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Human study of ion implantation as a surface treatment for dental implants


Abstract. This clinical study evaluated a new surface treatment of ion implantation with CO ions which has previously been subjected to extensive study in animal models. The aim of this work was to assess its effect in humans. Experimental mini-implants were used; half of their longitudinal surface was machined and the other half was treated with CO ion implantation. The study was conducted in healthy volunteer patients who required prosthetic treatment with dental implants, and in accordance with the corresponding ethics committees. Coinciding with the insertion of commercial implants for oral restoration, one or two mini-implants were placed in the upper maxillary tuberosity or in the retromolar trigone of the mandible. The mini-implants were removed with a trephine jointly with a small volume of surrounding bone after a 3-month period. Two evaluation methods were used and both showed a greater degree of bone integration in the mini-implant section that underwent CO ion implantation treatment in comparison with the non-treated surface: 62.9% vs. 57.9%, and 54.8% vs. 46.2%. In addition, no adverse reactions were observed in the surface treatment with CO ion implantation. These results confirm the positive benefits in humans, based on the findings obtained from previous animal experiments.

Titanium dental implants represent a good solution for the restoration of the partially or totally edentulous patient. Numerous studies have shown that different surface treatments for dental implants improve the results with regard to obtaining a greater degree of bone–implant contact. However, the number of failures is relatively important when these implants are inserted in low-density bone areas. This research aimed to assess the possibility of improving the prognosis in these cases by the application of a new surface treatment based on CO ion implantation technology, which has previously been evaluated in vitro (cellular adhesion and proliferation assays, apoptosis tests, alkaline phosphatase expression, and evaluation of cellular morphology, using human osteoblasts in all cases) and in vivo (osteointegration studies in New Zealand white rabbit and beagle dog mandibles), with satisfactory results.

Human clinical studies, including those by Jensen and Shennerby, Lazzara et al., Trisi et al., and Ivanoff et al., were taken into account when determining the design of this study. We used mini-implants treated with CO ion implantation in their longitudinal half, and the other non-treated half served as control. The implants were removed for histomorphometric study 3 months after insertion.

Materials and methods
The design and execution of this study was conducted in accordance with the ethical principles for medical research in humans as stipulated by the Declaration of Helsinki, the regulations of directive 93/42/CEE relative to medical devices, and the
circular number 07/2004 regarding clinical research with medical devices of the Spanish Agency of Medicines and Medical Devices. In addition, it followed the guidelines of the ISO 14155 standard related to the clinical research of medical devices in human subjects.

A total of 19 volunteer patients participated: 10 females and 9 males; age range 36–79 years. Thirty-seven mini-implants were inserted.

Inclusion criteria were as follows: healthy male and female patients, with a prior loss or absence of partial or total dentures, for whom a replacement with commercial dental implants commonly used in clinics and the corresponding prosthesis was prescribed. The bone quality in the areas of the experimental mini-implant insertion was type III or IV, according to the Lekholm and Zarb classification.

Exclusion criteria were as follows: minors, pregnant women, and those with local or systemic contraindications for surgical interventions in general or in relation to the prosthesis placement.

In this clinical trial we used 37 commercial (CE marked) mini-implants with a 1.8 mm diameter and 5 mm length, manufactured and modified according to the study specifications with titanium alloy Ti6Al4V (Implant Microdent System, Santa Eulalia de Ronçana, Barcelona, Spain) (Fig. 1). A surface treatment was applied by means of CO ion implantation in one longitudinal half, while the other half of the mini-implant was masked (Fig. 2) and thus remained in the as-machined condition to be used as control. A small mark was made in the upper area to maintain the original position during the removal and histological preparation.

CO ion implantation is a surface treatment in which the sample to be treated is bombarded at high energy levels with selected ions extracted from plasma. The ions are embedded onto the surface, where they produce modifications at the nanotopographic, physical (e.g. modification of surface energy), and chemical levels of the first superficial layers. The treatment affects cellular differentiation in osteoblasts and facilitates its apposition on the implant’s surface, thus triggering a cascade of events that lead to osteointegration.

The surface treatment for CO ion implantation took place in a high-energy ion implanter (Danfysik 1090 Ion Implanter, Danfysik, Jyllinge, Denmark) at low temperatures (−170 °C). Implants were sterilized with dry heat at 125 °C for 4 h.

Local or regional anaesthesia by means of lidocaine with epinephrine at 1:80,000 was used for the surgical procedures. Ibuprofen (600 mg) every 12 h or paracetamol (600 mg) every 8 h were administered during the next 3 days. Amoxicillin (2 g) was administered 1 h prior to the surgical intervention as antibiotic prophylaxis. If there was a penicillin allergy, 1.5 g oral erythromycin was administered 1 h before, and 0.5 g was administered 6 h after the procedure. The patients used mouthwash with 0.12% chlorhexidine every 12 h during at least the first 15 days of the postoperative period.

A minimal 1–2 cm incision in the crestal mucosa was performed with two release incisions. We then lifted the full thickness of the flap, drilled the osseous bed in accordance with the manufacturer’s instructions, with abundant irrigation, and manually inserted the micro-implant; suture was performed with 3/0 silk stitches, which left the hexagonal head of the implant subject to transmucosal exposure (Fig. 3).

The experiment mini-implants, which have built-in healing abutments in their body, were placed in the maxillary tuberosity or in the retromolar trigone of the mandible, adjacent to the commercial implants scheduled for subsequent prosthetic restoration (observing a safety distance greater than 5 mm), or in the future osseous bed, where a conventional commercial implant was subsequently placed after the extraction of the experimental one and a minimal quantity of peripheral bone. The mini-implants were removed after a 3-month period inside the patient, jointly with the surrounding osseous material, by means of a trephine with a 3.5 mm diameter and plentiful irrigation with saline solution (Fig. 4).

All samples were analyzed by two different and complementary methods: scanning electron microscopy (SEM) and light microscopy. The surface type of the two half sections of the implant was not evident or revealed to the personnel assessing them. The SEM evaluation was performed directly on the block containing the sample in a resin inlay after undergoing reduction techniques and fine polish (Fig. 5A), using a JEOL JSM-5910LV scanning electron microscope (JEOL, Tokyo, Japan). Evaluation of the bone–implant contact percentage (BIC%) was performed by photographing the complete image of the implant, where titanium, resin, and bone are clearly identifiable in different grey shades, marking the clearly identifiable areas of the close bone–implant contact and the entire implant profile inserted in the bone. Then, measurements were made on the marked images and the BIC determined accordingly using image analysis program Omnimet (Buechler Ltd, Lake Bluff, IL, USA); digital planimetry was used for verification.

Histological preparation of samples for light microscopy up to a thickness of 50 μm was performed with the authors’ own resin inlay procedure, cutting, and fine polishing, followed by the application of toluidine blue (Fig. 5B). BIC% evaluation of histological samples after toluidine blue application was performed using a digital microphotography system (Nikon Kodak Ltd, Rochester, NY, USA), Adobe Photoshop 7 (Adobe System Inc., San José, CA, USA), and the Omnimet image analysis system.

The results obtained were subjected to statistical analysis, which established the statistical significance of the differences between the BIC% of the surfaces by means of the Student’s t-test (significance at $p < 0.05$).

Finally, a 3-year clinical follow-up of the patients was performed to make sure that there were no side effects.

**Results**

Of the initial 19 patients, only 13 completed the study; this was due to the loss of the micro-implants in six patients before the planned extraction time. Thus, 15 of the 37 mini-implants were lost. As a result, 22 mini-implants were available for further evaluation and underwent analysis. A double histomorphometric evaluation was performed for the BIC of each sample.
Discussion

Numerous animal studies have shown a higher BIC% for dental implants that have undergone different surface treatments and modifications.\textsuperscript{1,2,4–8,15,18} In contrast, little research has been carried out on the histomorphometric evaluation of mini-implants using humans as the study model.

Trisi et al.\textsuperscript{3} studied six patients in whom 12 mini-implants with 3.3 mm diameter and 5 mm length were used. Six of the implants were treated with corundum shot blasting and the other six were polished to obtain a smooth surface. Three months after the insertion, they had a BIC of 58.9% for the group treated with shot blasting and 6.2% for the control group (polished after the machining procedure). Lazzara et al.\textsuperscript{20} placed 11 mini-implants with 2 mm diameter and 5 mm length in 11 patients; the mini-implants were treated on their longitudinal half and the other half was machined. The implants in that study remained in place for 6 months prior to removal, which is twice the length of time used in our study. Ivanoff et al.\textsuperscript{21} placed 40 mini-implants with 2.3 mm diameter and 5 mm length in 20 patients. Twenty implants were machined and 20 were anodized. They detected values of 37% BIC for the treated (anodized) implants and 15% for the machined (control) implants in the 22 mini-implants inserted in the mandible and maintained for an average of 3.5 months.

Lang et al.\textsuperscript{31} studied 28 patients in whom 49 mini-implants with 2.8 mm diameter and 4 mm length were inserted in the retromolar areas. Out of 49, they were able to analyze 30 implants, of which 15 carried the SLA surface treatment and the remaining 15 the SLActive treatment. The implants in this study remained in place for 1, 2, 4, and 6 weeks prior to removal. No differences were observed at the first week (a BIC of approximately 6%), no statistically significant differences were observed at week 2 (BIC of approximately 12.2 and 14.8% for SLA and SLActive, respectively), while at week 4, where differences were statistically significant, SLA showed a BIC of 32.4% and SLActive of 48.3%. Nevertheless, at week 6 no

by means of transmission microscopy as well as SEM.

The results obtained from the SEM analysis showed a greater BIC% in the half section subjected to the CO ion implantation treatment (54.8%) than in the machined half (46.2%) (Table 1). Using transmission light microscopy, we obtained BIC% values of 62.9 and 57.9%, respectively (Table 2).

Although the ion implanted halves showed larger values when compared with the control halves, the difference was not statistically significant (based on the Student’s $t$-test).

On the other hand, this study confirmed the absence of all types of negative reaction in the surrounding tissue on the surface of the mini-implant treated with CO ion implantation.

Fig. 3. Insertion of the mini-implant in the upper maxillary tuberosity (A–C) and radiological control (D).
differences were observed, with a BIC of 62% for both surfaces. All the authors in the previously cited studies placed the mini-implants in the rear maxilla areas. In all cases, after the corresponding placement durations determined by each author (7, 14, 28, 42, 90, 105, and 180 days on average for each study), the sample collection was carried out by means of a trephine that enclosed the experimental implant and a minimal 1–2 mm portion of surrounding bone. The BIC% values obtained in our study of CO ion implantation (62.9%) are higher than those found by Ivanoff et al.21 and Trisi et al.3 in their respective treatments. The implant durations (3 months) were similar in these studies. In the work by Lazzara et al.,20 the implant placement duration was twice as long (6 months) before removal, hence the results cannot be compared. Likewise, this occurred in the other studies published by Trisi et al. in 2002 and 2003,32,33 where the implants were removed after 6 months in the first study and after 2 months in the second study. The results obtained by Goené et al.34 and Orsini et al.35 are also not comparable. In both cases, the experimental mini-implants obtained BIC% values below those of CO ion implantation.

Table 1. Percentage of bone implant contact (BIC %) obtained by scanning electron microscopy analysis of non-treated (control) areas and those treated with CO ion implantation, and statistical significance.

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<td>Number of implants</td>
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<tr>
<td>Mean</td>
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<td>54.8%</td>
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<tr>
<td>Standard deviation</td>
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Table 2. Percentage of bone implant contact (BIC%) obtained by transmission microscopy analysis of non-treated (control) areas and those treated with CO ion implantation, and statistical significance.

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<tr>
<td>Number of implants</td>
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<td>Mean</td>
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Fig. 4. Incision and lifting of the full thickness of the flap at 3 months (A). Osseous defect after the extraction of the sample (B). Mini-implant with peripheral bone obtained with a trephine (C) and sample type to be studied (D).
but they were removed after shorter durations (4–8 weeks). On the other hand, also with a shorter placement duration (6 weeks), Lang et al.\(^3\) reported similar BIC\% values to those obtained in our study (62%).

We have not found any clinical human experimentation studies using CO ion implantation as an implant or mini-implant surface treatment in the literature that has included a histomorphometric evaluation.

The objective of this study was to assess whether the higher and statistically significant BIC\% values previously detected in ‘in vivo’ studies in low-density bone areas for the implants treated with CO ion implantation were equally found in human subjects. The two evaluation methods that we used showed higher osteointegration levels, measured by the BIC\%, in the surfaces treated with CO ion implantation vs. non-treated surfaces when using the SEM (54.8\% vs. 46.2\%) and conventional microscopy (62.9\% vs. 57.9\%), in line with the previous study results in New Zealand white rabbits and beagle dogs.\(^1,14,15,17,18\) However, the differences found in this study were not statistically significant.

Based on the differences in the evaluation methods used, the lower values for both groups analyzed with SEM may be attributed to the greater precision of this technique in the definition of osseous tissue in close contact with the implant (Tables 1 and 2).

The 15 mini-implants that were lost and not evaluated involved patients with removable prosthetics in all cases; we believe that this problem was caused by the force exerted by the prosthesis on the mini-implants during mastication in the early osteointegration phases. This phenomenon of implant loss did not occur in patients who did not have this type of removable prosthetic.

Although the implants with surface treatment by means of CO ion implantation presented a slightly higher degree of osteointegration in low-density osseous areas, results obtained in this clinical study showed no statistically significant differences.

No adverse reaction related to the applied treatment was observed in the patients.

**Funding**

The study was partially funded by Fondo Tecnológico Sortek.

**Competing interests**

None of the authors have any financial interest in the patent applications covering CO ion implantation. M. A. De Maeztu, I. Braceras, and J. I. Alava are inventors on a patent covering CO ion implantation surface treatments.

**Ethical approval**

The clinical trial was evaluated and approved by the Committees of Ethics of Clinical Research (CECR), corresponding to the two centres where the research was conducted. The study obtained the authorization for clinical research number 277/06/EC from the Spanish Agency of Medicines and Medical Devices.

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