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BIOTECHNOLOGY

Odontology

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ABSTRACT:

During the processes of guided bone regeneration in the maxillary bones, which aim to recover or preserve support tissue for the placement of implants on which dental prostheses are retained, the use of various particulate graft biomaterials from different sources (animal or synthetic) is standardized. At present, the pressure of compaction of this material in the recipient bone is manual, dependent on the clinician, although there is some scientific evidence on the effects of different compressive forces on angiogenesis and prognosis of the regeneration of the grafted areas.

The aim of the present study is to design, calibrate and verify in vitro a compaction instrument for clinical use, which allows a controlled and precise compaction pressure of the particulate graft biomaterial and standardize the procedure.

The designed instrument is a precision compactor of adequate size for proper intra and extraoral clinical manageability and manufactured in a sterilizable material by autoclaving. The range of compression that allows (0 -1,82 Newton), is within the forces that are commonly applied in surgery and that have been determined by a specific test on 8 oral surgeons. Instrument calibration has been performed by an independent accredited company.

The testing of the instrument was carried out by an in vitro test where the biomaterial was compacted at different forces (0,80 and 1,82 Newton) and was observed by a computerized micro-tomography that when increasing the compression force, decreased the space between particles provided for the migration and proliferation of new blood vessels and cells.

Key Words: bone regeneration, compaction, instrument, compactor, particle biomaterial, bone graft.

RESUMEN:

Durante los procedimientos de regeneración ósea guiada en los huesos maxilares, que tienen como objetivo recuperar o preservar tejido de soporte para la colocación de implantes sobre los que se retienen las prótesis dentales, está estandarizado el uso de diversos biomateriales de injerto particulado de diferente procedencia (animal o sintético). En la actualidad la presión de compactación de dicho material en el hueso receptor es manual, clínico dependiente, pese a que existe cierta evidencia científica sobre los efectos de las diferentes fuerzas de compresión en la angiogénesis y pronóstico de la regeneración de las zonas injertadas.

El objetivo del presente estudio es el de diseñar, calibrar y comprobar in vitro un instrumento de compactación para uso clínico, que permita una presión de compactación controlada y precisa del biomaterial de injerto particulado y estandarizar el procedimiento.

El instrumento diseñado es un compactador de precisión de tamaño adecuado para una correcta manejabilidad clínica intra y extraoral y fabricado en un material esterilizable por autoclavado.

El rango de compresión que permite (0 – 1,82 Newton), está dentro de las fuerzas que se aplican comúnmente en cirugía y que se han determinado mediante una prueba específica sobre 8 cirujanos orales. La calibración del instrumento se ha realizado por una empresa acreditada independiente.

La comprobación del instrumento se ha realizado mediante un ensayo in vitro donde se compactó el biomaterial a diferentes fuerzas (0,80 y 1,82 Newton) y se observó mediante micro-tomografía computerizada que al aumentar la fuerza de compresión disminuía el espacio entre partículas provisto para la migración y proliferación de los nuevos vasos sanguíneos y células.

Palabras Clave: regeneración ósea, compactación, instrumento, compactador, biomaterial particulado, injerto óseo.

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1.- INTRODUCTION

The disciplines of Medicine and Dentistry are constantly developing to obtain better diagnoses and treatments for patients. In this sense, technology and engineering are crucial for the ever-increasing supply of more reliable and effective tools that involve less invasive and more predictable treatments.

Oral implantology is a medical discipline with a high level of development that has obtained major benefits from technological innovations. This discipline deals with the functional and aesthetic recovery of edentulous patients by placing implants of various metal alloys in the maxillary bones to provide support and retention to dental prostheses [1].

The use of dental implants for such purpose has experienced exponential growth since its inception. In fact, in the United States in 2001, it was estimated that approximately 450,000 implantations were carried out [2], while in 2013, this figure reached 1.26 million, and it is expected to continue increasing [3].

The reabsorption of the maxillary bone that inevitably follows tooth loss often causes a significant problem in achieving satisfactory oral rehabilitation with dental implants [4]. On the one hand, the remaining bone volume can be so critical that it does not even allow an implant to be housed, even one with a narrow (less than 4 mm) or short (less than 8 mm) diameter. On the other hand, there is enough evidence to show that an adequate bone volume ensures good long-term results [5,6].

The development over the last 30 years of guided bone regeneration (GBR) techniques, based on new materials and procedures, allows the predictable modification of the maxillary bone anatomy that has been altered by resorption [7,8], thus recovering adequate bone volumes for the placement of dental implants.

GBR is the best documented technique for the treatment of bone defects located in the maxillary bones. This is a procedure with high success rates that is based on priming the development of the cell biotype sought to be regenerated (in this case, the bone), isolating it from other unwanted tissues (soft tissues) by using barrier membranes [9,10]. The success or failure of these procedures ultimately depends on the efficiency of the barrier membrane, the maintenance of the space and a correct surgical technique.

Barrier membranes are essential for guided bone regeneration. Their main function is to act as a physical obstacle to prevent soft-tissue invasion into the bone defect [11]. In experimental and clinical studies, a wide variety of membrane materials, both resorbable and non-absorbable, have been used.

Different types of graft materials are available. These are classified according to their origin as autografts (tissue that is transferred from one position to another within the same individual), allografts (tissue that is transferred between members of the same species), xenografts (tissue transferred between members of different species) and synthetic materials or alloplastic grafts (artificially generated in laboratories), for which different properties have been described.

Currently, the maintenance of the spatial volume of the bone to be regenerated is considered the main function of the bone graft or substitute material. Essentially, the membrane separates the different types of tissues, and the graft prevents the membrane from collapsing, generating a scaffolding that allows the migration and proliferation of blood vessels and cells, which are crucial for the formation of new bone [12,13].

Xenografts are the most used materials for this purpose. There is an extensive bibliography that supports their use. Bovine, porcine and natural coral origin xenografts are most commonly used. Generally, the commercial presentation of these biomaterials comes in particles of 0.25 mm to 2 mm in size. An example of a bovine-origin xenograft of 0.5 to 1 mm in particle size (Cerabone® Botiss Biomaterials GmbH, Dieburg, Germany) is shown in fig. (1)

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Fig. 1: Particulate Xenograft 0.5 - 1.0 mm.

The morphological characteristics and surgical technique are very important for the outcome of bone regeneration. The placement technique and packaging of the biomaterial also seem to influence the outcome [14,15].

The compaction of the biomaterial during surgery is usually carried out with different manual compactors, disregarding the force applied on the biomaterial, which is inherent to the subjective sensation of each surgeon.

It is assumed that an excessive compaction of the biomaterial could cause, on the one hand, a fracture of the particles and, on the other, a reduction in the space between them, which could hinder the penetration of cells and new blood vessels. In turn, a poor compaction could leave an excessive space between particles, obtaining a smaller area of biomaterial for cellular apposition, which could allow small micro-movements. Several preclinical studies in animal models have attempted to establish the relationship between the compression of the graft material and the result of the regeneration [14,15]. The great limitation of these studies is that the methods used for graft compaction (weights and coins) are not transferable to the clinic.

Therefore, this work aims to design and calibrate an instrument to accurately control the compaction pressure of a particulate graft, with characteristics suitable for clinical use in the oral cavity. A second objective is to verify (using our instrument) the influence of the pressure applied on the resulting spaces between the particles on the migration and proliferation of new vessels and cells.

2. MATERIAL AND METHODS

2.1.- PROCEDURE

Currently, although bone regeneration by means of particulate grafts is a frequent procedure in oral surgery, there is no compaction tool capable of measuring the force applied, Therefore, our research team had the need to develop this tool.

Initially, we based our design on the idea of a dynamometer and its possible clinical uses and manageability. The dynamometer, invented by Sir Isaac Newton (1643-1727), is a tool that allows the calculation of the weight of a body or the measurement of a force based on changes in the deformation of a spring with a certain calibration.

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The traditional dynamometer bases its operation on the stretching of a spring, following Hooke's law of elasticity, where the deformation is proportional to the force applied:

Where:

$$F = k \, . \, x$$

F *is the force applied to the spring;*
k *is the spring's elasticity constant; and*
x *is a vector that indicates the variation of the length of the spring.*

In this case, our objective was to measure compression. To clarify what we intended to achieve, a simple homemade compactor was developed using a ballpoint pen, a metal shank and a compression spring.

To determine the pressure range of the compactor, we conducted a study with the participation of 8 experienced oral surgeons. A biomaterial was placed in a container on a precision scale (SBS-LW-2000A-2000g/0.01g by Steinberg Systems, Poland), while the surgeons applied pressure to it simulating the compaction performed during an intra-surgical intervention.

Table 1 shows a descriptive statistical analysis of the pressure values obtained by each surgeon. The mean values reveal certain differences in the pressures applied by the different surgeons. Additionally, there is an important difference between the minimum and maximum pressures applied, 0.09 newtons (N) and 1.49 N, respectively. The overall mean was 0.52 ± 0.24 N.

Surgeon	N	Mean	Standard deviation	Standard error	95% confidence interval		Minimum	Maximum
					Lower limit	Upper limit		
1	50	37.6078	15.75827	2.20660	33.1758	42.0399	9.00	72.00
2	50	37.0200	15.48863	2.19042	32.6182	41.4218	10.00	87.00
3	50	65.0600	20.23778	2.86205	59.3085	70.8115	20.00	105.00
4	50	78.8400	31.78265	4.49475	69.8075	87.8725	24.00	152.00
5	50	42.1600	17.11708	2.42072	37.2954	47.0246	13.00	98.00
6	50	67.0400	22.11469	3.12749	60.7551	73.3249	15.00	123.00
7	50	48.0577	18.13718	2.51517	43.0083	53.1071	14.00	91.00
8	50	52.8269	20.31876	2.81770	47.1701	58.4837	19.00	91.00
Total	400	53.5062	24.98996	1.24176	51.0651	55.9473	9.00	152.00

Table 1: Descriptive statistical analysis (gram-force units).

Next, Levene's statistical method was used to evaluate the equality of the variances for a calculated variable (pressure) for two or more groups (surgeons). This analysis tests the null hypothesis "Ho: There is a homogeneity of variances or homoscedasticity". Once the analysis was carried out, we obtained a probability value, significance or p value <0.05, so the null hypothesis is rejected. It was thus concluded that not all variances are equal; that is, it was confirmed that the differences between the mean values of the sample are too large to be attributed only to chance.

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Once the possibility of homoscedasticity within the analysed population was discarded, Dunnett's T3 post hoc test was carried out, which allows a pairwise comparison to determine whether there are certain sample populations (pressure applied by certain surgeons) different from one another and identify them. Once the test was done, we observed that certain sample populations are relatively homogeneous with each other (GROUP 1: Surgeons 1, 2 and 5, with p value >0.9; GROUP 2: Surgeons 3 and 6, with p value >0.9; and GROUP 3: Surgeons 7 and 8, with p value >0.9). Therefore, it is possible to affirm that there are significant differences between the pressures applied by the surgeons according to the groups indicated above, as shown in Fig. (2).

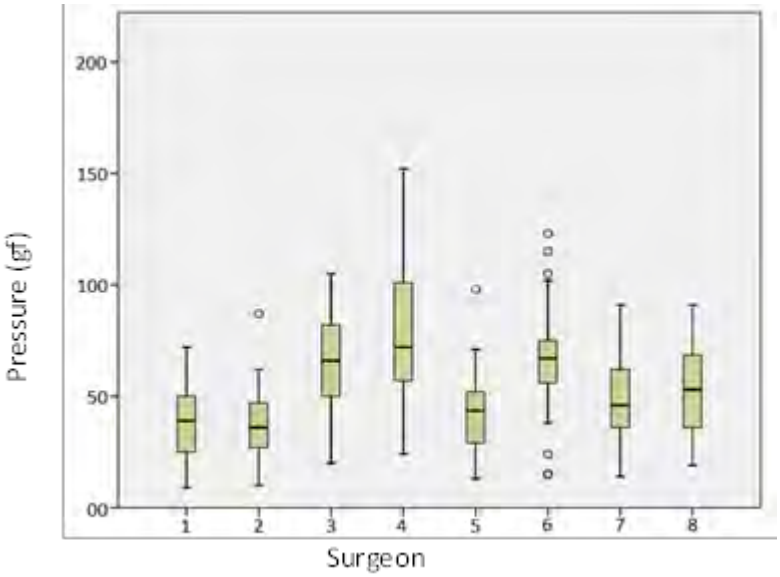

Fig. 2: Box plot presenting the data obtained.

After analysing the results and concluding that the sample differences are not due to random variations in the sampling and that there are significant differences between the different sample populations, we decided to consider a pressure range in the instrument's design to cover at least the full pressure range exerted by the surgeons in the study (between 0.09 and 1.49 N).

All the statistical analyses were carried out using IBM SPSS Statistics software, version 22.0 for Windows and the different office tools included in Microsoft Office 2010.

2.2.- CHARACTERISTICS OF THE INSTRUMENT

From this initial idea and considering certain desirable characteristics, we developed this design, best represented by the plans in Fig. (3).

It was manufactured in a conventional lathe (SC200 by Pinacho, Huesca, Spain) by an expert lathe machinist from a specialised workshop. It has been mechanised in stainless steel so that it can be sterilised. It is similar in size to a ballpoint pen or manual compactor to allow its use in intraoral compaction.

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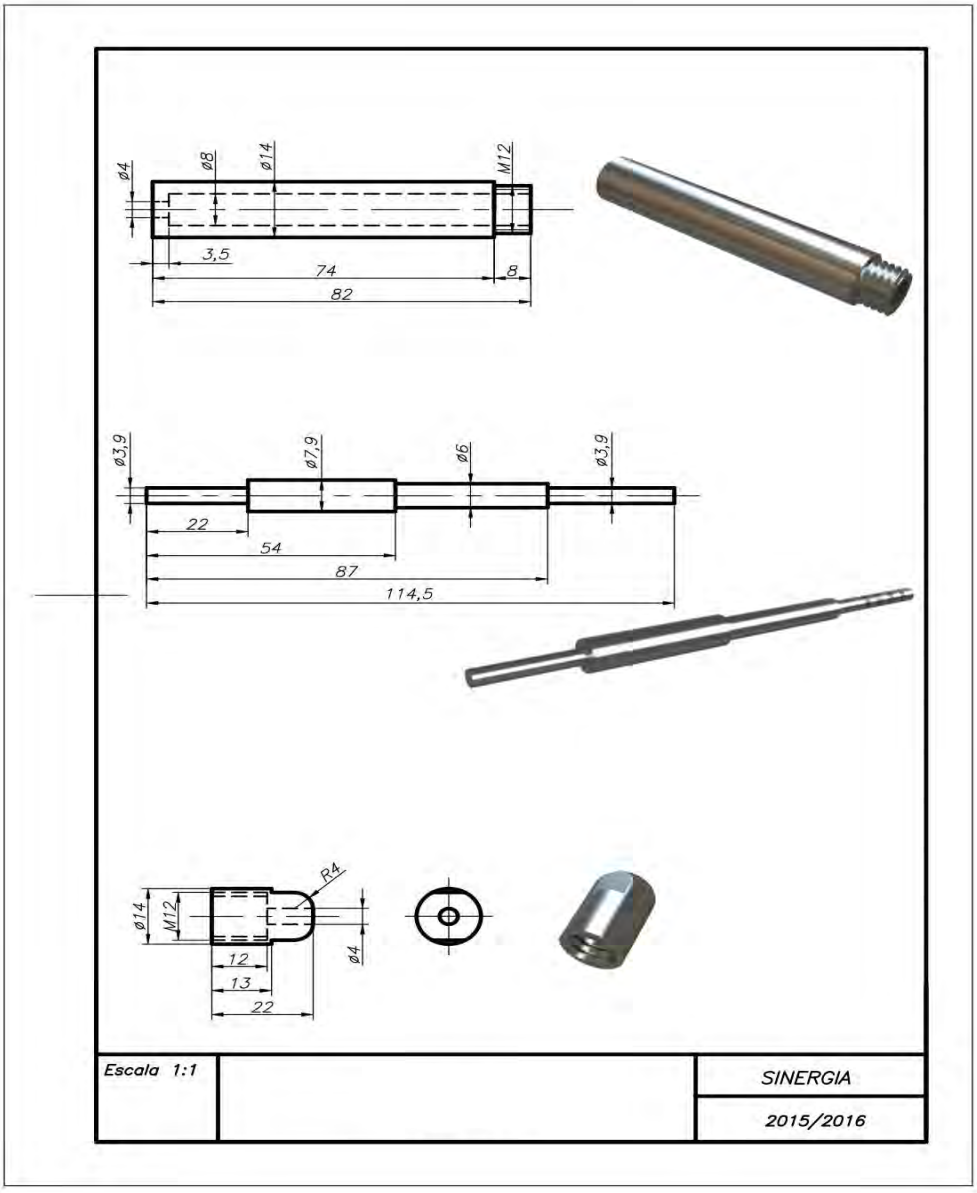

Fig. 3:Plans for the instrument's prototype.

The instrument consists of a compactor whose operation is based on a simple compression dynamometer. It features a solid shank of 7.9 mm in diameter that slides inside a hollow cylinder with an internal diameter of 8 mm. The shank has at one end a circular active tip of 3.9 mm in diameter, similar to that of any clinical compactor. At the other end, it has a recess where the spring is inserted and a visible posterior extension (outside the hollow cylinder) with a stripe-marking system. The hollow cylinder through which the shank slides has a threaded end for the insertion of the cap. The cap has a threaded design that allows the replacement of the spring if it loses its properties or achieving greater compaction forces by replacing the spring or adding stops.

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A compression spring was specially designed for this study, complying with the necessary characteristics in terms of the design and the range of compression forces to be measured. The spring is made of stainless steel (EN 10270-3, INOX-AISI 302) and is 67.55 mm in length, with an outside diameter of 7.1 mm and an inside diameter of 6.1 mm. The wire diameter (thickness) is 0.5 mm. The spring has 30 turns with a pitch (average distance between two active turns of the spring) of 2.37 mm.

The spring will compress at a distance proportional to the force applied on it, and the elasticity constant (k) is equal to 0.0076 DaN/mm. With the maximum load (0.40 DaN), the spring compresses entirely, reaching a length of 15 mm.

2.3.- CALIBRATION

This instrument is capable of compacting with a precise and calibrated force range. Table (2) shows the calibration values at the different shank markings.
The calibration was carried out by an independent calibration company (Ac6 Metrología SL, Navarra, Spain) accredited by the National Accreditation Entity (Entidad Nacional de Acreditación- ENAC). Three measurement series were performed with increasing force values at compression by comparison with a standard transducer (Z30, nº 09130043 of HBM, Madrid, Spain). The resolution is 0.00980665 N. The measurand was established between the start and end of each mark, confirming that the variation between the start and end is approximately 0.0686 N.

Línea (L)	F_N (N)	c (%)	W (%)
 1	0.57	-0.69	0.73
2	0.80	-0.11	0.45
3	1.29	-0.24	0.45
4	1.82	-0.27	0.56

Table 2: Calibration results at the different forces measured by this instrument.

F_N: Force indicated by the instrument to be verified for increasing force values; c = Relative correction (values indicated in %, corresponding to the amount that must be algebraically added to the reading of the measurand to obtain the conventionally real force);W = Relative expanded uncertainty (corresponding to a coverage probability of approximately 95%, considering contributions due to the relative errors of the repeatability, zero, resolution and the standards used in the calibration).

2.4.- IN VITRO ASSAYS

To test the objectives, we conducted an assay performing 3 compactions using our instrument on 0.20 ± 0.01 grams of bovine-origin xenograft with a 0.5 to 1 mm particle size (Cerabone® by Botiss Biomaterials GmbH, Dieburg, Germany). The assay was conducted at different forces in test tubes, and the compaction and reorganisation of the xenograft particles were observed by means of microcomputed tomography (micro-CT).

To quantify the 3D microstructure, the samples were scanned by a high-resolution micro-CT (SkyScan 1174 by Bruker, Kontich, Belgium). The images were obtained by X-rays at a voltage of 50 kV and an amperage of 800 µA.

All samples were scanned using a 1 mm aluminium filter at a resolution of 11.8 pixels. We obtained a set of 613 images for each sample, with a rotation pitch of 0.3° and an average of 2 frames for a total rotation of 180 °. The scanning time for each sample was approximately 3 hours using an exposure time of 8500 ms. A flat-field correction was performed at the beginning of each scan. The images obtained during the scanning were reconstructed using the software NRecon

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(Control Software, SkyScan 1174 by Bruker, Kontich, Belgium). The correction values of the attenuation coefficient, beam hardening, smoothing and reduction of ring artefacts were the same in all samples. A porosity analysis was performed with the software CTAn (Software for measurements and visualisation, SkyScan 1174 by Bruker, Kontich, Belgium). The volume of interest (VOI) was manually delimited in each sample. The global greyscale threshold levels for these areas were between 68 and 255.

3. RESULTS

A compactor instrument capable of measuring the force at which a biomaterial is being compacted has been manufactured. Its characteristics (size, easy handling and material of elaboration) make it applicable for clinical use. A 3D simulation is presented in Fig. (4) to facilitate the understanding of the characteristics and operation of the instrument.

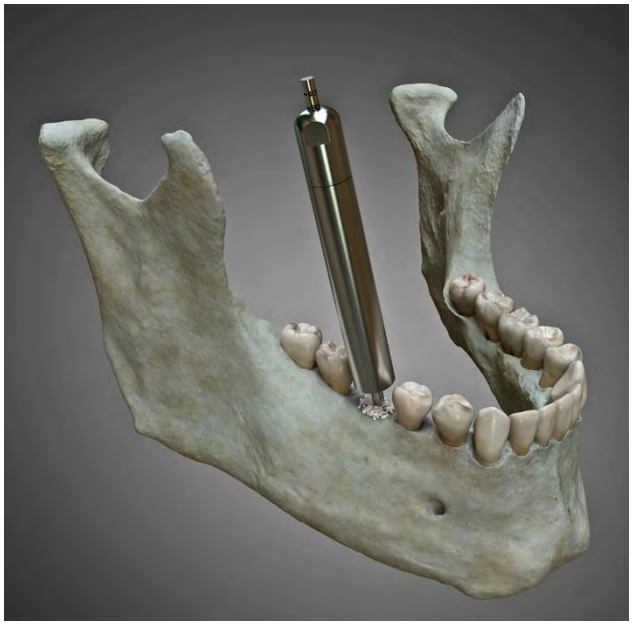

Fig. 4: Simulation of the instrument in alveolar regeneration.

The instrument can compact to certain standardised and calibrated forces.

The micro-CT shows the compaction and reorganisation of the xenograft particles used (Cerabone® from Botiss Biomaterials GmbH, Dieburg, Germany) at different compression forces, obtaining variations in the area where the vessels and cells should penetrate. In fact, without compression, free spaces occupy 55.80% of the sample. **When applying forces** of 0.80 and 1.82 N, **the spatial percentages decrease by 1.3 and 3.2%, respectively.** Figure 5 shows the representation of the images obtained by micro-CT.

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Fig. 5: Micro-CT images of the structure of the particulate graft with a resolution of 11.8 pixels, a scanning time of 3 hours and an exposure time of 8500 ms.

4.- DISCUSSION

An instrument with clinical manageability capable of compacting a biomaterial and measuring the compaction force applied has been successfully designed and developed. To date, the compaction of the biomaterial is carried out using different manual compactors, disregarding the force applied on the graft.

Since the development of the new bone depends on the creation of new blood vessels that provide progenitor cells and nutrients to the area under regeneration [16-19], the maintenance of the spaces between the biomaterial particles seems essential. This is a very relevant issue because it is understood that if small differences such as the micro- and nano-roughness of the surface or the wettability and porosity of the biomaterial can influence the results [14, 20], the disposition of the particles and therefore of the resulting spaces between them should also influence the results of the bone regeneration.

However, there is no clear scientific evidence regarding the influence of the force applied and the technique used for compacting the biomaterial on the results of bone regeneration. The only two studies available in the literature [14, 15] that evaluate the role of the compaction pressure of particulate bone grafts have been performed in animals, although they conclude that it does influence the results of the bone regeneration. However, these two studies apply compression using methods that cannot be extrapolated to oral or clinical surgery (one uses coins wrapped in aluminium foil [14], and another uses a weight system [15]). In addition, in one of the studies [14], the tested forces (4.1 - 8.2 g) are quite different from those that our first test with a group of oral surgeons has shown to be used in clinical practice.

The designed instrument bases its operation on a compression spring. The spring will compress at a distance proportional to the force applied on it; the constant of proportionality or elastic constant (k) of the spring in this case is 0.0076 DaN/mm. The newly developed instrument can compact a biomaterial with determined, standardised and calibrated forces. These forces are correlated with those most commonly used in clinical practice because according to the aforementioned test, the average force applied by an experienced oral surgeon is 0.52 ± 0.24 N, and the maximum force is 1.49 N. Nevertheless, with this design, different ranges of compressive force can be generated depending on the results of future in vivo research or different demands because springs with different elastic constants (k) or stops in the spring route can be incorporated.
This instrument will allow us to:

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- Determine in applied research studies (experimental animals) whether the compressive force on the bone graft packaging influences angiogenesis and bone regeneration and how such force influences the results and establish which compaction condition is preferable in a range corresponding to common clinical standards;
- Standardise future research studies on these biomaterials, eliminating possible confounding factors such as the compaction force; and
- Obtain better results in our bone regeneration procedures by performing the compaction in the force range considered the most suitable.

Regarding the influence of pressure on the reorganisation of the particulate graft, the micro-CT test showed that increasing the compressive force reduces the space between the particles provided for cell proliferation and migration, which may influence the angiogenesis in vivo and the final results of the bone regeneration. Although the reductions in the free space with applied forces of 0.80 and 1.82 N have been determined to be 1.3 and 3.2%, respectively, future research should evaluate whether this variation in the porosity will result in significant differences in in vivo studies.

In dentistry, the appearance of 2nd-generation periodontal probes was an advance similar to what our instrument offers. Compared to conventional probes, 2nd-generation probes are able to perform measurements with a controlled force. Periodontal catheterisation is one of the methods used to diagnose and monitor patients with periodontal disease [21, 22]. With conventional probes, the force applied during the probing process can be misleading [23-25]. In fact, the probing force with conventional probes varies between 3 and 140 grams, depending on the location to be probed and the professional who performs the probing [26]. The controlled strength achieved with the 2nd-generation periodontal probes produces an increase in inter-examiner reproducibility [26]. Therefore, 2nd-generation probes are a better tool for the diagnosis and control of these patients, providing greater validity to studies using this tool.

5. CONCLUSIONS

Currently, the placement of graft biomaterials during bone regeneration is done manually and is therefore clinically dependent. The force applied on the biomaterial during its implantation is neglected, despite the fact that there seems to be scientific evidence for the effects of different compressive forces on the biomaterial on the angiogenesis and on the prognosis of the regeneration.

A calibrated compaction instrument was designed and is suitable for clinical use due its characteristics (size and materials of elaboration) that could allow controlled and precise compaction of biomaterials.

An in vitro micro CT assay showed a reduction of the free spaces (provided for the penetration of vessels and cells during bone regeneration) when the compaction force increases. In fact, the spatial percentage decreases by 1.3 and 3.2% after applying forces of 0.80 and 1.82 N.

This instrument could allow us to standardise future research studies conducted on biomaterials and could even yield better results in bone regeneration procedures if we can prove, through in vivo studies, that these differences in the percentage of free space between biomaterial particles are significant.

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