UNIVERSIDADE PAULISTA – UNIP
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

INFLUÊNCIA DA MEMBRANA NÃO ABSORVÍVEL PARCIALMENTE EXPOSTA PARA PROCEDIMENTOS DE PRESERVAÇÃO ALVEOLAR: UM ESTUDO CONTROLADO RANDOMIZADO

Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Paulista – UNIP, para obtenção do título de Doutor em Odontologia

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Orientadora: Prof.a Dr.a Mônica Grazieli Corrêa

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DEDICATÓRIA

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SUMÁRIO

RESUMO

Objetivo: Este estudo controlado randomizado avaliou o impacto da membrana inabsorvível parcialmente exposta (dPTFE) em procedimentos de Preservação Alveolar Ridge (ARP) por meio de vedação de alvéolo com base em uma avaliação de resultados clínicos, radiográficos, imunoenzimáticos, relacionados ao implante e centrados no paciente. Materiais e Métodos: Foram incluídos pacientes com dente uniradicular maxilar sem esperança e futura reabilitação com terapia de implantes. Os indivíduos foram randomizados para um dos dois grupos após a extração dentária: dPTFE (Grupo de teste, n = 22) - extração dentária seguida de ARP usando uma membrana dPTFE parcialmente exposta e não ARP (Grupo de controle, n = 22) - extração dentária e não terapia adicional com ARP. Análises clínicas e radiográficas foram realizadas no início e após 3 meses. Após 3 meses, os pacientes receberam um implante dentário. O quociente de estabilidade do implante foi medido após a colocação do implante. Marcadores relacionados ao osso de biópsias ósseas coletadas na colocação do implante foram analisados usando ensaio imunoenzimático. Resultados: Maior Largura da Mucosa Queratinizada (KMW) foi observada nos sítios dPTFE em comparação aos não-ARP ($p<0,05$). Menos perda óssea linear vertical e horizontal foi observada no grupo dPTFE ($p<0,05$). No entanto, não foram observadas diferenças entre as terapias nas alterações ósseas volumétricas, estabilidade primária do implante e níveis de marcadores relacionados ao osso ($p>0,05$). Os resultados centrados no paciente mostraram redução da dor/desconforto, edema e interferência na vida diária a partir do 7º dia ($p<0,05$), sem diferenças entre os grupos ($p>0,05$), como também verificado em relação aos resultados estéticos após a provisionalização do implante ($p> 0,05$). Conclusão: Este estudo mostrou que a terapia ARP foi superior à cicatrização de alvéolos não assistida no ganho de KMW, atenuando a reabsorção óssea alveolar após a extração dentária sem aumentar a morbidade.

ABSTRACT

Objective: This randomized controlled trial evaluated the impact of partially exposed nonabsorbable membrane (dPTFE) in Alveolar Ridge Preservation (ARP) procedures via socket sealing based on an evaluation of clinical, radiographic, immunoenzymatic, implant-related and patient-centered outcomes. **Materials and Methods:** Patients with a hopeless maxillary single-rooted tooth and future rehabilitation with implant therapy were included. Subjects were randomized to one of two groups after tooth extraction: dPTFE (Test Group, n=22) - tooth extraction followed by ARP using a partially exposed dPTFE membrane and non-ARP (Control Group, n=22) – tooth extraction and no further therapy with ARP. Clinical and radiographic analyses were performed at baseline and after 3 months. After 3 months, patients received one dental implant. Implant stability quotient was measured following implant placement. Bone-related markers of bone core biopsies collected at implant placement were analyzed using immunoenzymatic assay. **Results:** Greater Keratinized Mucosa Width (KMW) was observed in the dPTFE sites as compared to non-ARP ($p<0.05$). Less linear vertical and horizontal bone loss was observed in the dPTFE group ($p<0.05$). However, no differences between therapies were observed in volumetric bone changes, primary implant stability and levels of bone-related markers ($p>0.05$). Patient-centered outcomes showed reduction of pain/discomfort, edema, and interference with daily life from the 7^{th} day ($p<0.05$), without differences between groups ($p>0.05$), as also verified concerning aesthetic outcomes after implant provisionalization ($p>0.05$). **Conclusion:** This study showed that ARP therapy was superior to unassisted socket healing in the gain of KMW, attenuating alveolar bone resorption after tooth extraction without increasing the morbidity.

INTRODUÇÃO

A atrofia do rebordo alveolar após a extração dentária pode influenciar negativamente as terapias de substituição dentária com restaurações suportadas por implantes (Couso-Queiruga et al. 2021). Dependendo da extensão e magnitude das alterações dimensionais pós-extração, procedimentos de aumento do rebordo por meio de regeneração óssea guiada (GBR), enxerto autógeno em bloco ou outros procedimentos cirúrgicos extensos são necessários antes ou no momento da colocação do implante. No entanto, esses procedimentos têm sido relacionados com aumento da morbidade, custo e duração da terapia.

Para atenuar eventos de reabsorção e evitar procedimentos regenerativos extensos, uma ampla variedade de modalidades de ARP por meio de enxerto e/ou vedação de alvéolo foi proposta (Avila-Ortiz et al. 2019, Wongpairojpanich et al. 2021). O ARP via selamento do alvéolo utiliza um material de barreira (autógeno ou exógeno) para cobrir o alvéolo. A barreira facilita a exclusão de células epiteliais e bacterianas, permitindo que as células osteogênicas migrem e formem osso dentro do alvéolo. No entanto, a exposição da membrana ao ambiente oral pode levar à colonização do patógeno e promover a degradação prematura, comprometendo os resultados ideais das terapias (Garcia et al. 2018, Alkanan et al. 2019). No entanto, outros estudos mostraram que o fechamento primário da ferida pode não ser necessário para o gerenciamento eficaz dos locais pós-extração usando uma membrana densa de politetrafluoretileno (dPTFE) (Owens & Yukna 2001, Barber et al. 2007, Barboza et al. 2014, Laurito et al. 2016, Mazzucchi et al. 2020, Antonious et al. 2021) e seu uso tem sido relacionado a uma maior taxa de regeneração óssea em comparação com membranas mais oclusivas (Linde et al. 1993, Lundgren et al. 1998, Gutta et al. al. 2009).

No entanto, há falta de evidências sobre os mecanismos de reparo e o perfil local de moléculas relacionadas ao reparo ósseo quando membranas de dPTFE são usadas. Não há ensaios clínicos controlados avaliando parâmetros críticos, como reabsorção óssea alveolar linear e volumétrica, resultados relacionados ao implante, marcadores relacionados ao osso e medidas de resultado centradas no paciente. Além disso, o objetivo deste ensaio clínico prospectivo, simples-cego e randomizado de braço paralelo foi avaliar o impacto das membranas dPTFE parcialmente expostas com base em uma avaliação de resultados clínicos, radiográficos, imunoenzimáticos, relacionados ao implante e centrados no paciente.

ARTIGO

Influence of Partially Exposed Nonabsorbable Membrane for Alveolar Ridge Preservation: A Randomized Controlled Trial.

INTRODUCTION

Alveolar ridge atrophy following tooth extraction may negatively influence tooth replacement therapies with implant-supported restorations (Couso-Queiruga et al. 2021). Depending on the extent and magnitude of post-extraction dimensional changes, ridge augmentation procedures via guided bone regeneration (GBR), autogenous block grafting, or other extensive surgical procedures are required prior to or at the time of implant placement. However, these procedures have been related with an increase in morbidity, cost, and duration of therapy.

To attenuate resorptive events and avoid extensive regenerative procedures a wide variety of ARP modalities via socket grafting and/or socket sealing have been proposed (Avila-Ortiz et al. 2019, Wongpairojpanich et al. 2021). ARP via socket sealing utilizes a barrier material (autogenous or exogenous) to cover the alveolar socket. The barrier facilitates epithelial and bacterial cell exclusion, allowing osteogenic cells to migrate and form bone inside the socket. However, membrane exposure to the oral environment may lead the pathogen colonization and promote premature degradation, compromising the optimal outcomes of therapies (Garcia et al. 2018, Alkanan et al. 2019). Nevertheless, other studies have shown that primary wound closure may not be necessary for the effective management of post-extraction sites using a dense polytetrafluoroethylene (dPTFE) membrane (Owens & Yukna 2001, Barber et al. 2007, Barboza et al. 2014, Laurito et al. 2016, Mazzucchi et tal. 2020, Antonious et al. 2021) and its use has been related to a higher rate of bone regeneration

compared to more occlusive membranes (Linde et al. 1993, Lundgren et al. 1998, Gutta et al. 2009).

However, there is a lack of evidence about the repair mechanisms and local profile of molecules related to bone repair when dPTFE membranes are used. There are no controlled clinical trials evaluating critical parameters such as linear and volumetric alveolar bone resorption, implant-related outcomes, bone-related markers, and patient-centered outcome measures. Moreover, the aim of this prospective, single-blinded, parallel-arm randomized clinical trial was to evaluate the impact of partially exposed dPTFE membranes based on an evaluation of clinical, radiographic, immunoenzymatic, implant-related and patient-centered outcomes.

MATERIALS AND METHODS

Study design

This study was designed as a prospective, single-blinded, parallel-arm randomized clinical trial and performed in compliance with the CONSORT guidelines. This trial is registered at www.clinicaltrials.gov under code NCT04329351.

Population screening

Patient recruitment was initiated in December 2018 and finalized in January 2020. The clinical components of the study were conducted at Paulista University between January 2019 and December 2020. Data entry and statistical assessments were completed by the end of February 2021. The inclusion criteria were: 1) patients aged between 25 and 70 years old, 2) with a maxillary single-rooted tooth indicated for extraction and future rehabilitation with a dental implant, 3) whose teeth were deemed unrestorable due to the presence of extensive carious lesions, root fractures, restorability, or endodontic-related factors, 4) the region should

present, radiographically, adequate bone and prosthetic dimensions for future implant placement with the subsequent prosthetic rehabilitation, 5) at least three bone walls should be present at the time of extraction. Exclusion criteria were: 1) pregnancy, 2) lactation, 3) current or former smokers, 4) systemic conditions that could affect bone metabolism (e.g., immunologic disorders), 5) use of anti-inflammatory, antibiotic, anti-resorptive, and immunosuppressive medications. Clinical and radiological evaluations were performed prior to including the subject in the study. In case of active periodontal disease, endodontic alterations and/or caries, the required treatments were made to provide good oral health prior to enrolling the subject in the study. All eligible subjects were thoroughly informed of the purpose, potential risks, and benefits of their participation in the study and signed an informed consent document. This study was approved by the ethics committee of Paulista University (2.818.052).

Sample size calculation

The sample size was determined using α=0.05 and 80% power. For the variability (σ=SD), a value of 1.5 mm was applied, with radiographic vertical measurements recognized as the primary outcome variable. The minimum clinically significant value (δ) established was 1 mm. A minimum sample size of 18 participants per group was determined. Considering that several individuals may be lost throughout follow-up, 22 individuals were included in each group.

Randomization

Patients were randomly assigned using a computer-generated list to one of the two treatment modalities: dPTFE (Test Group, n=22) - tooth extraction followed by ARP using a dPTFE membrane and non-ARP (Control Group, n=22) – tooth extraction with no further treatment. The flowchart of the study is described in Figure 1.

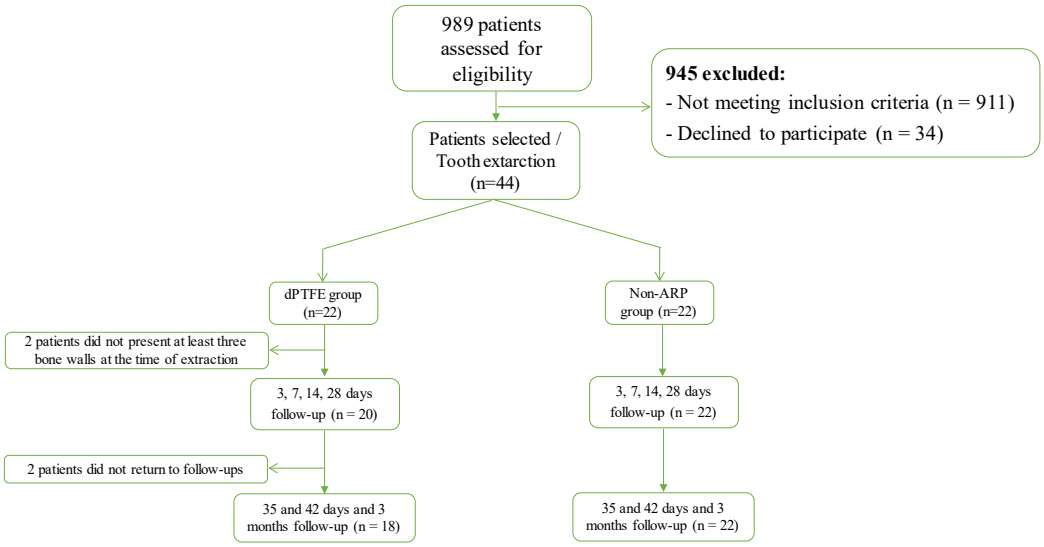


Figure 1. Flowchart of the study

Treatment protocol

A minimally traumatic extraction procedure was carefully performed by the same operator (E.K.M). After local anesthesia, an intrasulcular incision was made around the tooth to be extracted and a full thickness mucoperiosteal flap was cautiously elevated. A periotome was utilized to luxate and extract the tooth in an attempt to minimize the trauma to the periodontal structures. All extraction sockets were gently curetted and irrigated with sterile saline. At this point, subjects were randomly designated to receive one of the treatments: dPTFE Group: the dPTFE membrane (CytoplastTi250 Titanium-Reinforced, 12 mm x 24 mm, Osteogenics, Lubbock, TX, USA) was trimmed and positioned over the alveolar bone extending 3 mm under the buccal and palatal soft tissues taking as a reference the most coronal part of the marginal mucosa. A cross-mattress and single interrupted dPTFE sutures was placed over the socket repositioning the flap and stabilizing the membrane (Cytoplast 4-0 Suture: CS0618PREM, Osteogenics, Lubbock, TX, USA) (Fig. 2 A-L). Non-ARP Group: No additional treatment was provided, and the sockets were left to heal spontaneously. The flaps were repositioned with single interrupted sutures with 5-0 Nylon. (Nylon 5.0 Ethicon, Johnson & Johnson, São Paulo, SP, Brazil) (Fig 2M-T). Provisional crowns were temporarily

cemented to adjacent teeth and removed on the day of implant placement. For plaque control, all patients were instructed to rinse with 0.12% chlorhexidine (twice a day, for four weeks). Anti-inflammatory therapy (4 mg dexamethasone, single dose) was recommended for both groups prior to and post-surgery analgesic (500 mg dipyrone sodium every 4 hours, for 3 days) in combination with antibiotic medication (500mg amoxicillin every 8 hours, for 7 days). Sutures were removed after 15 days postoperatively. In the dPTFE group, the membrane was gently removed 28 days under local anesthesia (Hoffmann et al. 2007, Carbonell et al. 2014, Cheon et al. 2017).

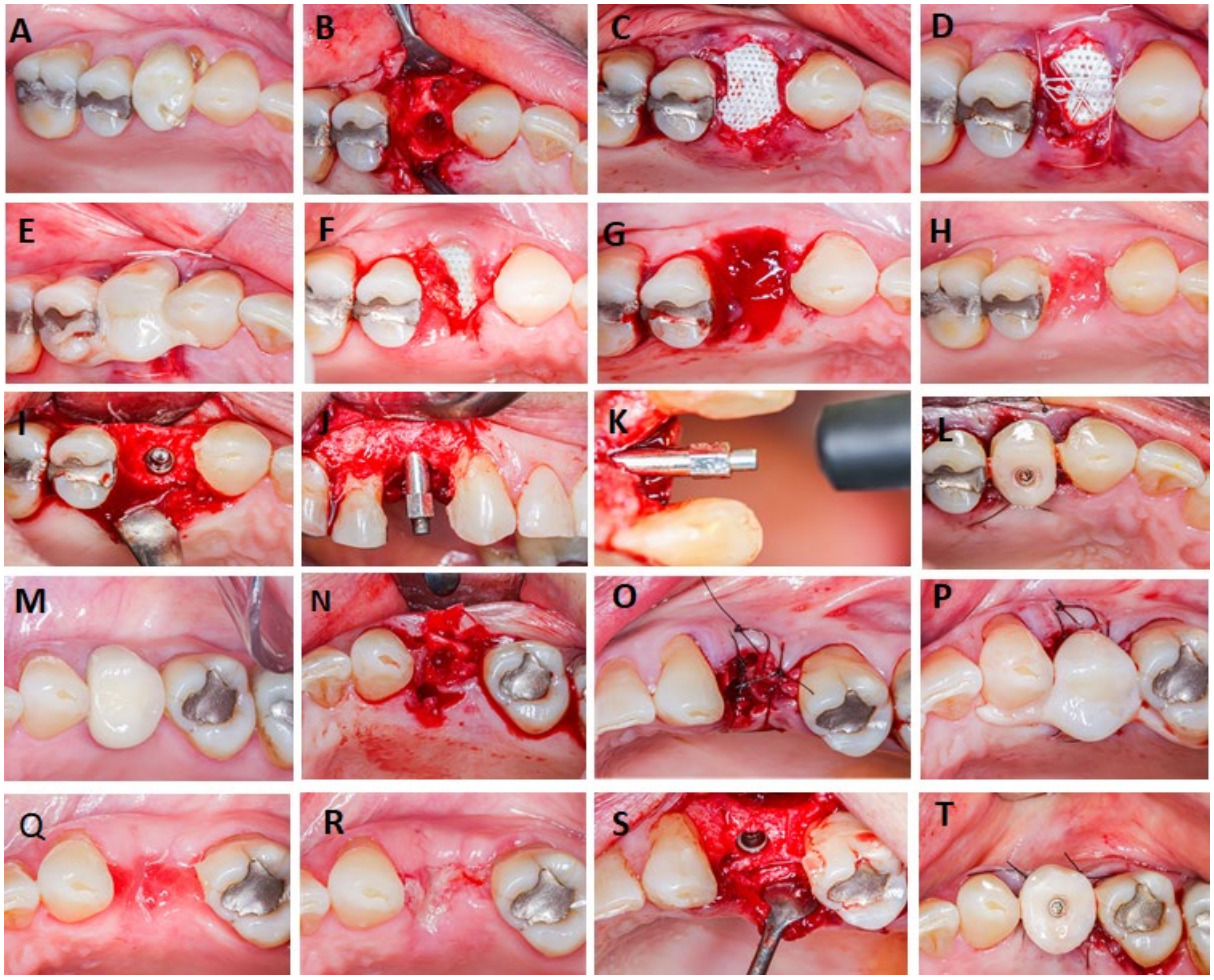


Figure 2. **A- L) dPTFE group** – (A) Baseline; (B) Tooth extraction; (C) Approximation of the wound edges through suture with PTFE thread keeping the wound open; (D) Suturing; (E) Provisional crown; (F) Sutures removal; (G) Barrier removal; (H) 3 months post-extraction; (I) Implant placement; (J) Smartpeg; (K) Implant stability measurement; (L) Immediate implant provisionalization. **M – T) Non-ARP group** – (M) Baseline; (N) Tooth extraction; (O) Suturing; (P) Provisional crown; (Q) Sutures removal; (R) 3 months post-extraction; (S) Implant placement; (T) Immediate implant provisionalization.

Clinical examination

The same examiner (S.H.G.B.) completed all clinical measurements. To monitor the full mouth periodontal condition of patients, the following parameters were measured (four sites/tooth), before extraction and after 3 months: Probing Depth (PD/mm) - distance from the

bottom of the periodontal sulcus/pocket to the gingival margin; Clinical Attachment Level (CAL/mm) - distance from the bottom of the periodontal sulcus/pocket to the cemento-enamel junction (CEJ), Full Mouth Plaque Score (FMPS) (Ainamo & Bay 1975) and Bleeding Score (FMBS) (Muhlemann & Son 1971). To perform the intra-examiner calibration, the examiner measured the CAL of 15 non-study subjects with dental implants twice within 24h, using a UNC probe (North Carolina, Hu-Friedy, Chicago, IL, USA). The intra-class correlation was computed as 96%. In addition, before extraction and after 3 months, the following assessments were performed (under local anesthesia) on the buccal region involving the tooth in question: Keratinized Mucosa Width (KMW): distance from the gingival margin to the mucogingival junction (or, after extraction, distance from the mucosal margin to the mucogingival junction), stained by Schiller's solution and measured with a UNC probe; and Keratinized Mucosa Thickness (KMT): measured 3 mm apical to the gingival margin (or, after extraction, 3 mm apical to the mucosal margin), through the perforation of the gingival tissue by an endodontic spacer with a cursor, being quantified by a digital caliper with centesimal precision (Absolute®, Mitutoyo Sul Americana Ltda., Suzano - São Paulo).

Radiographic assessment

To ensure data quality, linear and volumetric assessments were performed by two independent, blinded, and calibrated examiners (E.C.Q and Z.G.), who used DICOM (Digital Imaging and Communication in Medicine) files from the CBCT scans obtained at baseline and three months post-extraction. To achieve inter-examiner calibration, measurements of a total of 10 sites were performed by both examiners, to verify an interclass correlation of at least 0.8, after which data collection ensued. A software package (Romexis, Planmeca, v.5.2.1 Hoffman Estates, IL, USA) was utilized for this purpose. To standardize the linear measurements, a sagittal section at the middle of each corresponded extracted socket was

obtained. Vertical mid-buccal and mid-palatal bone changes were evaluated using a reproducible landmark between scans (i.e., a horizontal line connecting the CEJ of the adjacent teeth) for consistency of assessment. Horizontal bone changes were assessed using three predetermined reference points located at 1, 3 and 5 mm from the most coronal baseline mid-buccal or mid-lingual crestal points, as shown in Figure 3. To conduct the volumetric assessments, DICOM files were imported into the software package aforementioned (Romexis, Planmeca, v.5.2.1 Hoffman Estates, IL, USA). The same greyscale value and region of interest in a 2D sagittal section view in millimeters was standardized between examiners and both datasets. Manual segmentation was used to define the volume of interest (VOI) using reproducible landmarks. The VOI was confined to the following boundaries: a horizontal plane located at the apex of adjacent teeth; two vertical planes placed at the interproximal height of contour of adjacent teeth, the buccal and palatal bone plates and the alveolar bone crest as shown in Figure 3. Bone volume assessments were expressed in mm^3. Subsequently, the percentual loss of volume that took place from baseline to 3 months post-extraction was calculated.

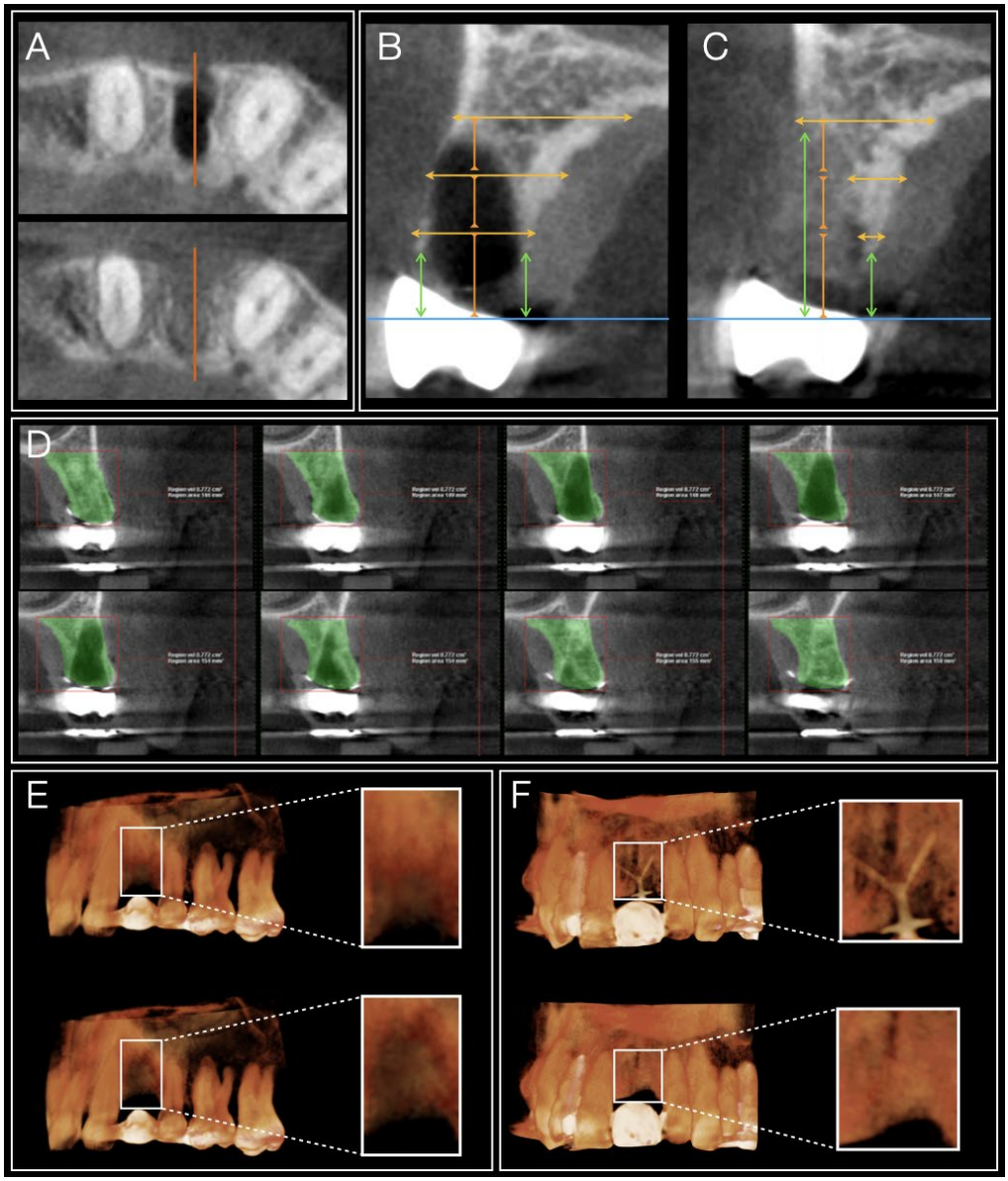


Figure 3. Multipanel illustrating linear and volumetric assessment. (A) A sagittal section was made at the middle of each extracted socket image at baseline and 3 months post-extraction. (B) Horizontal reproducible landmark (blue line), vertical mid-buccal and mid-palatal bone changes (green lines), highest baseline mid-buccal or mid-lingual line + 1, 3 and 5 mm (orange line) and horizontal bone changes at the predetermined reference points (yellow lines). (C) Manual segmentation of the VOI. (D) Volumetric changes in the control group between datasets. (F) Volumetric changes in the test group between datasets.

Implant placement

Tapered dental implants with surface blasted with TiO2, cone morse connection, and 3.5mm diameter (Implacil de Bortoli, São Paulo, SP, Brazil) were placed 3 months after tooth extraction by the same operator. Bone core biopsies were harvested from the sites where the implants were placed. A device that collects bone during implant osteotomy through a suction hose were used, following the manufacturer recommendations. In both groups, a delayed implant protocol with immediate provisionalization was performed.

Implant stability analysis

The implant stability quotient (ISQ) was determined by resonance frequency measurements using Osstell® (Integration Diagnostics ABGöteborg, Sweden) at the time of implant placement. The measurements were performed in triplicate by the same examiner (S.H.G.B.).

Immune-enzymatic assay

Bone core biopsies samples were deposited in tubes containing phosphate-buffered saline (PBS)/Tween and stored at -70°C for immunoenzymatic quantification of the levels of Dickkopf Wnt signaling pathway inhibitor 1 (Dkk1), tumor necrosis factor (TNF)-α, Osteoprotegerin (OPG), Osteocalcin (OC), Osteopontin (OPN), receptor activator of NF-KB ligand (RANKL), Sclerostin (SOST), Tartaric-resistant acid phosphatase (TRAP) and Osteonectin (OSN), using the multiplexing instrument (MAGpix™ MiraiBio, Alameda, CA, USA). The samples were separately assessed, corrected according to volume, and the concentrations were projected from the standard curve using a five-parameter polynomial equation and specific software (Xponent® Millipore Corporation, Billerica, MA, USA). Thus, the mean concentration (pg/ml) of each mediator was determined.

Patient-centered outcomes

The assessment of patient-centered outcomes including symptoms related to morbidity and quality of life in the postoperative period was carried out at 3, 7, 14, 28, 35, and 42 days of post tooth extraction, using questionnaires. Based on a horizontal line of 100 mm (Visual Analog Scale; VAS), the patient marked his/her response, indicating the degree of pain/discomfort, swelling and interference in daily life at each time point (Ribeiro et al. 2014, Kolbe et al. 2014, Barrela et al. 2016). In addition, after implant placement with immediate provisionalization, the subjects scored aesthetic satisfactions, choosing one of the following options: very satisfied, moderately satisfied, or unsatisfied (Ribeiro et al. 2011, Ribeiro et al. 2010, Ribeiro et al. 2014). The number of analgesic medications ingested by the patient in the postoperative period was also recorded. The explanation and monitoring of the filling out of the questionnaires were always carried out by the same operator, who was not aware of the treatments received by the patient.

Statistical analysis

The primary outcome variable was vertical linear bone loss. Secondary outcomes included horizontal and volumetric alveolar bone loss, clinical measurements, immunoinflammatory-markers concentrations, implant-related and patient-related outcomes. Data were inspected for normality using the Shapiro-Wilks test. When normal distribution was found, analysis of variance (ANOVA two-way) and Tukey's test were applied to distinguish intra-group and inter-group differences in clinical parameters, tomographic assays and patient-centered outcomes using VAS throughout the study. Immunoenzymatic assay, resonance frequency analysis and number of medications required were submitted to Student’s t-Test. Patient perceptions related to aesthetic outcomes after temporary implant-supported prosthesis were compared using Fisher's exact test. An experimental level of significance was established at

5% for all statistical evaluations. Statistical tests were performed using the SAS 9.3 program[#] [#].

RESULTS

Population

A total of 44 subjects (24 males and 20 females; aged 25 to 68 years) were included in this study. Twenty-two subjects were assigned to the dPTFE group and 22 subjects to the non-ARP group. There were no differences in the mean age and sex distribution among groups ($p>0.05$). Four patients were excluded in the dPTFE group. Two of them did not return for the follow-up visits and two of them were excluded due to severe bone damage after tooth extraction (Figure 1).

Clinical evaluations

No serious adverse events were observed during healing in either group. There was no significant inter or intra-group difference for FMPS and FMBS at any time point ($p> 0.05$; Table 1). No differences were also detected between groups for full mouth PD, CAL and KMT between baseline or after three months ($p> 0.05$; Table 1). However, a higher gain in KMW was observed in the dPTFE group at the end of the follow-up period compare to the non-ARP group (1.33 ± 1.0mm and 0.57 ± 0.96, for the dPTFE and non-ARP group, respectively) ($p<0.05$; Table 1).

[#] [#] Cary, NC, USA

Table 1. Mean (± SD) of full mouth plaque and bleeding score, of full mouth PD and CAL and soft tissue measurements before tooth extraction (baseline) and three months post-extraction.

	Period	Test Group	Control Group
FMPS (%)	Baseline	11.60 (± 6.95)	9.91 (± 5.08)
	3 Months	8.26 (± 3.31)	6.31 (± 2.76)
FMBS (%)	Baseline	9.10 (± 5.00)	7.61 (± 3.38)
	3 Months	6.69 (± 2.33)	5.24 (± 2.23)
PD (mm)	Baseline	2.26 (± 0.26)	2.14 (± 0.24)
	3 Months	2.24 (± 0.27)	2.12 (± 0.25)
CAL (mm)	Baseline	2.36 (± 0.30)	2.20 (± 0.22)
	3 Months	2.35 (± 0.32)	2.19 (± 0.23)
KMW (mm)	Baseline	3.38 (± 0.81)	3.42 (± 0.68)
	3 Months	4.71 (± 1.14) *ǂ	3.99 (± 0.86) *
KMT (mm)	Baseline	2.00 (± 1.02)	1.93 (± 1.01)
	3 Months	2.19 (± 0.80)	1.98 (± 1.06)

* Represents significant intra-group differences from baseline (ANOVA/Tukey test p>0.05).
ǂ Represents significant inter-group differences (ANOVA/Tukey test; p>0.05).

Radiographic outcomes

Mean horizontal crestal ridge width change in the dPTFE group was -3.36 $\pm$ 2.19mm, -2.18 $\pm$ 1.65mm and -1.50 $\pm$ 0.98mm at 1, 3 and 5 mm, respectively. Mean vertical mid-facial bone change was -1.43 $\pm$ 1.30 mm and mean vertical mid-palatal bone change was -1.50 $\pm$ 1.60 mm. For the non-ARP group, mean horizontal crestal ridge width change was -4.44 $\pm$ 2.48mm, -2.85 $\pm$ 1.91mm and -1.96 $\pm$ 1.44mm at 1, 3 and 5 mm, respectively (Table 2). No significant differences were observed between groups for volumetric alveolar bone reduction at 3 months (27.01$\pm$8.40% and 27.74$\pm$13.52% for the dPTFE and non-ARP group, respectively) as shown in Table 3.

Table 2. Radiographic data (linear vertical and horizontal alveolar bone measurements in mm) at baseline and three months post-extraction.

		Baseline	**3 months**	**Bone loss (0-3 months)**
Vertical Measurements				
Test Group	Buccal Height	5.08±1.76	6.51±1.97*	1.43±1.30 ǂ
	Palatal Height	3.34±1.51	4.84±1.28*	1.50±1.60
Control Group	Buccal Height	5.28±2.32	7.53±3.02*	2.26±2.38
	Palatal Height	3.57±1.78	5.55±1.79*	1.99±1.09
Horizontal Measurements				
Test Group	1mm	9.77±1.49	6.18±1.85*	3.36±2.19
	3mm	10.11±1.72	7.93±1.62*	2.18±1.65 ǂ
	5mm	10.04±1.75	8.54±1.62*	1.50±0.98
Control Group	1mm	9.43±1.17	4.99±2.41*	4.44±2.48
	3mm	9.67±1.30	6.82±2.31*	2.85±1.91
	5mm	9.91±1.53	7.95±1.86*	1.96±1.44

* Significant differences from baseline by ANOVA/Tukey test (P <0.05).

ǂ Significant inter-group differences by ANOVA/Tukey test (P <0.05).

Table 3. Radiographic data (bone volumetric measurement in mm^3) at baseline and three months post-extraction.

	Baseline	**3 months**	**Volumetric bone loss (0-3 months)**	**% Volumetric bone loss (0-3 months)**
Test Group	732.56±168.93	533.19±125.09*	199.38±86.91	27.01±8.40
Control Group	735.32±163.12	532.11±161.32*	203.20±108.08	27.74±13.52

* Significant differences from baseline by ANOVA/Tukey test (P <0.05).

Implant outcomes

All implants were placed without additional bone grafting augmentation procedures. The resonance frequency analysis did not detect a statistically significant difference between the groups (64.05±5.17 and 63.63±5.50, for the dPTFE and non-ARP groups, respectively) ($p>0.05$).

Immunoenzymatic outcomes

No inter-group differences were observed for DKK1, TNF-α, OPG, OC, OPN, RANKL, SOST, TRAP and OSN ($p>0.05$, Table 4).

Table 4. Mean (± SD) concentrations (pg/µl) of immunoenzymatic mediators for both groups.

Mediator	Test Group	Control Group
DKK1 ($x10^{-4}$)	10.00 (± 9.99)	14.46 (± 12.24)
TNF-α	11.94 (± 7.18)	20.13 (± 18.28)
OPG ($x10^{-3}$)	9.69 (± 9.95)	10.26 (± 8.12)
OC ($x10^{-5}$)	11.47 (± 16.35)	11.02 (± 13.01)
OPN	4.21 (± 1.33)	4.58 (± 1.60)
RANKL ($x10^{-3}$)	2.09 (± 2.18)	2.57 (± 2.55)
SOST ($x10^{-4}$)	12.83 (± 11.99)	18.26 (± 15.15)
TRAP ($x10^{-4}$)	6.56 (± 5.09)	9.40 (± 7.72)
OSN	11.50 (± 14.29)	17.11 (± 9.79)

No significant differences were detected between groups (Student T test; $p>0.05$).

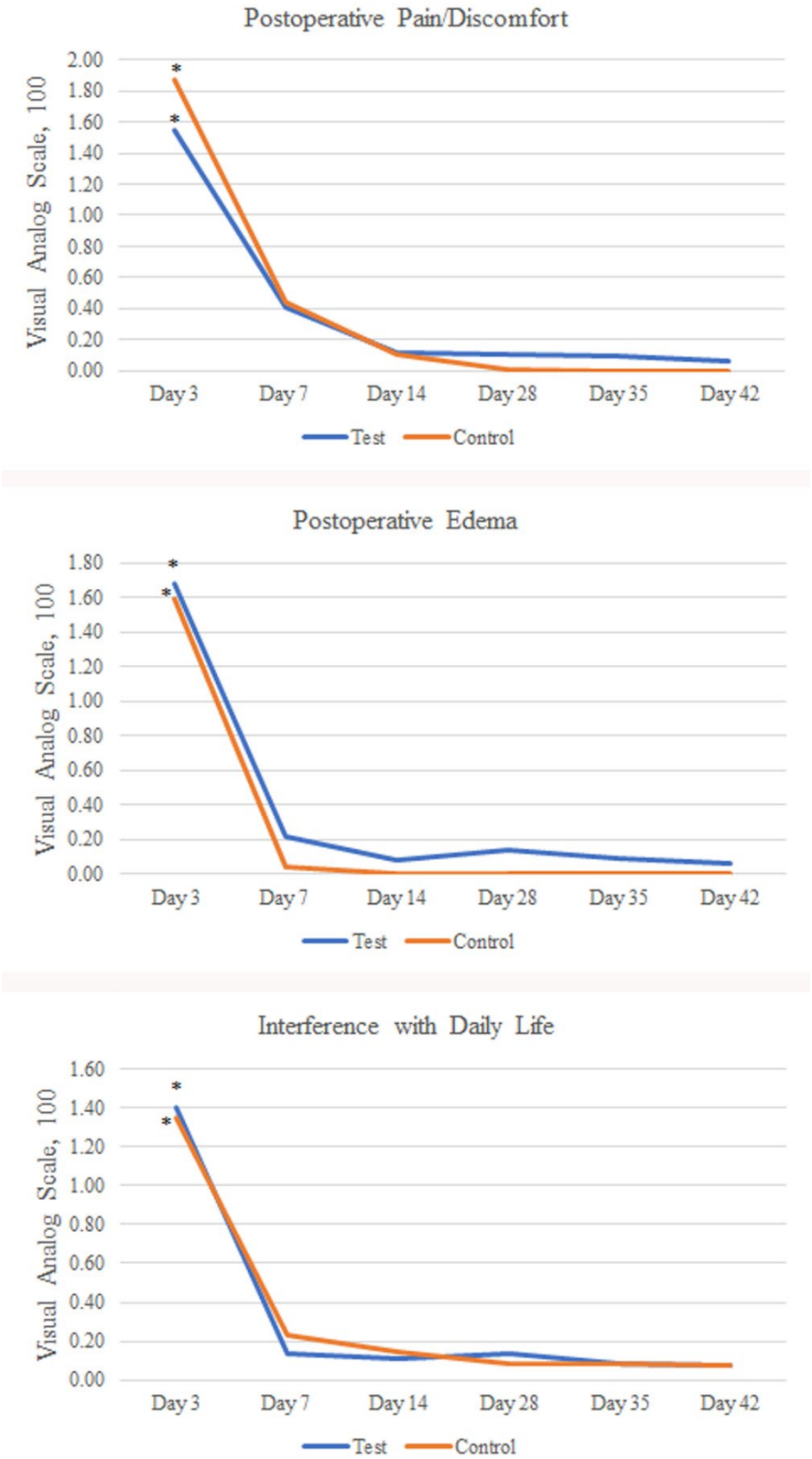
Patient-centered outcomes

Regarding the number of analgesic medications taken, no statistically significant differences were observed between groups (2.40±2.11 and 2.65±2.71, for the dPTFE and non-ARP groups, respectively) ($p>0.05$). Concerning the VAS questionnaire, a significant reduction in

the intensity of each parameter evaluated was observed (pain / discomfort, edema, and interference in daily life) from the 7th day of follow-up, in both treatments ($p<0.05$; Figure 4). However, no significant differences were observed in future follow-ups or between therapies ($p>0.05$; Figure 4). Additionally, from the questionnaire applied to assess the patient's perception of the aesthetic results after the implant provisionalization, there were no statistical differences between groups regarding the scores "very satisfied", "moderately satisfied" and "unsatisfied" (65% very satisfied, 30% moderately satisfied and 5% unsatisfied, for the dPTFE group, and 63.3% very satisfied, 31.8% moderately satisfied and 4.6% unsatisfied, for the non-ARP group) ($p>0.05$).

Figure 4. Parameters Related to Patient Perception About Therapy throughout the study.

* Represents significant intra-group differences when compared to the other time-points (ANOVA, Tukey test; $p<0.05$).



DISCUSSION

Although several studies indicate the benefits of dPTFE membranes for bone grafting augmentation procedures, there is a lack of clinical studies evaluating the use of a partially exposed dPTFE membrane in ARP procedures via socket sealing based on an evaluation of clinical parameters, radiographic measures, bone-related markers, implant-related and patient-centered outcomes. In general, the findings of this study demonstrated that the use of a dPTFE membrane partially exposed to the oral environment for ARP therapy attenuates alveolar bone resorption and contributes to the gain of KMW 3 months after tooth extraction. However, no differences in the local profile of molecules related to osteogenesis, primary implant stability, nor benefits regarding the patient-centered outcomes were observed compared to unassisted socket healing.

The main indication for ARP procedures in clinical practice is to minimize dimensional changes of the alveolar ridge after tooth extraction facilitating dental replacement therapy with dental implants. A wide variety and combination of ARP modalities have been proposed (MacBeth et al. 2017, Avila-Ortiz et al. 2019, Wongpairojpanich et al. 2021, Saito et al. 2021). However, although no specific ARP therapy has been clearly shown to be superior, ARP via socket grafting and socket sealing is recommended (Tonetti et al. 2019). According to Avila-Ortiz & Zadeh (2019), although there is no agreement on the biological plausibility supporting the combined use of graft and membranes for ARP, a hypothesis would be based on the fact that the bone grafting material occupies the space of the alveolus inducing a slower healing pattern that translates into a phenomenon of delayed bone renewal, which ultimately contributes to preserving the architecture of the alveolar bone. In addition, sealing the alveolar orifice using a barrier limits or prevents the growth of soft tissue into the bone compartment by inhibiting the rapid proliferation of epithelial cells and fibroblasts and

contributes by minimizing leakage of the graft material during the initial stages of healing, as well as preventing the infiltration of microorganisms and debris from the oral cavity.

In the present study, the dPTFE barrier was used as an ARP modality via socket sealing without socket grafting. Test group showed less vertical and horizontal bone loss compared to the control group. These findings are in agreement with previous systematic reviews and meta-analyses on this topic, demonstrating that ARP is an effective therapy to attenuate the horizontal and vertical dimensional reduction of the alveolar ridge after tooth extraction when was compared with unassisted socket healing. (Vignoletti et al. 2012, Avila-Ortiz et al. 2014, Willenbacher et al. 2016, MacBeth et al. 2017). However, the differences between the findings observed in this study could be due to the methodology used or to the use of only a barrier membrane without the addition of bone grafting material into the socket.

Bone remodeling pattern observed in this study agrees with previous clinical studies (Chappuis et al. 2015; Misawa et al. 2016, Avila-Ortiz et al. 2020), or with the highest body of evidence (2021 Couso-Queiruga et al.) demonstrating the most coronal aspect of the alveolar crest as being the most affected area. Interestingly, the total bone volumetric reduction at 3 months was similar between groups ($p>0.05$; Table 3). This observation is not in agreement with a previous study, where less alveolar bone resorption with the use of dPTFE membranes was reported (Avila-Ortiz et al. 2020,). According to the study by Avila-Ortiz and collaborators, the analysis of volumetric changes measured between the baseline period and 14 weeks after extraction revealed that the control group showed almost two times more bone reduction (−15.83±4.48%) compared to the ARP group (−8.36±3.81%) (Avila-Ortiz et al. 2020). However, the differences between studies could be explained due to the methodology used, the inclusion criteria, the use of a bone grafting material into the socket, or the removal of the dPTFE membrane at 28 days post-extraction. For example, the study by Avila-Ortiz included only sites with CAL < 1 mm and complete alveolar bone integrity after

extraction. Conversely, in this study both damaged and intact extraction sites were included. Moreover, the heterogeneity in the characteristics of the alveolar socket at the time of extraction in ARP therapies (Couso-Queiruga et al. 2021), could have influenced the findings observed in this study. Also, only ARP via socket sealing was performed in the test group. Moreover, the addition of a bone grafting material into the socket may lead to less alveolar bone resorption.

Soft tissue is also an important component for the future peri-implant phenotype (Avila-Ortiz et al. 2020). When evaluating the changes in the soft tissue components after tooth extraction, data from this trial showed a higher increase in KMW in the ARP group compare to the control group ($p<0.05$, Table 1). This finding was also reported in previous studies evaluating ARP therapies (Barone et al. 2013; Barone et al. 2014). The fact that a surgical approach avoiding vertical and/or periosteum release incisions to achieve primary wound closure was performed in this study, could have contributed to this gain in KMW. In addition, similar findings were observed in previous studies, demonstrating an increase in KMW following the use of partially exposed dPTFE membranes (Fotek et al. 2009; Barboza et al. 2014, Mandarino et al. 2018), and with a systematic review, MacBeth et al. (2017) who reported that ARP resulted in a gain of KMW when no effort to achieve primary wound closure was made. Furthermore, the use of partially exposed dPTFE membranes could be used to increase the dimensions of KMW prior to implant placement, having a positive effect on maintaining future peri-implant health and reducing biologic complications in implants (Tan et al. 2012, Avila-Ortiz et al. 2020). KMT remains stable during the healing period, which could be explained by the level where the mucosa was measured without the use of stent. Even though, transgingival probing can be considered the gold standard compared with other methods of assessment (Kloukos et al.2018, Couso-Queiruga et al. 2021).

Analysis of patient-centered outcomes showed no differences between groups concerning the number of analgesic medications taken, pain/discomfort, edema, and interference in daily life ($p<0.05$; Figure 4), corroborating data from previous studies that compared the use of ARP with dPTFE barriers compared to unassisted socket healing (Avila-Ortiz et al. 2020). Furthermore, it could be advised that this ARP modality does not increase the morbidity when compared with sites that did not receive additional therapy. Additionally, from the questionnaire applied to assess the patient's perception of the aesthetic results after the installation of the provisional implant-supported prosthesis, there were no statistical differences between the groups regarding the scores "very satisfied", "moderately satisfied" and "unsatisfied" ($p>0.05$). To the best of the author's knowledge, this is the first study that evaluates patient's perception of the aesthetic results obtained after ARP with the use of dPTFE barriers intentionally exposed to the oral environment.

Interestingly, the immunoenzymatic analysis did not show a statistically significant difference between groups in any of the analyzed bone-related markers (DKK1, SOST, TNF-α, OPG, OC, OPN, RANKL, OSN and TRAP) ($p>0.05$; Table 4). Similar to our findings, Mandarino and collaborators showed no differences in the levels of OPG/RANKL between the sites treated with dPTFE membranes compared to sites that did not receive additional treatment after tooth extraction. Furthermore, these findings corroborate and support the hypothesis that the use of dPTFE membrane does not have a detrimental effect on the healing process after ARP therapies. (Mandarino et al. 2018). These molecular findings could also reflect the clinical findings related to the primary implant stability observed since no differences in ISQ were observed between groups ($p> 0.05$). These findings agree with previous studies in this topic (Pang et al. 2016, Wongpairojpanich et al. 2021).

However, this study is not exempt from limitations. First, the heterogeneity of the extraction sites with complete bone integrity and slight or severe damage could have had an

impact in the extent and magnitude of the alveolar bone changes observed. Second, the use of dPTFE membrane for ARP via socket sealing, without the combination of a bone grafting material could also influence the outcomes. Third, components of the periodontal phenotype such as the facial bone thickness that play a role in the dimensional changes after tooth extraction, could not be measured because of the lack of socket integrity in several patients. Fourth, dPTFE membranes were removed only 28 days after tooth extraction, which could potentially influence the alveolar bone resorption in the test group. Fifth, only three months of follow-up was reported without additional information about the effect of this therapy on the peri-implant health or marginal bone loss around implants.

CONCLUSÃO GERAL

Em comparação com a cicatrização de alvéolos sem assistência, o ARP via selamento de alvéolos utilizando uma membrana de barreira de dPTFE parcialmente exposta proporcionou ganho superior em KMW e atenuou a reabsorção do osso alveolar após a extração dentária sem aumentar a morbidade. Além disso, esta modalidade de ARP poderia ser uma alternativa para o manejo do local da extração e futura reabilitação com implantes dentários.

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ANEXOS

1. TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Comitê de Ética em Pesquisa - CEP

UNIVERSIDADE PAULISTA – UNIP
Campus Indianópolis

Rua Dr. Bacelar, 1212 – 4º andar – Vila Clementino
CEP: 04026-002 – Fone: (11) 5586-4090
e-mail: cep@unip.br
Horário de funcionamento: das 08:00 às 19:00

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Caro Participante:

Gostaríamos de convidá-lo a participar como voluntário da pesquisa intitulada Impacto da exposição intencional de barreiras de PTFE-d na regeneração óssea guiada para preservação de alvéolo: Análise microbiológica, radiográfica, de parâmetros centrados no paciente, do padrão molecular de reparo ósseo e da estabilidade peri-implantar que se refere a um projeto de Doutorado do(s) participante(s) Edson Ken Matumoto e Silvia Helena Garcia Braz do(a) mestrado qual pertence ao Curso de Periodontia da Universidade Paulista.

O(s) objetivo(s) deste estudo será analisar dois tipos de técnicas para regeneração óssea com e sem barreira para posterior colocação de implantes. Os resultados contribuirão para utilização ou não de membrana para regeneração óssea.

Sua forma de participação consiste em colocação ou não de barreira exposta intencionalmente para formação óssea e colocação de implantes.

Seu nome não será utilizado em qualquer fase da pesquisa, o que garante seu anonimato, e a divulgação dos resultados será feita de forma a não identificar os voluntários.

Não será cobrado nada e não haverá gastos, decorrentes de sua participação, se houver algum dano decorrente da pesquisa, o participante será indenizado nos termos da Lei.

Considerando que toda pesquisa oferece algum tipo de risco, nesta pesquisa o risco pode ser avaliado como: baixo e o paciente poderá ter algum desconforto/dor, inchaço, interferência na vida diária (hábitos alimentares, mastigação, atividades cotidianas.

São esperados os seguintes benefícios imediatos da sua participação nesta pesquisa: Proporcionarão conhecimentos que contribuirão para a tomada de decisão sobre o uso de barreiras para preservação de alvéolo nos casos em que a colocação de implantes dentais subsequente à exodontia for necessária.

2. APROVAÇÃO DO COMITÊ DE ÉTICA

UNIVERSIDADE PAULISTA - UNIP / VICE-REITORIA DE PESQUISA E PÓS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Impacto da exposição intencional de barreiras de PTFE-d na regeneração óssea guiada para preservação de alvéolo: Análise microbiológica, radiográfica, de parâmetros centrados no paciente, do padrão molecular de reparo ósseo e da estabilidade peri-implantar

Pesquisador: EDSON KEN MATUMOTO

Área Temática:

Versão: 1

CAAE: 92062418.8.0000.5512

Instituição Proponente:

Patrocinador Principal: FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

DADOS DO PARECER

Número do Parecer: 2.818.052

Apresentação do Projeto:
De acordo

Objetivo da Pesquisa:
De acordo

Avaliação dos Riscos e Benefícios:
Riscos mínimos em relação aos benefícios

Comentários e Considerações sobre a Pesquisa:
Nada a dizer

Considerações sobre os Termos de apresentação obrigatória:
Nada a acrescentar

Recomendações:
Sem recomendações

Conclusões ou Pendências e Lista de Inadequações:
Sem pendências ou inadequações

Considerações Finais a critério do CEP:
Ao término da pesquisa enviar relatório final.

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