A histological study also showed that the topical use of bisphosphonate produced better bone quality around implants placed in posterior maxillary sites irrigated with a clodronate solution, as compared with control implants.[32]

The aim of this split-mouth prospective study was to evaluate the clinical efficacy of the topical administration of bisphosphonates at the implant surface and at the implant site in terms of implant survival up to 5 years of functional loading.

MATERIALS AND METHODS

This study was conducted according to the principles of the Helsinki Declaration of 1975, as revised in 2000. The Research Board of the IRCCS Galeazzi Orthopedic Institute approved the study protocol.

Inclusion criteria were:

- presence of a bilateral edentulism or totally edentulous arch;
- ability to tolerate conventional surgical and restorative procedures (American Society of Anesthesiologists physical status 1 or 2);
- older than 18 years.

Exclusion criteria were:

- active infection or inflammation in the area intended for implant placement;
- need for bone augmentation at the intended implant site;
- presence of uncontrolled systemic diseases;
- a history of radiotherapy to the head;
- past or current treatment with oral/i.m./i.v. bisphosphonates.

The number of cases needed to treat was estimated based on the question of how many cases are required in order to establish that use of bisphosphonates as adjunct provides better implant survival given a 4% difference in survival rate between the test and the control group (assuming a 94% implant survival for the control), a power of 80% ($b = 0.2$) and a 5% level of significance. The estimated sample size is 31 cases (bilateral patients) for each group. Taking into account a 15% to 20%

dropout at 5 years, it was planned to treat a total of at least 38 cases.

Based on the above criteria, 39 patients were selected for this study. Ten patients were edentulous in both upper and lower jaw. Twelve had a complete edentulism in the upper or lower jaw. Seventeen patients had a bilateral partial edentulism; out of these, 9 were toothless in the inferior arch, whereas the remaining 8 patients were edentulous in the upper jaw. Ten of the patients were smokers (less than 10 cigarettes per day).

All patients provided detailed medical history and signed a written informed consent. Partially edentulous patients underwent an initial therapy that included oral hygiene instruction, scaling, and root planning.

Patients' edentulous areas were divided according to a split-mouth design. The assignment of implants to the test or control side was decided by computer-generated randomized sequence. The indication of the site allocation to the test or control group was contained in an opaque closed envelope that the surgeon opened soon before surgery. The implants were tapered and dual etched-surface with external connection (Osseotite NT, 3i Biomet, Palm Beach Gardens, FL, USA).

All patients underwent antibiotic prophylaxis: 1 hour prior to the surgery, 2 g of amoxicillin + clavulanic acid were administered, followed by rinsing with 0.2% chlorhexidine digluconate for 3 minutes. Local anesthesia was induced by using Ultracain DS with epinephrine 1:100000 (articaine 4%, Sanofi Aventis, Geneva, Switzerland). A crestal full-thickness flap was elevated, avoiding any releasing incision. The drilling sequence was identical for the test and control sites.

On the test side, an aqueous solution of clodronate 3% (Moticlod, Lisapharma S.p.A., Erba, Italy), combined at a 1:3 ratio with another aqueous solution containing a nonionic surfactant (polyoxyethylene sorbitan monolaurate, also known as Tween 20) at a concentration of 0.1%, was topically administered at the implant's surface (Figure 1A–B). The osteotomy site was flushed with the same solution (Figure 2). Adsorption of the clodronate solution on the implant surface was done according to a standardized procedure, by leaving the implant in contact with the solution for 5 minutes. The surfactant has the role of reducing the surface tension at the interface, thereby improving bioadhesion of clodronate solution to implant surface. Improving bioadhesion means obtaining an intense and prolonged action of the drug over time, possibly reducing quick dispersion of the solution from the site of application.

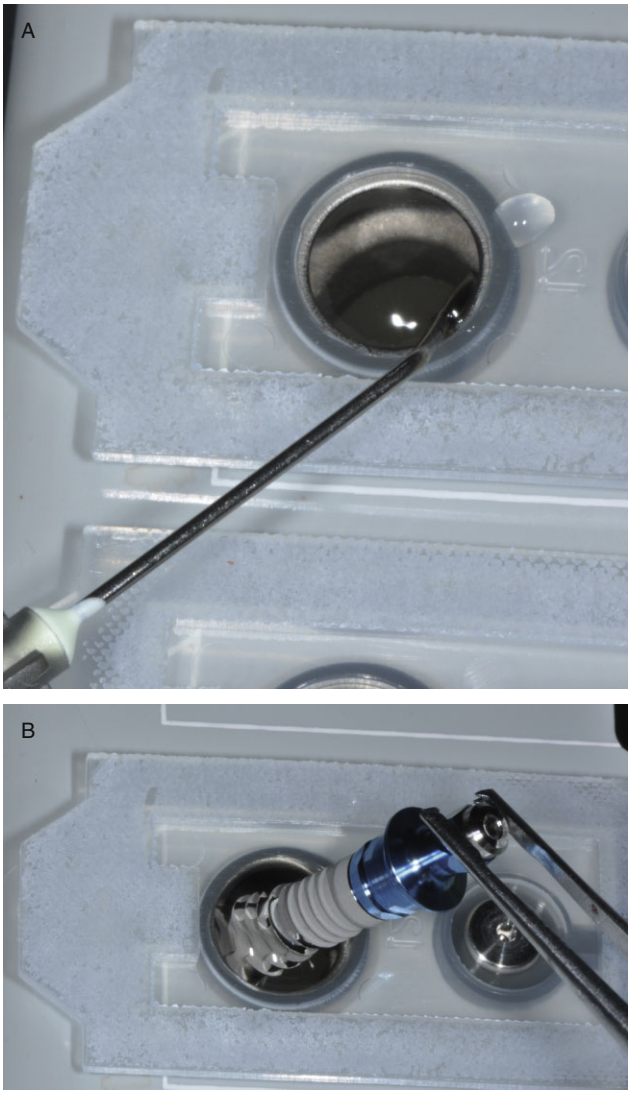

Figure 1 *A*, Customized device used to coat implant surface. The device is filled with the same 3% clodronate solution used to irrigate the implant site. *B*, The implant is submerged in the solution and left for a few seconds before being carefully extracted and placed in the implant site.

The implant insertion was performed according to the manufacturer's instructions, achieving a minimum torque of 30 Ncm. Once the surgery was completed, a healing abutment was placed on the implants and the incision margins were repositioned and sutured. Finally, periapical and panoramic radiographs of the implant site were taken. The implants were left to heal in a non-submerged manner. The suture was removed 10 days after surgery. The oral hygiene control session and the healing cap cleaning, performed by using a prophylaxis paste, were done every 3 weeks until loading.

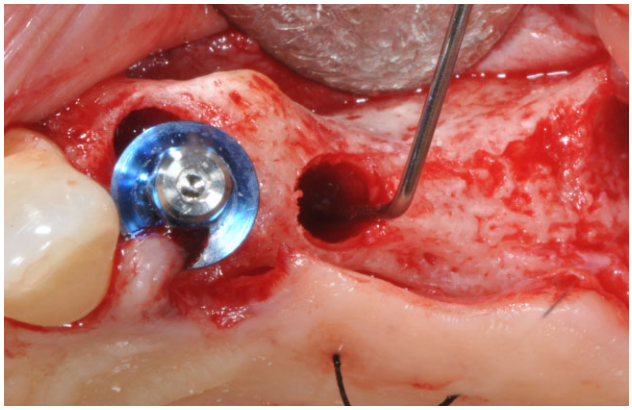

Figure 2 The site is irrigated with a modified clodronate 3% solution.

The prosthetic phase began 10 weeks after implant insertion. The final prosthesis was delivered 3 months later than the temporary prosthesis. Patients were recalled at 6 and 12 months and yearly up to 5 years of loading for control visits. At each control visit a standard clinical assessment of the surgical site was made and a periapical radiograph was taken with the parallel technique to evaluate the presence of peri-implant radiolucency. Periapical radiographs were scanned at 600 dpi with a scanner (Epson Perfection Pro, Epson Italia, Rome, Italy) and the peri-implant bone level was assessed with image analysis software (ImageJ version 1.46, National Institutes of Health, Bethesda, MD, USA; http://rsb.info.nih.gov/ij/) by an experienced evaluator. The known distance between the screw threads or the length of the implant was used to calibrate each image. The implant platform was used as the reference for each measurement. Radiographs taken at prosthesis delivery served as the baseline for evaluation of the marginal bone level change over the study period. The linear axial distance between implant platform and the most coronal bone-to-implant contact was measured. In order to have a single value for each implant, mesial and distal values were averaged. In order to perform paired tests, data from implants of the same side were averaged so as to have one value of bone loss for the test implants and one for the control implants for each patient. Any complication was recorded when it occurred.

The success criteria proposed by Buser and colleagues in 1997[49] and Cochran and colleagues in 2002[50] were adopted for each implant at each recall. Briefly, such criteria were:

- no clinically detectable mobility when tested with opposing instrument pressure;
- no evidence of peri-implant radiolucency;
- no recurrent or persistent peri-implant infection;
- no complaint of pain;
- no complaint of neuropathies or paresthesia.

Statistical Analysis

Data were summarized by means of descriptive statistics and tables. The outcomes of test and control groups after 5 years of loading were compared by means of Pearson's chi-square test using the implant as the analysis unit, and the result was expressed using relative risks along with 95% confidence intervals. The difference in marginal bone level change between groups was evaluated by means of the paired *t*-test, using the patient as the analysis unit. The level of significance was set at $p = .05$.

RESULTS

Thirty-nine patients (22 men and 17 women, mean age 52.6 ± 14.2 years, range 38–68 years) were recruited and treated from February 2006 to July 2007. A total of 155 implants were inserted (80 control and 75 test implants). The implant size was decided according to the clinical and functional needs of the patients. Implant length and diameter distribution is reported in Table 1. Implant distribution according to the group, the type of edentulism, and the arch is shown in Table 2.

All patients could be rehabilitated as planned. All patients attended regular follow-ups and could be evaluated after 5 years of functional loading.

During the suture removal at 10 days after surgery, a light paresthesia at the inferior lip of one partially edentulous patient was observed, disappearing 6 months later.

Among patients receiving full-arch rehabilitations, two implants inserted in the maxillae of two nonsmoker

TABLE 1 Distribution of Implants according to Size

	Diameter (mm)	
Length (mm)	4	5
8.5	18	0
10	42	6
11.5	39	2
13	48	0
Total	147	8

TABLE 2 Distribution of Implants according to Location, Type of Edentulism, and Study Group

			All Sites		Control Sites		Test Sites			
Edentulism	Arch	Number of Prostheses Delivered	Number of Failed Implants Out of Total	Implant Survival (%)	Number of Failed Implants Out of Total	Implant Survival (%)	Number of Failed Implants Out of Total	Implant Survival (%)	*p* Value	Risk Ratio (95% CI)
Fully edentulous	Maxilla	10	2/82	97.6	2/42	95.2	0/40	100	0.08	0.95 (0.89, 1.02)
	Mandible	12	2/37	94.6	2/20	90.0	0/17	100	0.10	0.90 (0.78, 1.04)
	Subtotal	22	4/119	96.6	4/62	93.5	0/57	100	0.02*	0.93 (0.88, 0.99)
Partially edentulous	Maxilla	12	1/17	94.1	1/8	87.5	0/9	100	0.19	0.87 (0.67, 1.14)
	Mandible	14	2/19	89.5	2/10	80.0	0/9	100	0.08	0.80 (0.59, 1.09)
	Subtotal	26	3/36	91.7	3/18	83.3	0/18	100	0.03*	0.83 (0.68, 1.03)
Total		48	7/155	94.3	7/80	91.3	0/75	100	0.001*	0.91 (0.85, 0.98)

*Significantly different ($p = .05$).
CI, confidence interval.

patients on the control side failed before loading. Another implant placed in the mandible of a smoker patient on the control side failed before loading. In these patients, the removal of the implants did not prevent the positioning of the provisional prosthesis. All the failed implants were replaced, and 4 months later, the definitive prosthesis was inserted. An intermediate mandibular implant on the control side in a smoker patient failed 1 year after loading. This implant was not replaced, as it was judged that the prosthesis could function even with the loss of one implant. No further implant was lost by 5-year follow-up. No failures were recorded on the test side.

Among the partially edentulous patients, one implant in the maxilla on the control side in a nonsmoker patient failed before loading. In this case, the implant was not replaced, as it was the middle implant of a total of three implants, and the patient manifested a firm intention not to undergo a new surgical intervention. Therefore, the final prosthetic rehabilitation consisted of a bridge supported by two implants. Another two failures occurred in the mandible on the control side before provisional prosthesis delivery. The failed implants were substituted with new implants 4 months later. No failures were recorded on the test side.

Table 2 summarizes the implant survival analysis results after 5 years of loading. An overall implant survival of 94.3% was recorded. Implant survival in the control group was significantly lower than in the test group, survival rates being, respectively, 91.3% and 100% ($p = .001$). This difference was confirmed in fully edentulous patients ($p = .02$) as well as in partially edentulous patients ($p = .03$).

Radiographic evaluation showed marginal bone loss of 0.85 ± 0.71 mm and 1.12 ± 0.85 mm, respectively, in the test and control groups ($n = 36$ patients in all) after 1 year of loading. Three patients had to be excluded from the analysis because the 1-year radiographs were not available. Bone levels remained essentially stable at the 5-year follow-up, being 0.98 ± 0.76 mm and 1.26 ± 0.88 mm in the test and control groups, respectively ($n = 32$ patients in all). The radiographic analysis at the 5-year follow-up could not be performed for 7 patients because of missing or poor-quality periapical radiographs. The difference was not significant at either follow-up ($p = .15$ at 1 year and $p = .18$ at 5 years). Throughout the study, no complications were recorded in either group.

DISCUSSION

The final aim of implant therapy is to achieve both implant osseointegration and long-term implant success. The latter depends on several factors, among which the bone tissue anatomical characteristics play a substantial role. In fact, poor bone quality has long been related to poor clinical outcomes, corresponding to a high percentage of failures.[51]

The administration of substances such as bisphosphonates has the purpose of influencing the healing process by enhancing implant osseointegration. Some early animal studies showed improved fixation of bisphosphonate-coated implants in the bone tissue.[22,30] Other clinical studies have demonstrated maintained or increased stability of implants coated with bisphosphonates placed simultaneously with the performance of the sinus augmentation procedure.[33,34] Further clinical histological evidence has shown that the topical use of bisphosphonates might lead to improved bone quality around implants during the healing phase.[32] The maintenance of primary implant stability, the greater retention of the implant in the bone, and the reduced peri-implant bone loss may improve the treatment success rate in the short and the long term, reducing implant failure rate.

Experimental studies have previously been conducted to figure out how to use these drugs in the implant field in order to impair the mechanism of bone resorption through osteoclast inhibition.

In a study performed by Meraw and colleagues,[23] the use of alendronate at the implant surface increased the percentage of bone surrounding the implants. In another study, Skoglund and colleagues[26] demonstrated that the systemic and topical administration of ibandronate improved the initial stability of the implant.

Narai and Nagahata demonstrated that the removal torque of implants inserted into the femur of induced-osteoporosis rats was higher in those animals treated with alendronate compared with animals not treated with bisphosphonate.[25]

Kajiwara and colleagues[29] demonstrated that bone formation around implants inserted into rats' shinbones was stimulated when the implant surfaces were treated with pamidronate. Meraw and colleagues[22] reported that the topical administration of alendronate in dogs for the rehabilitation of peri-implant defects favored initial bone formation around implants. Testori and

colleagues[52] studied the topical use of bisphosphonates in humans in order to prevent peri-implant osteolysis and also to improve new-bone formation around the implants. As a conclusion of their study, they found that implant survival percentage in lateral-posterior regions of the jaws could be increased by the topical use of clodronate disodium, which did not have any side effects.

Zuffetti and colleagues[32,53] studied the bone tissue response around an implant treated with a solution of bisphosphonates compared with an untreated implant. After analysis of the bone biopsies, the conclusion was that the bisphosphonate-treated implant showed a greater bone formation 2 months later compared with the control implant.

A 3-year follow-up study conducted by Jeffcoat[54] demonstrated that the oral administration of bisphosphonates (alendronate and risendronate) may increase the percentage of successful implant therapies compared with control cases without being associated with osteonecrosis of the jaw.

However, a recent study evaluating alveolar bone loss around osseointegrated implants in patients on bisphosphonate therapy reported that these patients may be at higher risk for implant thread exposure as compared with patients not taking such drugs.[55]

In the present study, no significant effect of bisphosphonates on peri-implant bone remodeling was found, suggesting that local and short-duration exposure to such drugs is not detrimental to implant longevity. In addition to the bisphosphonate drug, the solution used in the present study contained a nonionic surfactant (Tween 20), which was added in order to increase adsorption of the solution onto the contact surfaces. It is believed that solutions with high adhesivity with regard to both the bony walls of the implant site and the implant surface have increased efficacy. In fact, if there is a lack of affinity between the medicating solution and any one of the two systems (patient or implant), when the implant is introduced into the implant site, air pockets can be created between the implant and the drug or between the drug and the patient, which may push part of the medicating solution toward the outside, expelling the drug from the site of action. The air pockets may remain even once the implant is applied, limiting the contact surface between drug and patient/implant, and thus reducing the pro-ossifying activity of the drug around the implant and, consequently, the implant stability. Instead, if the solution adheres in a balanced way to both surfaces, no air pockets are formed, and the entire space between the walls of the implant site and the implant remains occupied by the medicating solution.

This study based on implant survival rate showed a significant benefit to the group in which the medicating solution was used as compared with the control group. This result is in agreement with previously published scientific data. The survival rate of 91.3% in the control group is in line with the 5-year survival rate found in a recent systematic review that reported a range between 89.2% and 95.5% for different implant systems.[56] Nevertheless, more studies with larger sample size and longer follow-up and with an accurate evaluation of peri-implant bone remodeling are needed to confirm the favorable outcome of the present study.

Given the growing number of reports on bisphosphonate-related osteonecrosis of the jaws published in the last 10 years, there can be reasonable concern about the safety of the clinical use of such drugs. Most such complications, however, have been related to long-term administration of intravenous aminobisphosphonates in patients affected by bone metastases.[56–58] Though it is necessary to evaluate patients over the long term to detect possible unwanted effects, it can be hypothesized that low-dose, single administration of nonamino bisphosphonates, as used in the present protocol, might not be sufficient to elicit osteonecrosis of the jaws.

CONCLUSIONS

The results of the present study indicate that the use of a bisphosphonate solution as adjunct might be beneficial to initial implant osseointegration without interfering significantly with peri-implant bone remodeling over time. The encouraging outcomes of this preliminary study support the use of bisphosphonates in implant dentistry to improve the implant survival rate.

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