CARLOS GUILLERMO BENÍTEZ SILVA

Peri-implant tissue changes at sites treated with alveolar ridge preservation in the esthetic zone: twenty-two months follow-up of a randomized clinical trial

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Corrected version

Thesis presented to the School of Dentistry University São Paulo by the Postgraduate Program in Dental Sciences to obtain the degree of PhD in Sciences.

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Everything we hear is an opinion, not a fact.
Everything we see is a perspective, not the truth.
Marcus Aurelius

ABSTRACT

Benítez Silva CG Peri-implant tissue changes at sites treated with alveolar ridge preservation in the esthetic zone: twenty-two months follow-up of a randomized clinical trial [thesis]. São Paulo: University of São Paulo School of Dentistry. 2020. Corrected Version.

There is a paucity of randomized clinical trials (RTC) to assess peri-implant tissue alterations for delayed implants placed at sites previously treated with alveolar ridge preservation, especially after implant restoration. Thus, the aim of this study was to compare tissue changes at sites treated with two different materials for alveolar ridge preservation (ARP) in the esthetic zone up to one year after the crown installation. A total of sixty-six participants were treated with ARP in the esthetic zone using demineralized bovine bone mineral (DBBM) or DBBM + 10% of collagen (DBBM-C), both were covered with a collagen matrix (CM). Dental implants were placed and six months later, the final restorations were installed. Silicon impressions were taken before tooth extraction (T0), two weeks after the crown insertion (T1) and one year after the restoration (T2). Mid-facial mucosa level (ML), estimated soft tissue thickness changes (eTT), and marginal bone loss (MBL) were analyzed. Fifty-four participants were included in the final analysis. The ML between T0–T1 and T1–T2 showed a mean of -1.53 ± 0.95, -1.46 ± 0.99 and 0.08 ± 0.42, 0.13 ± 0.54 for DBBM and DBBM-C respectively. Between T0–T1 for eTT, a significant difference ($p<0.05$) favoring DBBM was found at 3 and 5mm below the mucosal margin. From T1 to T2 no significant differences were found for eTT and MBL between groups. The findings suggest that at the esthetic zone, similar results of mid-facial recession from tooth extraction to crown placement can be expected irrespectively of the demineralized bone presentation used. Moreover, it is suggested on the one hand that for tissue thickness maintenance, DBBM performs better at middle and apical levels of the ridge when compared to DBBM-C up to crown insertion. And on the other, that after crown insertion, both materials are able to provide tissue stability for the implants for the first year after loading, at least.

Keywords: Alveolar bone loss, Dental Implants, Tissue Preservation, Bone Remodeling, Follow-Up Studies

RESUMO

Benítez Silva CG. Alterações dos tecidos peri-implantares em sítios tratados com preservação do rebordo alveolar na área estética: acompanhamento de vinte e dois meses de um estudo clínico aleatorizado [tese]. São Paulo: Universidade de São Paulo, Faculdade de Odontologia. 2020. Versão Corrigida.

Atualmente existe uma escassez de estudos clínicos aleatorizados (RCT) avaliando as alterações dos tecidos peri-implantares em implantes tardios colocados em sítios previamente tratados com preservação do rebordo alveolar, especialmente após a restauração definitiva dos implantes. Portanto, o objetivo desse estudo foi comparar as alterações teciduais em sítios tratados com dois diferentes materiais para preservação do rebordo alveolar (ARP) na área estética até um ano após a instalação da coroa. Sessenta e seis pacientes foram tratados com ARP na área estética usando matriz mineral ósea bovina (DBBM) ou DBBM + 10% de colágeno suíno (DBBM-C) ambos cobertos com uma matriz de colágeno (CM). Foram instalados implantes dentários e seis meses após foram colocadas as restaurações definitivas. Moldagens de silicona foram feitas antes da exodontia dentária (T0), duas semanas após a instalação da cora (T1) e um ano após a restauração (T2). O nível da mucosa vestibular (ML), as alterações estimadas de espessura de tecido mole (eTT), e a perda óssea marginal (MBL) foram analisadas. Cinquenta e quatro participantes foram incluídos no análisis final. O ML entre T0-T1 e T1-T2 mostrou uma média de -1.53 ± 0.95, -1.46 ± 0.99 e 0.08 ± 0.42, 0.13 ± 0.54 para DBBM e DBBM-C respectivamente. Entre T0-T1 para eTT houve uma diferença significativa ($p<0.05$) favoreciendo DBBM foi achada a 3 e 5mm aquém da margem mucosa vestibular. Desde T1 até T2 não houve diferenças significativas para eTT e MBL entre os grupos. Na área estética, resultados similares do nível da mucosa vestibular desde a exodontia dentária até a instalação da coroa pode ser esperada independentemente da apresentação da matriz mineral óssea bovina utilizada. Para manutenção da espessura, DBBM mostrou um melhor desempenho na região média e apical do rebordo quando comparado com DBBM-C até a instalação da cora. Após a instalação da coroa ambos materiais apresentaram estabilidade dimensional.

Palavras-chave: Perda óssea alveolar, implantes dentários, preservação tecidual, remodelação óssea, estudos de acompanhamento.

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LIST OF ABBREVIATIONS AND ACRONYMS

ARP	alveolar ridge preservation
CAD	computer assisted design
CM	collagen matrix
DBBM	demineralized bovine bone mineral
DBBM-C	demineralized bovine bone mineral added with 10% of collagen
eTT	estimated soft tissue thickness changes
ICC	interclass correlation coefficient
MBL	marginal bone loss
ML	mid-facial mucosa level
Mm	millimeter
P	p-value
RCT	randomized clinical trial
ReBEC	Brazilian trials registration platform
SD	standard deviation
STL	stereolithographic
T0	before tooth extraction
T1	two weeks after crown insertion
T2	one year after restoration

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1 INTRODUCTION

After tooth extraction, a wound healing process that leads to alveolar ridge reduction takes place (1–3). Dental implant placement in the ideal three-dimensional position is one of the major challenges that results after this phenomenon (4). At the maxillary anterior region, this may be associated with additional esthetic issues due to specific anatomical characteristics (5,6).

Modern implantology aims to provide predictable treatments that offer comfort and esthetics for the patients. In this regard, ARP has been developed with the goal of simplifying implant site development by limiting ridge reduction through making use of biomaterials at the time of tooth extraction (7–9). DBBM and DBBM-C have been widely documented for ARP, and demonstrating a reduction of alveolar ridge resorption after tooth extraction (10–14).

A study by Llanos (12) in which these two materials were compared, both covered with a collagen matrix, at upper anterior post extraction sites showing buccal bone defects of less than 50%, demonstrated the high predictability for implant installation in a prosthetically driven position. Interestingly, it was found that only a small percentage of the cases needed additional grafting simultaneous with implant placement (10.8%). This information suggests the effectiveness of ARP for implant site development and for eliminating the need for major bone augmentations.

Previous randomized clinical trials have shown the effectiveness of different techniques for improving implant survival and maintaining clinical parameters at grafted sites (15–20). A systematic review (21) that assessed the effect of different ARP approaches, highlighted the paucity of studies documenting the performance of implants and their respective restorations over the long term. Moreover, there are few studies documenting the stability of and changes in peri-implant tissue, using quantitative methods of implant-supported restorations at grafted areas (22). Additionally, there is no available evidence that reports gingival recession and soft tissue thickness changes after crown insertion at sites treated with ARP that consider, as baseline reference, the position of the original soft tissue margin before tooth extraction.

2 LITERATURE REVIEW

2.1 Bone resorption of the alveolar ridge after tooth extraction

After tooth extraction, a series of healing phenomena occur at the alveolar ridge, and particularly at the dental alveolus (2,23,24). The healing process, a repair response of the body, can be divided in three stages: inflammatory, proliferative and bone modeling (25). When these stages conclude, there is an inevitable reduction of the ridge dimensions (3,26).

To explain this resorption process, it is important to acknowledge that the dental arches are constituted by the basal bone and the alveolar process; the latter is a bony tissue formed by the dental follicle during the development of the tooth germs (27,28). The alveolar process is responsible for supporting the tooth roots through the alveolar bone proper which makes part of the insertion apparatus of the tooth. The alveolar bone proper houses the Sharpey fibers of the periodontal ligament, which on the other side are inserted into the radicular cementum (29). This lamellar bone is a tooth dependent structure that resorbs once tooth extraction is performed (24,30).

Resorption was explored in classic studies. An example of this is the one conducted by Amler et al. (31) in which the histologic processes that occur after a tooth extraction, based on human biopsies at first stages, were described. They detailed the phenomena that begin with the coagulum formation, then passing through crest resorption before the new bone formation at the alveolar process (31). Carlsson et al. (32) later conducted a clinical study investigating tooth extractions made at the anterior maxilla of patients who received complete dentures. Radiographic changes of the bone profile were described; in addition, they showed the increase in the bone resorption during the first six months after tooth extraction (32).

Histological studies on animals later demonstrate that after tooth extraction, the bone resorption behaves differently on the palatal and buccal crests (23,24). Moreover, these studies suggest that, even when resorption is found on both the palatal and buccal crests, it is more pronounced at the buccal plate of the alveolar process due to the difference in thickness on each crest. Literature reports that the

latter is interrelated to the alveolar bone proper (2,23,24). In this terms, the paper published by Araujo and Lindhe (24) assessing biopsies on dogs at post extraction sites and the different stages of healing of the alveolus, is a milestone. Considering that Araujo and Lindhe not only focus on the histological process that leads to the alveolar ridge reduction, but they also highlight the importance of the resorption of the alveolar bone proper in relation with the buccal crest (24).

In humans, after tooth extraction, it is expected that horizontal and vertical shrinkage of the hard and soft tissues occurs, as recent systematic reviews (26,33) demonstrate. The buccal aspect generally presents a greater resorption than the lingual or palatal (23). Schropp (3) reported that a reduction of up to 50% horizontally can be expected in the first twelve months after tooth extraction, with two thirds of that resorption occurring in the first three months of healing (3). In a systematic review by Van der Weijden et al. (33) exploring the dimensional alterations after tooth extraction, it was found in the meta-analysis that a reduction of 3.87mm horizontally and 1.67mm vertically can be expected in the first 6 months of healing (33). This study is consistent with the findings offered by Tan et al (26), who report that bone loss accounts for 29–63% (2.46–4.56mm) reduction horizontally and 11–22% (0.8–1.5 mm) vertically six months after the tooth extraction, occurring faster between the first 6 months (26).

2.2 Alveolar ridge preservation procedures

Alveolar ridge preservation refers to any procedure that aims to limit the negative effect of the ridge resorption after tooth extraction. This is important in order to maintain the volume of the hard and soft tissues, mainly to enable site development for later implant placement (34).

One of the first reports in the literature on ridge preservation is offered by Nevins and Mellonig (8). They reported clinical cases in which tooth extractions were undertaken and sites were grafted with freeze-dried allograft in combination with an e-PTFE membrane. Moreover, they illustrated that this procedure allows the placement of dental implants in a position in which they can be properly restored (8).

Nevins and Mellonig's study broadly was supported by the principles of the work of Seibert and Nyman (35) who performed experiments on defects created in post-extraction sockets in dogs, applying the principles of guided tissue regeneration (35). Relevant literature reports after that they started using this approach with different materials, flap approaches, and diverse surgical techniques (36–39).

One of the first records of the term 'alveolar ridge preservation' is found in an article by Nemcovsky and Serfaty (40). It described the use of a technique in which hydroxyapatite was placed and covered by a rotated flap from the palate. Moreover, it is reported that minimal deformation of the ridge was found on the follow-up (40).

Once the principle of alveolar ridge preservation was supported experimentally, there was an increase in studies conducted with better study designs and with a wide range of therapeutic approaches. For instance, Carmagnola et al (41), conducted a clinical study in which the use of membranes and bovine xenograft was compared with unassisted socket healing and analyzed histologically. The study suggests that new woven bone was formed around the graft particles in combination with connective tissue (41).

Iasella et al. (42) offer one of the first randomized clinical trial (RCT) on alveolar ridge preservation. Their study compares the use of freeze-dried bone allograft (FDBA) in combination with collagen membranes with unassisted socket healing. Moreover, it reports that the sites that received the biomaterials present greater thickness and height in comparison to the unassisted socket healing sites (42).

Experimental studies with humans and animals demonstrate that dental implant placement at post extraction sockets not only fail to counteract the bone remodeling of the socket walls (43–46), but also that the implant placement results in a significant decrease of the alveolar ridge (47). Furthermore, it has been reported that, similarly to the alveolar ridge healing, at the immediate implant placement, a more prominent buccal resorption is found in comparison to the palatal wall. Therefore, it is suggested that the presence of the implant is unable to arrest the bone dimensions (44).

Diverse techniques and materials have been proposed for alveolar ridge preservation. These depend on the aim of each case and the selected time for implant placement as well on the deficiency of the tissue at each site (34). During treatment with dental implants, alveolar ridge preservation might guarantee a

prosthetically driven position and contribute to avoiding additional regeneration procedures at the moment of implant placement (4,7,21,48).

One of the most widely used materials for these techniques has been the DBBM. This xenograft has been tested in the granules presentation (DBBM) (41,49,50), and granules added with 10% of porcine collagen (DBBM-C) (51,52).

Nart et al. (14) performed the first RCT exclusively at anterior sites of the maxilla, comparing the use of DBBM with DBBM-C, both covered with a collagen membrane. Cone Beam Computed Tomography (CBCT) analysis was performed through superposition of the radiographic images, and it was reported that there were no significant differences between groups for any of the assessed measurements (14). Afterwards, Llanos et al. (12) conducted a non-inferiority randomized clinical trial. This trial also used CBCT's analysis to compare the effect of DBBM with DBBM-C, both covered with a collagen matrix, also at anterior teeth of the maxilla. The study demonstrated the non-inferiority of DBBM when compared to DBBM-C, proving that an equal performance can be expected for both materials (12). Later, the previously mentioned researchers (53), undertook a profilmetric analysis showing the alveolar ridge preservation four months after extraction; the same pattern of volume preservation took place for both materials without differences between the two materials (53).

2.3 Dental implants at sites previously treated with alveolar ridge preservation

Treatment with dental implants has become one of the treatments of choice for replacing missing teeth. This therapeutic alternative has been demonstrated to be predictable, with good rates of survival in the long term (54,55). However, one of the most common difficulties for dental implant installation is the insufficient quantity of bone tissue vertically and horizontally (56).

At the anterior region of the maxilla, inherent anatomical conditions exist in the hard and soft tissues, representing a challenge in reaching ideal functional and esthetic results while using dental implants (4). The proportion of the alterations after tooth extraction has to be considered for better decision making at the moment of the

proposal of the restorative and esthetic treatment. This treatment aims to reduce complications caused by the anatomic conditions (26).

Park et al. (57) compared the benefits of alveolar ridge preservation with unassisted socket healing in a retrospective study in which timing for implant placement was considered; it was concluded that the sites treated with the intervention required fewer complementary regenerative procedures when compared to the control sites. In a similar manner, alveolar ridge preservation at the posterior sites of the maxilla reduces significantly the quantity of sinus lift grafts by lateral window at the implant placement. (57). A systematic review by Ramanauskaite et al. (22) reported outcomes related to implants placed at grafted sites, suggesting that implants placed at these sites presented a high rate of survival (95–100%) up to 1–4 years of follow-up, which was comparable to implants placed at pristine sites. Interestingly, it was reported that a reduced marginal bone loss was found at the grafted sites, compared to controls with no regenerative procedures (22).

Literature reports that more invasive procedures at the moment of the implant placement surgery can be significantly reduced when alveolar ridge preservation is applied, especially at the anterior sites of the maxilla (57). Implant placement at grafted sites is a predictable treatment alternative. However, studies showing peri-implant tissue alterations with quantitative assessments are needed to record the changes that occur over time (22). These need to consider that the aim of treatment is to obtain peri-implant health reflected in tissue stability over long term and observed in follow-ups (58).

3 PROPOSITON

The aim of the present study was to assess, in the upper anterior sites of the maxilla treated with ARP (DBBM versus DBBM-C), the dimensional alterations of peri-implant tissues from tooth extraction to one year after final restoration, completing twenty-two months of follow-up.

4 MATERIALS AND METHODS

4.1 Study design

The present investigation is a twenty-two month follow-up study of subjects of a previous randomized clinical trial that compared two bone substitutes for ARP in the esthetic zone (12). This study was approved by the ethical committee of the Dental School of the University of São Paulo, Brazil (nº 1.664.774). It was registered on the Brazilian trials registration platform (ReBEC, RBR-354q7d), and performed according to the Helsinki declaration of 1975 as revised in 2013.

4.2 Patient population

Participants' enrollment in this study followed the criteria as published in the main RCT (12). These are detailed below;

4.3 Inclusion criteria

(1) Participants over 18 years of age, (2) need for tooth extraction at the anterior zone of the maxilla (13–23) who required a single-tooth restoration, (3) presence of one adjacent tooth, (4) bleeding on probing and plaque index of <20%, (5) presence of at least 50% of the buccal bone plate, (6) signed consent form.

4.4 Exclusion criteria

(1) Pregnant or lactating women; (2) existence of bone metabolic disease; (3) advanced periodontal disease; (4) presence of acute periapical lesion; (5) heavy

smokers (>10 cigarettes/day); (6) history of malignancy; radiotherapy or chemotherapy; (7) patients who failed to return to the follow-up visits.

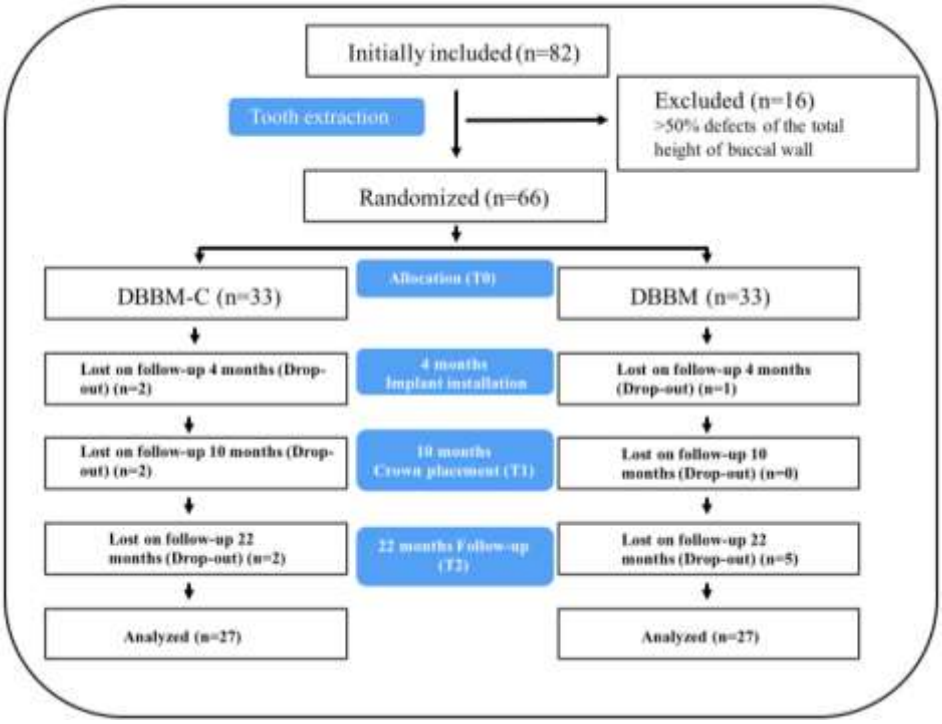
4.5 Procedures and interventions

In the main study (12), extractions were performed of the upper anterior teeth (13–23) of 82 patients, 66 of them had a buccal defect <50% of socket height and were randomized to receive alveolar ridge preservation using DBBM (Bio-Oss, Geistlich Biomaterials, Wolhusen, Switzerland) or DBBM-C (Bio-Oss, Geistlich Biomaterials, Wolhusen, Switzerland) both covered with a collagen matrix (Mucograft seal, Geistlich Biomaterials, Wolhusen, Switzerland). Impressions were taken preoperatively (T0).

Radiographic and profilometric evaluations had been previously published up to four months of ridge healing (12,53). Once four months were completed after ARP, bone level dental implants (Straumann Bone level tapered, Basel, Switzerland[)] were placed at those sites.

Six months after implant placement, single implant-supported crowns were delivered. Additional impressions and radiographs were taken at T1 and T2 (Fig. 4.1). During the entire experimental period, the patients received oral hygiene instructions and professional tooth cleaning every three months.

Figure 4.1 - Flow chart of the study



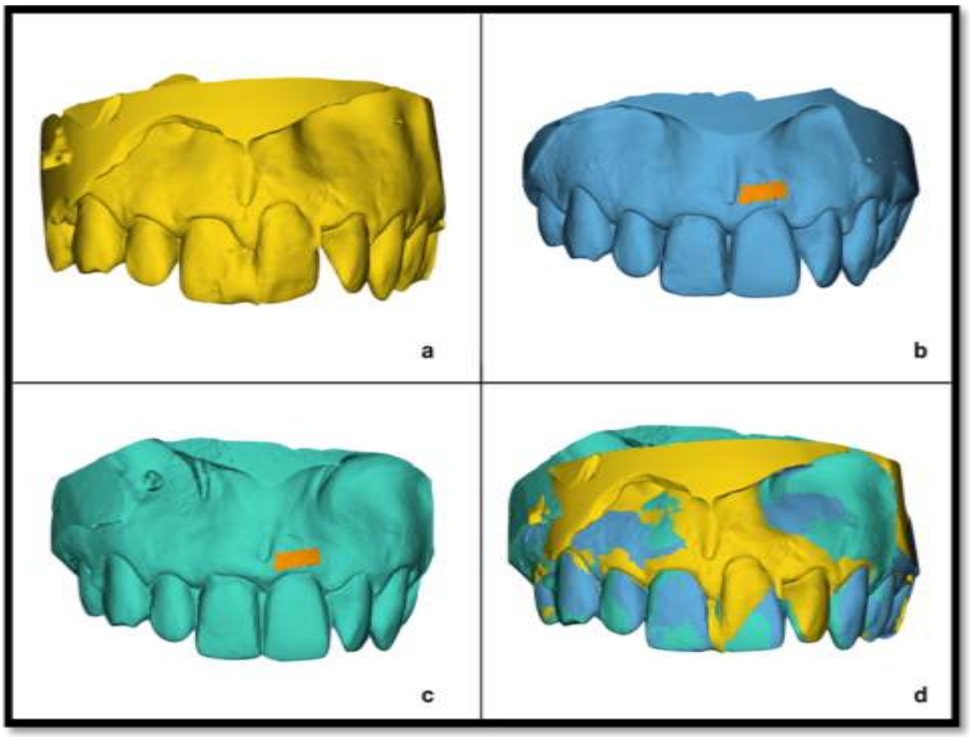
Source: Author

4.6 Outcomes

4.6.1 Soft Tissue Analysis

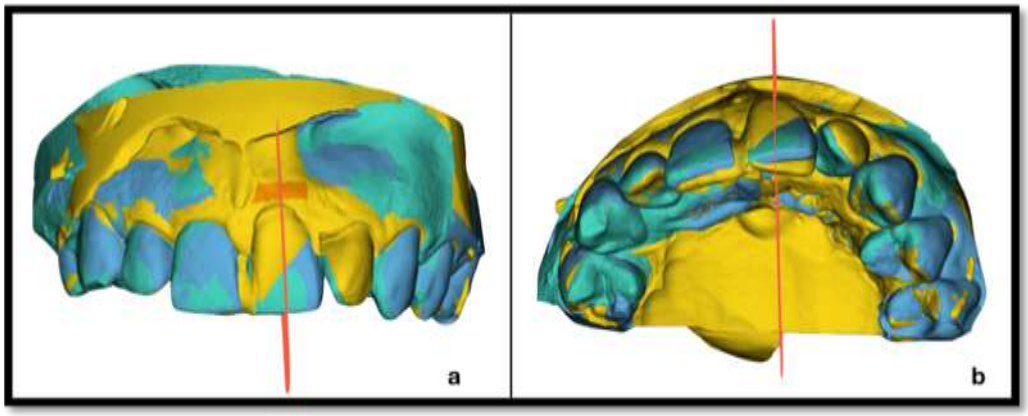
For soft tissue analysis, impressions were taken as follows: before tooth extraction (T0), two weeks after implant crown insertion (T1) and one-year after restoration (T2). This was made using silicone material (Variotime, Heraeus Kulzer GmbH, Germany). Casts were obtained using type 4 dental stone (GC Fujirock, GC Europe, Belgium). Furthermore, all casts were scanned using a laboratory scanner (Imetric 3D, Courgenay Switzerland) to acquire stereolithographic (STL) files (Fig. 4.2). These STL's were imported to an implant planning system (CoDiagnostix, Dental Wings GmbH, Chemnitz, Germany) and all models were superimposed (Fig. 4.3). A sagittal cross section at the center of each region was obtained and exported as an image file. Image files were imported to computer assisted design (CAD) software (AutoCAD, Autodesk, USA). Relevant landmarks were set and measured by a calibrated (ICC>0.9) examiner (C.G.B.S), blinded for the treatments as follows:

Figure 4.2 - (a) Pre-extraction model (T0: yellow), (b) two weeks after crown placement (T1: blue), (c) one-year after restoration (T2: light blue). (d) Superimposed models of the three time points



Source: Author

Figure 4.3 - Selected cross-sectional region of interest of the superimposed models following the long axis of the crown. (a) Frontal view, (b) occlusal view



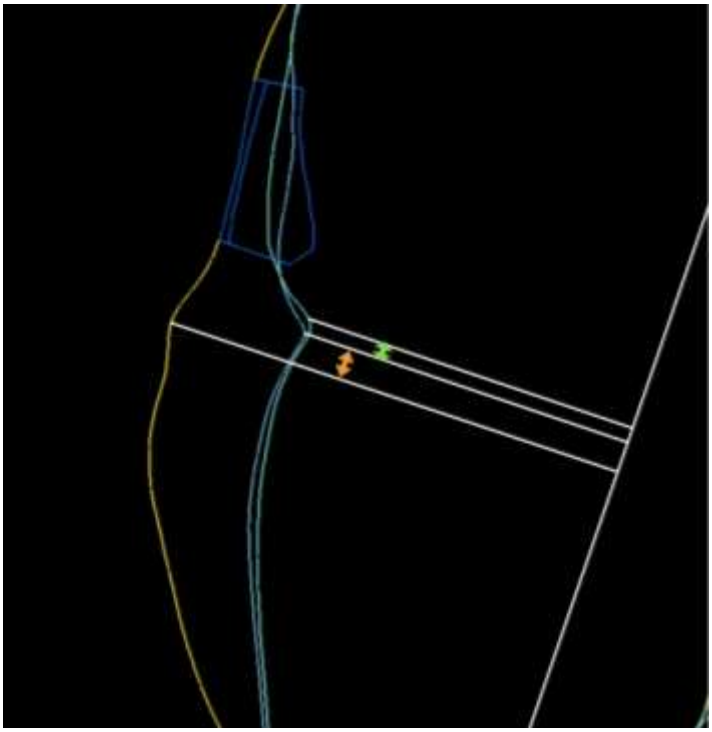
Source: Author

4.6.1.1 Mid-facial mucosal vertical change

Measurements were performed to record the degree of mid-facial mucosal level change (MLC) from original position before tooth extraction (T0) up to two weeks after implant crown insertion (T1); this was followed by the assessment from T1 up to one year after restoration (T2).

Using as reference a vertical line at the long axis of the ridge, three lines perpendicular to it were drawn; each line was tangent to the most coronal mid-facial soft tissue margin of the STL's at the three time points. The mid-facial mucosal level change (MLC) was considered as the distance between lines, with positive and negative values representing marginal gain or recession respectively (Fig. 4.4).

Figure 1.4 - Image of a cross-sectional view of the superimposed models, showing the outlines of the different time points. Pre-extraction (yellow), two weeks after crown insertion (blue), one-year after restoration (light blue). Mid-facial mucosal level change (MLC) was calculated as the distance between the lines representing the mucosal margin of each time point. See MLC between T0 and T1 (orange arrow), and between T1 and T2 (green arrow)

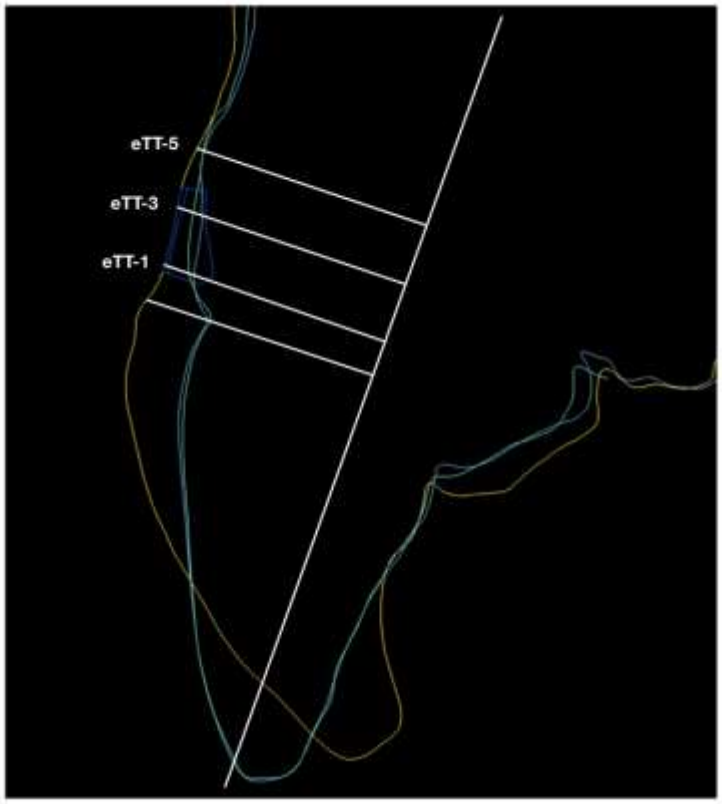


Source: Author

4.6.1.2 Estimated soft tissue thickness changes (eTT)

A standardized grid was created, according to the methodology previously described for the profilometric study by Sapata et al. (53) over the cross-sectional images of the superimposed models. Using a perpendicular line drawn at the long axis of the implant as reference, four perpendicular lines were created at 0, 1, 3 and 5 mm below the buccal soft tissue margin to assess the eTT, measuring the difference between the soft tissue outlines from the different time points. For this investigation, the horizontal reference line of the grid was placed at the level of the mid-facial soft tissue level of the implant crowns, instead of using the original margin before tooth extraction due to the height loss that occurs after socket healing (Fig 4.5).

Figure 4.5 - A cross-sectional view showing the different time point model outlines for the evaluation of estimated tissue thickness at 1 mm below the mucosal margin (eTT-1), estimated tissue thickness at 3 mm below the mucosal margin (eTT-3), estimated tissue thickness at 5 mm below the mucosal margin (eTT-5). Pre-extraction (yellow), two weeks after crown insertion (blue), one year after restoration (light blue)



Source: Author

For soft tissue dimensional analysis, the comparisons mentioned below were made:

I. Mid-facial mucosal levels change from tooth before extraction to implant crown two weeks after insertion (T0-T1).

II. Mid-facial mucosal levels change from implant crown two weeks after insertion and implant crown one year after restoration (T1-T2).

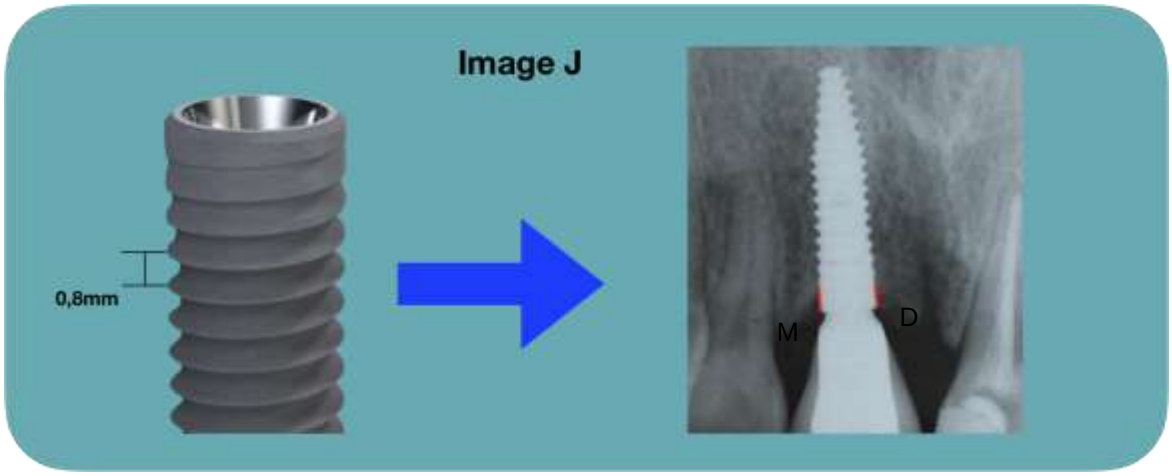
III. Estimated soft tissue thickness changes (eTT) from tooth before extraction to implant crown two weeks after insertion (T0-T1).

IV. Estimated soft tissue thickness changes (eTT) from implant crown two weeks after insertion and implant crown one year after restoration (T1-T2).

4.6.2 Marginal bone loss (Radiographic analysis)

Marginal bone loss and remodeling was assessed adjacent to the implants. Periapical radiographs were obtained using the parallel technique with customized film holders to standardize the image obtained for both visits. Radiographs were digitalized and analyzed in a digital image processing program (Image J, National Institutes of Health, Bethesda, MD, USA). The distance from the implant thread pitch was used for calibration of the software. Marginal bone levels at mesial and distal aspects of each implant were evaluated, measuring the distance from the implant shoulder to the most coronal bone-to-implant contact. Marginal bone loss (MBL) was calculated as the difference of measurements between T1 and T2 (Fig.4.6).

Figure 4.6 - Representative implant image and periapical photograph of the methodology used for MBL assessment from T1 to T2. Implant thread pitch (0.8mm) was used for calibration of the measuring tools at the digital image processing program (Image J). Differences between time points were assessed at the mesial and distal aspects of the implants



Source: Author

4.7 Sample size

Since this is a follow-up study, the sample size calculation was previously performed for the primary outcome (radiographic horizontal width 1 mm below the most coronal point of the palatal crest) of the original non-inferiority randomized clinical trial (12).

4.8 Statistical analysis

For descriptive analysis, means, medians, standard deviations and quartiles Q1 and Q3 are presented. The Shapiro-Wilk test was performed for all variables to assess data distribution. Student's t and Mann-Whitney's U tests were used for comparisons between groups for parametric and non-parametric distributions, respectively. The level of significance was set to 5%, and confidence intervals of 95% were obtained. Assessment of the intra-class correlation coefficient (ICC) was obtained for the reproducibility of measurements performed by the examiner. For all analyses, a statistical software package was used (Jamovi Version 1.2, https://www.jamovi.org).

5 RESULTS

Sixty-six participants were included in the original study (12). Out of them, one patient in the DBBM-C group lost the implant at the second stage surgery, three subjects were lost before crown placement, one participant was excluded because he received a soft tissue graft at the implant site and seven subjects received the crown but did not attend the one year follow-up visit and consequently were excluded from the final analysis. Thus, a total of fifty-four patients completed the twenty-two months of follow-up and were included in the final evaluation, twenty-seven per group (Table 5.1).

Table 5.1 - Demographic data of included patients and sites

	DBBM	DBBM-C
Age (years ± SD)	46.9 ± 10.4	45.6 ± 11.7
Male/Female	16/11	12/15
Non-smoker/Light smoker	23/4	21/6
Implants in central incisor position	15	13
Implants in lateral incisor position	9	10
Implants in canine position	3	4
Regular platform/Narrow platform	8/19	7/20

Source: Author

5.1 Mid-facial mucosal vertical change

The MLC between T0 and T1 was -1.53 ± 0.95 and -1.46 ± 0.99 for DBBM and DBBM-C, respectively (mean±SD, p=0.79). Between T1 and T2 a mean change of 0.08±0.42 and 0.13±0.54 was observed for DBBM and DBBM-C, respectively (mean±SD, p= 0.49) (Table 5.2).

Considering the behavior of the complete sample between T0 and T1 (from tooth before extraction to crown insertion), 30% of the participants (n=16) showed MLC <1mm; 17% (n=9) between 1-1.5mm; 22% (n=12) between 1.5-2mm and 31% (n=17) presented MLC >2mm.

Table 5.2 - Mid-facial mucosa level changes from T0 to T1 and from T1 to T2, based on the models outlines at different time points at the cross-sectional images

	DBBM		**DBBM-C**			
	Mean ± SD	Median [Q1;Q3]	Mean ± SD	Median [Q1;Q3]	p-value	95% CI
mm						
MLC (T0-T1)	-1.53 ± 0.95	-1.62 [-2.25;-0.93]	-1.46 ± 0.99	-1.40 [-2.12;-0.72]	0.79	-0.60,0.47
MLC (T1-T2)	0.08 ± 0.42	0.00 [-0.14;0.36]	0.13 ± 0,54	0.07 [-0.12;0.62]	0.49	-0.35,0.21

Source: Author

5.2 Estimated soft tissue thickness difference (eTT)

No differences between groups were observed for eTT1 in all time intervals (T0–T1 and T1–T2). A similar figure was observed for eTT-3 and eTT-5 in the interval T1–T2. In contrast, DBBM-C presented a greater change when compared to DBBM for eTT-3 and eTT-5 between T0 and T1 ($p<0.05$). Detailed data can be found in Table 5.3.

Table 5.3 - Estimated tissue thickness change between T0 and T1, and from T1 and T2, based on the models outline at different time points at the cross-sectional images. *p< 0.05 (Tested with Mann-Whitney U test)

	DBBM		**DBBM-C**			
	Mean ± SD	Median [Q1;Q3]	Mean ± SD	Median [Q1;Q3]	p-value	95% CI
mm						
eTT-1 (T0-T1)	-0.99 ± 0,61	-0.99 [-1.43;-0.60]	-1.22 ± 0,71	-1.32 [-1.46;-0.87]	0.20	-0.13,0.59
eTT-3 (T0-T1)	-0.62 ± 0,50	-0.64 [-1.02;-0.35]	-1.04 ± 0,68	-1.05 [-1.42;-0.63]	0.01*	0.09,0.74
eTT-5 (T0-T1)	-0.43 ± 0,42	-0.41 [-0.77;-0.10]	-0.84 ± 0,64	-0.75 [-1.40;-0.26]	<0.01*	0.12,0.71
eTT-1 (T1-T2)	0.00 ± 0.29	0.04 [-0.23;0.22]	0.10 ± 0.45	0.18 [0.03;0.32]	0.30	-0.31,0.10
eTT-3 (T1-T2)	-0.10 ± 0.41	-0.04 [-0.22;0.14]	0.03 ± 0.33	0.10 [-0.13;0.28]	0.16	-0.29,0.05
eTT-5 (T1-T2)	-0.16 ± 0.43	-0.04 [-0.20;0.08]	-0.01 ± 0.35	0.00 [-0.18;0.27]	0.30	-0.29,0.08

Source: Author

5.3 Marginal bone loss

With respect to MBL, no differences between groups were detected at the time of crown insertion (T1): -0.64 ± 0.53 and -0.70 ± 0.71, for DBBM and DBBM-C, p>0.05, respectively. Changes T1 to T2 were -0.35 ± 1.05 and -0.25 ± 0.74 (mean ± SD, p= 0.82) for mesial and distal aspects of DBBM and -0.29 ± 0.86 and -0.21 ± 0.82 for mesial and distal aspects for DBBM-C, respectively (mean ± SD, p= 0.38) (Table 5.4).

Overall, data twelve months after restoration showed that 48% of the subjects (n=26) showed no change over time, 39% (n=21) lost <1mm of marginal bone and 13% (n=7) lost >1mm.

Table 5.4 - Marginal bone loss between T1 and T2. Changes expressed in millimeter

	DBBM		**DBBM-C**			
mm	Mean ± SD	Median [Q1,Q3]	Mean ± SD	Median [Q1;Q3]	p-value	95% CI
MBL-M (T1–T2)	-0.35 ± 1.05	-0,04 [-0.55;0.08]	-0.29 ± 0.86	-0.12 [-0.46;0.04]	0.82	-0.24,0.29
MBL-D (T1–T2)	-0.25 ± 0.74	-0.15 [-0.51;0.18]	-0.21 ±0.82	0.05 [-0.37;0.26]	0.38	-0.45,0.23

Source: Author

6 DISCUSSION

The present study was designed to evaluate the influence of ARP on peri-implant tissues after restoration. In addition, it establishes the transition of mid-facial soft tissue margin from tooth extraction up to 1-year after crown installation. To our knowledge this might be the first study that evaluates, with digital analysis, such transition in sites treated with ARP. A dimensional stability of buccal soft tissue thickness could be noticed at different levels with minimal changes after crown connection. In contrast, a mid-facial soft tissue recession of approximately 1.5 mm was observed from tooth extraction to crown insertion. The latter finding is crucial for clinical practice since it provides an objective parameter for practitioners and patients. Moreover, these findings suggest that ARP does not negatively affect the outcome and stability of soft tissue margin after restoration. The results obtained may be stable over time once the proper care in terms of oral hygiene and restorative contour are observed. When the two arms of the original study were compared, no differences between the groups were seen neither before crown connection (mean recession of 1.53mm and 1.46mm for DBBM and DBBM-C, respectively) or after it (0.08mm for DBBM and 0.13 for DBBM-C respectively). It reinforces our previous findings that both materials may be successfully employed for ARP (12,53).

One of the most relevant factors for implant success in the esthetic zone is the position of the soft tissue margin. The present study showed about 1.5mm of apical shift between extraction and restoration. Depending on the case, it may impact the final outcome and patient satisfaction. However, it is important to stress that our sample received exclusively ARP and no other attempt to prevent or correct a future defect was performed. Previous studies evaluating immediate implants with provisionalization revealed average recessions from 0.28 to 0.73mm, and they have also shown that connective tissue grafts (CTG's) can reduce the recession degree (59–64). Despite the favorable data, each case must fulfill several preoperative criteria to receive an immediate implant. Moreover, the lack of primary stability may change treatment planning even in cases considered ideal candidates for such therapy. It reinforces the need for data documenting the performance of other therapeutic options. Early implant placement studies have shown mid-facial mucosal recession of approximately 0.5 mm at the first year after loading (59,65), however

there is a paucity of studies comparing the recession from the original tooth margin up to crown installation at early and late implants (66). Most of the studies have used millimetric scales to analyze the changes over time. Conversely, some studies have demonstrated that patients can only identify discrepancies greater than 2mm (67), this puts all these results within the same range of patient satisfaction.

Despite the recession observed between T0 and T1, there is almost no recession between T1 and T2, i.e. after restoration and even a discrete gain was found. This data could be at least partially explained by tissue stability observed in peri-implant tissues of grafted sites (68,69). These data also suggest that subjects had well controlled oral hygiene and that ARP does not negatively affect the stability of soft tissue margin. Furthermore, when the contours of restorations have a correct buccal profile, there is low chance of apical displacement of the margin over time. A significant difference between the two materials was observed for thickness at 3 and 5mm below the mucosal margin and DBBM-C showed a more pronounced reduction when compared to DBBM. This finding may confirm the tendency previously observed by other studies (12,14,53).

Dental implants placed at grafted sites present similar survival rates (95–100% after 1 to 4 years) in comparison to implants placed at non-grafted sites (22). In the present study, one implant was lost in the DBBM-C group at the healing abutment connection. As the original RTC was designed to include only one site per participant, at the patient and implant level, the survival rates of this study was 98.44% for the entire sample. This high survival rate is in accordance with data from other reports of implants placed at sites treated with regenerative approaches (90–100%) (16,22,70–72). Additionally, the present study found about 0.3mm of marginal bone loss in the first year after loading. This is in line with data recently reported in a meta-analysis study (22). The present findings are also in agreement with Felice et al. (2011) and Esposito et al. (2015), which, respectively, reported 0.19mm and 0.29mm of MBL 1 year after loading of implants placed at grafted sites. The present radiographic findings suggest a high chance of stability in the long-term.

Although the present study represents a meaningful contribution to the systematic documentation of ARP long-term follow-ups, some limitations should be addressed. The original profile of the tooth was not copied or standardized for the final restoration, which could affect the marginal position and the thickness of the soft

tissues over time. Moreover, it is difficult to establish a direct comparison among the studies, since several methodologies, techniques, materials and oral sites have been investigated. But a rough comparison may allow us to infer that ARP associated with late implant placement presents more soft tissue recession (about 1mm) in comparison to immediate implants associated with CTG. On the other hand, it is unquestionable that outstanding results may be achieved with all discussed approaches. So, it seems reasonable to suggest that studies correlating preoperative conditions to positive and negative outcomes should be conducted to, refine the diagnostic process, and to better predict risky or favorable cases. In addition, in cases where ARP is needed, clinical maneuvers previously correlated with decreased marginal recession (e.g. CTG) may be incorporated to the clinical protocol (6). Further studies should also address the ideal technique, material and timing to indicate procedures for recession control. These may contribute to a better understanding of ARP potentials, limitations and optimal performance.

7 CONCLUSION

At the esthetic zone, similar results of mid-facial recession from tooth extraction to crown placement can be expected at sites treated with ARP using different materials. For tissue thickness maintenance, DBBM performs better at middle and apical levels of the ridge when compared to DBBM-C up to crown insertion. The present follow-up study demonstrated that from crown insertion up to 1 year of follow-up, peri-implant tissue stability can be expected at sites previously treated with alveolar ridge preservation where DBBM or DBBM-C was used.

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APPENDIX A – Informed consent

UNIVERSIDADE DE SÃO PAULO- FACULDADE DE ODONTOLOGIA
DEPARTAMENTO DE ESTOMATOLOGIA- DISCIPLINA DE PERIODONTIA

Termo de Consentimento Livre e Esclarecido

Titulo da Pesquisa: **Comparação entre dois substitutos ósseos em sítios pós-extração: ensaio clínico aleatório de não-inferioridade**

PESQUISADORES: Alexandre Hugo Llanos, Luis Marcelo M. Calderero, Prof. Dr. Claudio Mendes Pannuti e Prof. Dr. Giuseppe Alexandre Romito - Faculdade de Odontologia da Universidade de São Paulo (FOUSP).

LOCAL: Clinica de Periodontia da Faculdade de Odontologia da Universidade de São Paulo-USP. Av. Prof Lineu Prestes, 2227, Cidade Universitária-São Paulo-SP.

1. Dados de Identificação do Participante da Pesquisa ou Responsável Legal:
Nome:_____
Sexo: M ( ) F ( ) Data de Nascimento: _____/_____ / _____
Endereço:_____
Bairro:_____Estado:_____
CEP:_____Telefone( )_____

2. Informações sobre a pesquisa científica:

Este documento é um convite para participação voluntária deste projeto. Você foi convidado porque tem problema em um (ou mais) dente(s) que não pode ser recuperado, e este dente precisa ser tirado (extraído). Se você concordar em participar, você receberá tratamento de extração e os materiais de enxerto de osso (pó de osso) que são colocados no lugar do dente para evitar a chance que suas gengivas fiquem murchas depois de tirar o(s) dente(s). Você poderá desistir de participar da pesquisa em qualquer momento que quiser, sem perder nenhuma parte do resto do tratamento.

2.1. Objetivos da pesquisa

Esta pesquisa, que se chama "Comparação entre dois substitutos ósseos em sítios pós-extração: ensaio clínico aleatório de não-inferioridade", vai estudar como dois tipos de materiais de enxerto (pó de osso) vão manter o melhor formato das suas gengivas depois de 4 (quatro) meses, evitando que elas murchem muito. Os dois materiais de enxerto são um pó de osso de origem animal, tratado numa fábrica e colocados num vidrinho sem contaminação nenhuma. Os dois tipos de enxerto são de uma mesma marca, que é muito conhecida e muito utilizada nos consultórios do Brasil de outros lugares do mundo. Já sabemos que os dois materiais são muito bons. Queremos saber se um tipo de material é tão bom quanto o outro.

2.2. O que será realizado

Para fazer este tratamento você vai precisar preencher uma ficha com as suas informações de saúde, e também vamos medir sua pressão, ouvir seus batimentos do coração, medir seu peso e sua altura. No mesmo dia serão pedidos alguns exames de radiografias. Também realizaremos uma coleta de exame de sangue para saber como está o seu sangue e a sua coagulação para cicatrização. Nesse mesmo exame de sangue também vamos estudar se os seus ossos estão fortes. Os exames que serão requisitados são: hemograma, coagulograma, glicemia em jejum, hemoglobina glicada e marcadores bioquímicos do metabolismo ósseo. Depois você vai passar por uma avaliação dos dentes e da gengiva. Em seguida vamos fazer uma limpeza dos seus dentes e vamos te ensinar a melhor maneira de você escovar os seus dentes. Será feito também um molde da sua boca e será marcada a data da sua cirurgia para tirar o(s) dente(s). No dia da cirurgia você será anestesiado na região da boca (do mesmo jeito que fazemos para fazer obturações) e vamos tirar o(s) dente(s) que está com problema. Todo material que for usado será descartável e estéril. Para fechar a gengiva serão dados alguns pontos no local. Para facilitar a cicatrização vamos usar um material que é como um papelzinho mole, que chamamos de membrana de colágeno. Ele vai servir para o pó de osso não sair do lugar, e ajuda na cicatrização. Depois disso vamos fazer uma radiografia especial, que chamamos de tomografia, para ter certeza que o local que tinha o dente está bem, e que o pó de osso está bem colocado. Após a cirurgia você vai fazer repouso e comer alimentos mais moles. Assim que possível colocaremos uma ponte móvel, que chamamos de prótese parcial provisória, para substituir o(s) dente(s) que foi removido, e que estão faltando perto dele(s). Você poderá tomar algum remédio para dor, se precisar. Depois de sete (7) dias serão retirados os pontos na mesma clínica que fez a cirurgia. Depois de 4 meses você vai voltar para fazer uma nova consulta, tirar novas medidas do lugar que tinha o dente e fazer uma nova radiografia do tipo da tomografia para ver se ficou tudo bem. Todos os exames que serão solicitados para esta pesquisa serão gratuitos para o participante da pesquisa.

2.3. Uso de material biológico

Você vai fazer um exame de sangue antes de tirar o dente. Este sangue vai ser retirado por um profissional especializado. O sangue vai ser colocado num vidrinho especial, vai ser analisado e vai ser colocado numa geladeira. O vidrinho de sangue é chamado de material biológico. Ele pode ajudar muito para estudar melhor o seu caso e de outros pacientes. Por isso, eles serão guardados por um período de tempo para serem avaliados e depois serão descartados de forma apropriada de acordo com o procedimento operacional do laboratório.

2.4. Riscos e desconforto

O tratamento é bastante seguro e confiável, mas alguns problemas podem acontecer. Você poderá sentir dor no local depois da cirurgia, e essa dor normalmente passa se você tomar os remédios prescritos. O lugar da extração pode inflamar e sangrar se tiver algum problema de contaminação, e você poderá ter que tomar antibióticos para isso. Depois da colocação da ponte móvel (prótese parcial removível) você tem que escovar os dentes todos os dias com cuidado, senão a gengiva pode inflamar e também você pode ter cárie e perder a prótese com o passar do tempo. O participante da pesquisa receberá assistência integral e imediata, de forma gratuita, pelo tempo que for necessário, em caso de danos decorrentes da pesquisa.

2.5. Tempo (número de sessões e tempo de cada procedimento)

O tratamento pode durar por volta de quatro (4) meses. Serão 2 (duas) consultas de uma (1) hora antes de fazer a cirurgia de e a consulta da cirurgia será de até 1 (uma) horas. Depois você virá mais 1 (uma) vez para tirar os pontos, com duração de trinta (30) minutos. Então

você poderá voltar aos 30, 60 e 90 dias após a cirurgia, em consultas de trinta (30) minutos, para ver se está tudo bem. Depois de quatro (4) meses vamos fazer uma consulta de avaliação clínica e radiográfica para saber se está tudo bem com o formato da sua gengiva. Após o final do tratamento, você poderá ser chamado para fazer algumas consultas para retorno de rotina do tratamento. Não haverá custos para estes exames.

2.6. Benefícios

A sua participação neste projeto de pesquisa vai ser muito importante para todos nós. Você receberá uma limpeza de todos os seus dentes, com orientação especial para higiene dos dentes e da boca, além do principal que é tratar o lugar que você tirou o dente com de uma forma segura para a gengiva murchar bem pouco, além colocar dente provisório através de uma ponte móvel provisória nas regiões em que tirou os dentes. O resultado do seu tratamento pode nos ajudar a oferecer um tratamento cada vez melhor para todos os pacientes, já que os resultados podem ser divulgados para um grande número de profissionais que atendem muitos pacientes. Os participantes da pesquisa podem nâo ter benefício direto com a pesquisa mas a participação é importante no projeto que poderá trazer resultados benéficos a outros pacientes que necessitem extrair dentes permanentes.

2.7. Ajuda de custos

Por estar participando deste projeto de pesquisa você vai receber de graça a cirurgia de colocação do material do enxerto e da membrana de colágeno. Você deverá pagar o custo da confecção dos dentes, que terão o menor custo possível dentro da realizada do mercado brasileiro e da qualidade dos materiais utilizados. Para isto usaremos os laboratórios de próteses e a tabela de preços de serviços de prótese usada na Faculdade de Odontologia da Universidade de São Paulo, para cada tipo de prótese necessária. Não haverá nenhum custo adicional.

Serviços de terceiros – por arcada (laboratório de prótese):

- Prótese Parcial Removível Provisória: R$ 193,00 cento e noventa e três reais)

Os pagamentos serão realizados diretamente no serviço de Tesouraria da FOUSP.

2.8. Garantia de sigilo da identidade do paciente

Nós não vamos divulgar o seu nome para ninguém, nem qualquer informação pessoal da sua ficha (como endereço, telefone, e outras), de maneira nenhuma. Este projeto só tem interesse nas informações de saúde e nos resultados do tratamento. Em nenhum momento ninguém, além da equipe que vai te atender, saberá as suas informações de cadastro.

2.9. Direito de desistir da pesquisa

Você poderá desistir de participar do projeto de pesquisa em qualquer momento e por qualquer motivo. Uma vez iniciado o tratamento, você continuará sendo atendido pelo tempo que for necessário, mesmo se desistir de participar da pesquisa. O participante da pesquisa tem plena liberdade de retirar o seu consentimento a qualquer momento da pesquisa, e que esta decisão não vai gerar penalização por parte dos pesquisadores.

2.10. Métodos Terapêuticos Alternativos

Existem outras formas para tratar o seu caso como: não acrescentar nenhum material depois da extração e a cicatrização ocontecer de forma natural e ter a possibilidade da altura e largura do tecido ósseo ficar diminuída após a extração, Também pode-se inserir osso do

próprio paciente, o que poderia levar a um maior traumatismo e a necessidade de outra cirurgia. Outro jeito é inserir osso particulado vindo de banco de ossos humanos ou até mesmo inserir outros tipos de material de enxerto, com resultados diferentes em cada um dos casos.

2.11. Acesso aos Resultados dos Exames

O participante da pesquisa terá acesso ao resultado dos exames que foram realizados durante o estudo.

2.12. Reutilização de dados e do material biológico

Você autoriza o uso das informações do seu tratamento e do material recolhido da sua gengiva e exames de sangue em outras pesquisas?
( ) NÃO autorizo a utilização de dados ou material biológico (coleta de exudato em cone de papel e exame de sangue) em outra pesquisa.
( ) SIM autorizo a utilização de dados ou material biológico (coleta de exudato em cone de papel e exame de sangue) em outra pesquisa

2.13. Para utilizar os dados ou material biológico (exame de sangue) em outra pesquisa você quer ser consultado?
( ) NÃO quero ser consultado da utilização dos meus dados ou material biológico (coleta de exudato em cone de papel e exame de sangue) em outra pesquisa, desde que a nova pesquisa seja aprovado pelo Comitê de Ética em Pesquisa
( ) SIM quero ser consultado da utilização dos meus dados ou material biológico (coleta de exudato em cone de papel e exame de sangue) em outra pesquisa

3. Contato

Para qualquer dúvida ou ocorrência durante a pesquisa e seu atendimento, você poderá ligar para (11) 2942-0779 ou (11) 94738-9485, aos cuidados de Alexandre Hugo Llanos; ou para (11) 3091-7833 , aos cuidados de Giuseppe Alexandre Romito.

4. Endereço do comitê de ética em pesquisa

Se houver dúvidas sobre a ética da pesquisa entre em contato:
Comitê de Ética em Pesquisa (Seres Humanos)
Faculdade de Odontologia da Universidade de São Paulo
Av. Prof. Lineu Prestes, 2227-CEP:05508-000- São Paulo-SP Fone: (11) 3091.7960
E-mail: cepfo@usp.br . Horário de Funcionamento: segunda a sexta-feira das 8 às 17h (exceto feriados e recesso universitário).
O Comitê é um colegiado interdisciplinar e independente, de relevância pública, de caráter consultivo, deliberativo e educativo, criado para defender os interesses dos participantes da pesquisa em sua integridade e dignidade para contribuir no desenvolvimento da pesquisa dentro de padrões éticos. (Resolução CNS nº 466 de 2012).

CONSENTIMENTO ESCLARECIDO

Declaro que, tendo lido e compreendido o termo de informação e consentimento para a pesquisa clínica, concordo em participar deste estudo. Sei que minha participação é voluntária

e que posso interrompê-la a qualquer momento, sem penalidades. Autorizo a utilização dos dados obtidos pelos pesquisadores para a publicação em revistas científicas e apresentação em Congressos.

Este documento foi elaborado em duas vias, sendo uma do participante da pesquisa e outra do pesquisador responsável.

São Paulo, _____ de _____de_____

Participante da pesquisa_____

Assinatura do Participante/ Responsável Legal:_____

Nome do Pesquisador: _____

Assinatura do Pesquisador :_____

ANNEX A - Ethics committee approval

FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE DE SÃO

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Comparação entre dois substitutos ósseos em sítios pós-extração: ensaio clínico de não inferioridade.

Pesquisador: Giuseppe Alexandre Romito

Área Temática:

Versão: 3

CAAE: 51295615.2.0000.0075

Instituição Proponente: Universidade de São Paulo - Faculdade de Odontologia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.664.774

Apresentação do Projeto:

A proposta pretende estudar por meio de um ensaio clínico aleatório de não inferioridade, duplo cego, e paralelo se dois tipos de substituto ósseo comercialmente disponíveis são equiparáveis entre si quanto ao efeito de manutenção e regeneração óssea de alvéolos pós-exodontia de dentes permanentes.

A emenda ao projeto original explica que foi acrescentado parte metodológica que inclui a análise de fragmento ósseo retirado do local de enxerto com o substituto ósseo. OS pesquisadores descrevem que receberão doação de material e de implantes para confecção das prótese sobre os implantes e que a instalação e reabilitação não representará custo aos participantes envolvidos.

Objetivo da Pesquisa:

Verificar se o enxerto de BiOss Collagen é tão eficaz quanto o Bio-Oss na manutenção do volume do sítio de rebordo alveolar pós-extração.

Avaliação dos Riscos e Benefícios:

A avaliação de riscos e benefícios foi considerada e está adequada.

Endereço: Av Prof Lineu Prestes 2227
Bairro: Cidade Universitária **CEP:** 05.508-900
UF: SP **Município:** SAO PAULO
Telefone: (11)3091-7960 **Fax:** (11)3091-7814 **E-mail:** cepfo@usp.br

Comentários e Considerações sobre a Pesquisa:

Esta emenda inclui um procedimento metodológico de análise de um fragmento ósseo de região que será submetida a perfuração para instalação de implante. Os pesquisadores declaram que não haverá custo para os pacientes.

Considerações sobre os Termos de apresentação obrigatória:

As informação básicas, o texto do projeto detalhado e o TCLE foram adequados quanto a redação das informações desta emenda.

Recomendações:

Tendo em vista a legislação vigente, devem ser encaminhados ao CEP-FOUSP relatórios parciais anuais referentes ao andamento da pesquisa e relatório final, utilizando-se da opção "Enviar Notificação" (descrita no Manual "Submeter Notificação", disponível na Central de Suporte - canto superior direito do site www.saude.gov.br/plataformabrasil).

Qualquer alteração no projeto original deve ser apresentada "emenda" a este CEP, de forma objetiva e com justificativas para nova apreciação.

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_765914_E1.pdf	29/07/2016 12:33:19		Aceito
Projeto Detalhado / Brochura Investigador	PROJETOemenda.docx	29/07/2016 12:29:49	Giuseppe Alexandre Romito	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEemenda.docx	29/07/2016 12:29:09	Giuseppe Alexandre Romito	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	25/01/2016 10:31:33	Giuseppe Alexandre Romito	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	25/01/2016 10:31:08	Giuseppe Alexandre Romito	Aceito

FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE DE SÃO

Continuação do Parecer: 1.664.774

Outros	autclin.pdf	19/10/2015 17:31:51	Giuseppe Alexandre Romito	Aceito
Folha de Rosto	rosto.pdf	19/10/2015 17:29:02	Giuseppe Alexandre Romito	Aceito
Outros	Fichas.docx	04/10/2015 17:50:17	Giuseppe Alexandre Romito	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 05 de Agosto de 2016

Assinado por:
Maria Gabriela Haye Biazevic
(Coordenador)

Endereço: Av Prof Lineu Prestes 2227
Bairro: Cidade Universitária **CEP:** 05.508-900
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