

UNIVERSIDADE FEDERAL DO PARANÁ

GUILHERME KLEIN PARISE

EFICÁCIA DO L-PRF NO REPARO TECIDUAL EM PROCEDIMENTOS  
ODONTOLÓGICOS CIRÚRGICOS EM PACIENTES EM USO DE BIFOSFONATOS-  
ESTUDO CASO-CONTROLE

CURITIBA

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Orientadora: Profa. Dra. Juliana Lucena Schussel

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Dedico aos pacientes oncológicos,  
principalmente àqueles que sofrem  
com efeitos adversos da medicação  
quimioterápica e conseqüentemente  
tem sua qualidade de vida reduzida;

À Odontologia;

À ciência.

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A vida humana é feita de escolhas. Sim ou não. Dentro ou fora. Para cima ou para baixo. Aí existem as escolhas que importam. Amar ou odiar. Ser um herói ou covarde. Lutar ou desistir. Viver ou morrer. Viver ou morrer: esta é a escolha importante. E não está sempre nas nossas mãos.

– Derek Shepherd (Grey's Anatomy)

## RESUMO

A osteonecrose induzida por medicamentos é um efeito adverso de medicações anti-resorptivas e anti-angiogênicas muito utilizadas no controle de doenças ósseas metabólicas, como a osteoporose, e no controle de doença oncológica com metástases ósseas. Seu diagnóstico é estabelecido a partir da ocorrência de exposição óssea intra-bucal há pelo menos 8 semanas, sem histórico prévio de radioterapia em região de cabeça e pescoço e uso ou história prévia de utilização deste tipo de medicações. O tratamento ainda é bastante controverso na literatura mundial, porém evidências mostram que o tratamento cirúrgico local, realizado de forma precoce, com adição de membranas de fibrina rica em plaquetas e leucócitos (L-PRF) promove adesão, proliferação e migração de células que irão aumentar as concentrações de fatores de crescimento como PDGF, TGF e IGF, entre diversos outros. O objetivo desta dissertação foi o de discutir as diversas opções terapêuticas disponíveis na literatura atual a partir de um caso de sucesso realizado em um paciente em tratamento de mieloma múltiplo, utilizando ácido zoledrônico e com histórico de osteonecrose induzida por medicações após extração dentária. Com o sucesso deste caso foi realizada uma revisão integrativa da literatura com o objetivo de realizar um levantamento de todos os tratamentos indicados pela literatura e seus respectivos índices de sucessos e/ou insucessos. Nesta revisão avaliamos que o tratamento cirúrgico precoce possui os maiores índices de sucesso em todos os estágios da lesão e que o L-PRF potencializa e acelera a cicatrização dos tecidos moles envolvidos com a necrose. Com a revisão integrativa realizada optou-se em avaliar a real eficácia do L-PRF através de um estudo caso-controle com 20 pacientes portadores ou com alto risco de desenvolvimento da osteonecrose em um hospital oncológico de referência na cidade de Curitiba/PR. Em suma o tratamento cirúrgico local com a utilização de membranas de L-PRF se mostrou eficaz em todos os grupos avaliados, porém com maior destaque em pacientes que ainda não haviam desenvolvido a lesão mas que necessitavam de extração dentária. Dessa forma a utilização de L-PRF na prevenção e no tratamento das osteonecroses pode trazer excelentes resultados e devolver qualidade de vida à estes pacientes sem a necessidade de tratamentos com alto custo financeiro, visto que o L-PRF tem baixo custo, fácil obtenção e livre de efeitos colaterais.

Palavras-Chave: osteonecrose associada aos bifosfonatos; fibrina rica em plaquetas; resultado do tratamento.

## ABSTRACT

Medication-related osteonecrosis of the jaws is an adverse effect of anti-resorptive and anti-angiogenic medications widely used to control metabolic bone diseases, such as osteoporosis, and to control cancer disease with bone metastases. Its diagnosis is established based on the occurrence of intra-oral bone exposure for at least 8 weeks, with no previous history of radiotherapy in the head and neck region and use or previous history of use of this type of medication. The treatment is still quite controversial in the world literature, but evidence shows that local surgical treatment, performed early, with the addition of fibrin membranes rich in platelets and leukocytes (L-PRF) promotes adhesion, proliferation and migration of cells that will increase concentrations of growth factors such as PDGF, TGF and IGF, among many others. The aim of this dissertation was to discuss the various therapeutic options available in the current literature from a successful case performed in a patient undergoing treatment for multiple myeloma, using zoledronic acid and with a history of drug-induced osteonecrosis after tooth extraction. With the success of this case, an integrative literature review was carried out in order to carry out a survey of all treatments indicated in the literature and their respective success and/or failure rates. In this review, we evaluated that early surgical treatment has the highest success rates at all stages of the injury and that L-PRF enhances and accelerates the healing of soft tissues involved with necrosis. With the integrative review carried out, it was decided to evaluate the real efficacy of L-PRF through a case-control study with 20 patients with or at high risk of developing osteonecrosis in a reference cancer hospital in the city of Curitiba/PR. In short, local surgical treatment with the use of L-PRF membranes proved to be effective in all groups evaluated, but more prominently in patients who had not yet developed the lesion but required tooth extraction. Thus, the use of L-PRF in the prevention and treatment of osteonecrosis can bring excellent results and return quality of life to these patients without the need for treatments with high financial cost, since L-PRF is low cost, easy to obtain and free of side effects.

Key-words: bisphosphonate-associated osteonecrosis of the jaw; platelet-rich fibrin; treatment outcome.

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## 1 INTRODUÇÃO

A osteonecrose dos maxilares associada a medicamentos (ONAM) é um potencial efeito adverso grave da maioria das drogas antirreabsortivas utilizadas em pacientes oncológicos com metástases ósseas, mieloma múltiplo, bem como na osteoporose primária e secundária. Tem se tornado mais frequente ao longo destas últimas duas décadas não apenas para cirurgiões-dentistas, mas também para os oncologistas e outras áreas envolvidas com a oncologia, como ginecologistas, urologistas e cirurgiões-gerais. (BRUCKMOSER et al., 2021) Em 2003, foi relatado o primeiro caso de osteonecrose de mandíbula como efeito adverso desses medicamentos em pacientes com câncer. (MARX, 2003)

Os bisfosfonatos (BFs) são os medicamentos antirreabsortivos mais utilizados no manejo de doenças relacionadas ao câncer, como a prevenção de malignidades ósseas metastáticas, e também são utilizados no tratamento e prevenção da osteoporose (HE et al., 2020). Ao longo dos anos, outras classes de medicamentos não-BF (medicamentos antirreabsortivos ou antiangiogênicos) têm sido relacionadas a características clínicas de exposição óssea na mandíbula (FERNANDO DE ALMEIDA BARROS MOURÃO et al., 2020). Com isso, em 2014, a *Association of Oral and Maxillofacial Surgeons* (AAOMS) renomeou a complicação como 'osteonecrose da mandíbula associada a medicamentos' (ONAM). (RUGGIERO et al., 2014)

Os BPs atuam diminuindo o suporte vascular local e regulando o metabolismo ósseo, reduzindo a ação dos osteoclastos e diminuindo a angiogênese afetando a remodelação óssea e deposição de matriz óssea fisiológica. (MACIEL et al., 2020) Portanto, uma interrupção ou descontinuação da medicação com bisfosfonatos (“*drug holiday*”) não leva ao efeito terapêutico desejado. (STELLER et al., 2019) Ao longo desta última década a dosagem pré-operatória dos níveis de telepeptídeo carboxiterminal de colágeno tipo I (CTX), um bioproduto da remodelação óssea, tem sido utilizado como preditor do risco de desenvolvimento pós-operatório de ONAM, bem como fator prognóstico. Porém, estudos atuais apontam que a dosagem deste tipo de telepeptídeo não possui confiabilidade na predição de desenvolvimento de osteonecrose após procedimentos odontológicos em pacientes em uso de medicações antirreabsortivas. (SALGUEIRO et al., 2019)

A mandíbula é mais predisposta ao desenvolvimento de ONAM devido seu maior nível de *turn over* ósseo e maior facilidade de infecção bacteriana através dos dentes e da gengiva (KIM et al., 2020).

Um dos aspectos mais discutidos e controversos dessa complicação são os fatores de risco, mais comumente associados à terapia com bifosfonatos, como tratamento odontológico invasivo, doenças concomitantes e hábitos nocivos. Esses fatores de risco podem ser classificados em três grupos: 1. Fatores de risco relacionados ao medicamento (tipo de medicamento, dose, frequência e duração do tratamento), 2. Fatores de risco associados a doenças dentárias e/ou procedimentos odontológicos (extração dentária, colocação de prótese dentária, colocação de implante, infecção local ou trauma ósseo / tecidual e procedimentos periodontais (lesão do periósteo) e 3. Outros fatores de risco (idade, sexo, tipo de doença oncológica, uso de tabaco e álcool e corticosteroides). (HRISTAMYAN et al., 2021)

O diagnóstico clínico da ONAM segue três condições obrigatórias: presença de área de exposição óssea ou fístula intra ou extra-oral persistente por oito semanas ou mais em pacientes sem história de radioterapia que foram ou estão sendo tratados com agentes antirreabsortivos e/ou antiangiogênicos. (RUGGIERO et al., 2014) Radiograficamente, visualização da lâmina dura, esclerose óssea com aparência de favo de mel, ausência do espaço do ligamento periodontal, aumento do espaço do ligamento periodontal em casos avançados, mudanças escleróticas, e alvéolos dentários sem evidência de regeneração óssea são sinais importantes de necrose. (KRIEGER et al., 2013)

A ONAM pode ser difícil de tratar e pode causar dor significativa e redução da qualidade de vida (TORNIER et al., 2021). Muitos estudos estabeleceram que métodos preventivos de higiene bucal combinados com práticas eficazes de saúde bucal estão associados a uma taxa mais baixa de ONAM. (YAROM et al., 2019) Quando se trata de tratamento, não existe um padrão de cuidado definitivo e o tratamento mais eficaz ainda é controverso. As opções de tratamento são classificadas em terapias conservadoras, cirúrgicas e adjuvantes não cirúrgicas, podendo ser utilizadas em combinações.(YÜCE; ADALI; IŞIK, 2021) AAOMS descreve que a primeira escolha de tratamento é uma abordagem conservadora, incluindo debridamento local e desinfecção com enxágue antimicrobiano e/ou antibioticoterapia sistêmica, e quando o tratamento conservador não tem resposta, a terapia cirúrgica, como desbridamento ósseo, sequestrectomia ou ressecção é

recomendada.(RUGGIERO et al., 2014) Atualmente várias publicações relatam que em todos os estágios da necrose o tratamento cirúrgico é mais eficaz do que a conservadora, comprovando o sucesso da terapia cirúrgica em estágio inicial. (RUPEL et al., 2014)

Os concentrados de plaquetas autólogos têm sido usados no campo oral e maxilofacial por mais de 20 anos e, em 2007, foram usados pela primeira vez na ONAM. (INCHINGOLO et al.,2017) Existem quatro subtipos principais de derivados de plaquetas, classificados por suas propriedades de fibrina e células: plasma rico em plaquetas (PRP); plasma rico em plaquetas e leucócitos (L-PRP); fibrina rica em plaquetas (PRF); e fibrina rica em plaquetas e leucócitos (L-PRF).(SZENTPETERI et al., 2020) A base do L-PRF é uma rede de fibrina tridimensional com trombócitos, leucócitos e células-tronco incorporados, também inclui uma ampla variedade de fatores de crescimento, citocinas e proteínas. (BENNARDO et al., 2020)

## 1.1 OBJETIVOS

### 1.1.1 Objetivo geral

Avaliar a eficácia da utilização de membranas de L-PRF na prevenção e no tratamento das necroses ósseas de mandíbula e maxila associadas a medicamentos.

### 1.1.2 Objetivos específicos

Realizar uma revisão integrativa da literatura sobre os tratamentos preconizados para a osteonecrose associada a medicamentos

Avaliar clinicamente o protocolo de prevenção de osteonecrose associada a medicamentos após cirurgias odontológicas;

Avaliar clinicamente o protocolo de tratamento de osteonecrose associada a medicamentos;

Avaliar clinicamente o uso do L-PRF no processo de cicatrização em osteonecroses associadas à medicamentos.

## 2 ARTIGO 1

### THE ROLE OF FIBRIN RICH PLATELETS AND LEUKOCYTES (L-PRF) IN THE MEDICATION-RELATED OSTEONECROSIS OF THE JAW: REPORT OF PREMAXILLA NECROSIS

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#### **ABSTRACT**

Bisphosphonates (BPs), antiresorptive and antiangiogenic drugs are used to prevent metastatic bone cancers in prostate cancer, breast cancer and multiple myeloma and to treat osteoporosis and Paget's disease. Recently, in 2003 the first case of osteonecrosis of the jaws was induced, hitherto by bisphosphonates, but a few years later it was shown that other medications were also responsible for the development of this type of necrosis. Thus, in 2014 there was a change in the name for medication-related osteonecrosis of the jaws (MRONJ). Since then, the treatment for this type of necrosis is quite controversial in the world literature, and there is still no protocol for established treatment, be it clinical or surgical. The objective of this work is to demonstrate the efficacy of platelet and leukocyte-rich fibrin membranes

(L-PRF) after curettage of necrotic bone tissue in the management of drug-related jaw osteonecrosis, since they have innumerable biological benefits such as large amount of growth factors and cytokines, hemostatic capacity, angiogenesis capacity, and has been shown to accelerate and improve results in hard and soft tissue wound healing. The patient presented MRONJ and have been treated with surgical necrotic bone debridement, placement of L-PRF in the affected site and primary closure. Patient were followed up clinically and radiographically until total mucosal coverage of the necrotic bone was achieved.

**KEYWORDS:** Platelet-Rich Fibrin; Osteonecrosis; Maxilla; Multiple Myeloma; Diphosphonates

## INTRODUCTION

Medication-related osteonecrosis of the Jaw (MRONJ) is a severe adverse drug reaction, consisting of progressive bone destruction in the maxillofacial region of patients being a side effects of the antiresorptive and antiangiogenic therapies<sup>1</sup>. Was first reported in 2003 after intravenous administration of zoledronate and pamidronate in patients with multiple myeloma and metastatic breast cancer<sup>2</sup>.

The major cause of MRONJ occur is related to tooth extraction. However, in most cases it is not clear if the tooth extraction causes development of MRONJ. Nowadays it is proven that periodontitis and mucosal lesions such as pressure marks, smoking, and corticoids also represent risk factors<sup>3</sup>.

The clinical manifestations of MRONJ has been classified by AAOMS since 2009 and has been modified in 2014. To be considered to have MRONJ the patients must present the following clinical characteristics: Current or previous treatment with antiresorptive or antiangiogenic agents; Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws<sup>4</sup>.

The complex topic of management of this condition will depend on stage of the necrosis and patient's symptoms. There are no definitive guidelines as to how we should approach management of MRONJ. What we know is that non-surgical therapy is employed in mild disease or symptoms (prevention infection and symptom

control). Surgical therapy on the other hand, is reserved for larger, more painful, progressive and infected areas of necrosis and where conservative management has failed<sup>5</sup>.

Because of this, new alternative therapies has emerged, such as the use of laser therapy, hyperbaric oxygen, ozone therapy and platelet concentrates, being this last technique one of the newest and promising treatments for the management of MRONJ<sup>6</sup>. The Fibrin rich Platelets and Leukocytes (L-PRF) is a second-generation of autologous growth factors, wich encourages healing and is proposed to be associated with effective and early organization of bone substance and bone volume percentage. Moreover, L-PRF is a platelet concentrate with leukocytes in dense fibrin matrix, wich can be conveniently prepared from autogenous non anti-coagulated blood when centrifuged<sup>7</sup>.

## **CASE REPORT**

64-year-old male patient was referred to Department of Oral and Maxillofacial Surgery of the Erasto Gaertner Hospital with complaints of bone exposure in the premaxilla wich arrised after tooth extraction (Figure 1). Medical history showed that patient uses intravenous Zoledronic Acid (Zometa<sup>®</sup>) once a month due multiple myeloma since February 2017 and had teeth extractions five months before referring to our service. Computed Tomography (CT) examination revealed a poorly defined hypodensity area in the pre-maxilla region (Figure 2). With the help of anamnesis, clinical and CT examinations, MRONJ diagnosis was made wich caused by the treatment of multiple myeloma with zoledronic acid. As a medical treatment, mouthwash (0.12% Clorhexidine Gluconate) with a combination of Pentoxifylline and Tocopherol. Oral Clindamycin started as soon as the diagnosis was made advised for at least two weeks.

After consultations and consents, the patient was planned to undergo general anesthesia and L-PRF application after the lesion debridement. A large mucoperiosteal flap was elevated in the exposing bone tissue area. The area of the large necrosis was excised till a firm bone surface was left (Figure 3) and the application of L-PRF obtained from patient's blood that drewed preoperatively followed by primer wound closure (Figure 4). To prepare the L-PRF, 80mL of peripheral blood was collected from the antecubital vein into a 10 mL glass tube with no anticoagulant, and the blood samples were centrifuged at 2700rpm for 12

minutes. After centrifugation, 8 pieces of L-PRF were obtained from the middle of the tube (Figure 5). All membranes were arranged in layers covering the entire surgical bone bed (Figure 6). No suture removal was performed due to the use of absorbable suture and the Pentoxifylline and Tocopherol were not discontinued after surgical procedure. One month after the operation, it was determined that the mucosa in the area where osteonecrosis used to present was healthy but a small tissue dehiscence was observed, so follow-up period begun with monthly controls. Clinical and CT scans at the postoperative 2 years follow-up revealed healthy tissue, tissue dehiscence resolution (Figure 7 and 8) and patient's symptoms had passed. After that, the patient maintains semiannual follow-ups.

## DISCUSSION

Biphosphonates are currently the main class of medications used to treat osteoporosis and other diseases characterized by increased bone resorption<sup>8</sup>. Acting through two mechanisms of action related to antiosteoclastic and antiangiogenic activity alter the mechanism of bone tissue in several levels, inhibiting reabsorption and decreasing bone turnover<sup>9,10,11,12</sup>. Other drugs class has been utilized with similar indications than bisphosphonates, the monoclonal antibodies. Neutralizing the receptor activator of nuclear factor  $\kappa$ B ligand (RANKL), a member of tumor necrosis factor receptor superfamily. This factor is produced by osteoblasts and activates the RANK receptor on osteoclast precursor cells and osteoclasts. The RANKL-RANK signaling pathway is essential for the differentiation, function, and survival of osteoclasts<sup>13,14</sup>.

Nowadays the MRONJ staging is based on the Classification proposed by The American Association of Oral and Maxillofacial Surgeons (AAOMS) as showed in the Table 1 and its treatment still controversial because surgical procedures may induce disease progression and there is no a consensus regarding the best treatment<sup>12,15,16,17,18,19</sup>.

Platelet-rich fibrin (L-PRF) for specific use in oral and maxillofacial surgery was first developed in France by Choukroun et al. L-PRF is a new generation of platelet concentrates that is not only inexpensive and autologous, but also does not require any biochemical modifications compared to other platelet concentrations. Act as a bioactive surgical additive to regulate inflammation, reduce the healing time and stimulation of chemostactic agents<sup>5,6,15,20,21</sup>.

These concentrates allows the release of growth factors over a prolonged time (about 28 days), resulting in an acceleration in healing, reducing the risk of contamination, edema and postoperative pain, it helps in homeostasis, prevents tissue dehiscence and favors the remodeling and healing of both soft and hard tissues, increase tissue vascularization, overtaking one of the major factors in pathogenesis of MRONJ, the lack of vascularization. For these reasons, some researches propose applying L-PRF as a preventive measure in surgical interventions or as a treatment for cases of established MRONJ<sup>6,12,18,19,22,23,24,25,26</sup>.

Dinca et al. performed removal of the bone sequestrations and curettage in the bone tissue until clear bleeding appeared from the subjacent bone. After that, bone cavities were filled out with L-PRF clots. No postoperative complications were observed and all the 10 patients were treated successfully without evidence of exposed bone.

## **CONCLUSION**

The combined sequestrectomy and L-PRF has shown potential and good results for MRONJ healing but better communication from the prescribing physician to the dental surgeon is necessary to establish orientation and preventive treatment before initiation of the therapy with bisphosphonates or monoclonal antibodies. Furthermore the L-PRF is encouraging results and open a new path in the treatment of this pathology.

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Table 1 - Staging and treatment strategies of BRONJ according to AAOMS<sup>4</sup>

<b>Staging of BRONJ</b>		<b>Treatment modalities</b>
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms	Systemic management, including the use of pain medication and antibiotics
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	-Antibacterial mouth rinse -Clinical follow-up on a quarterly basis -Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	-Symptomatic treatment with oral antibiotics -Oral antibacterial mouth rinse -Pain control -Debridement to relieve soft tissue irritation and infection control
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e. inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor	-Antibacterial mouth rinse -Antibiotic therapy and pain control -Surgical debridement/resection for longer term palliation of infection and pain



Figure 1 - Maxillary osteonecrosis in a patient with multiple myeloma treated with Zometa® (Zoledronic Acid).

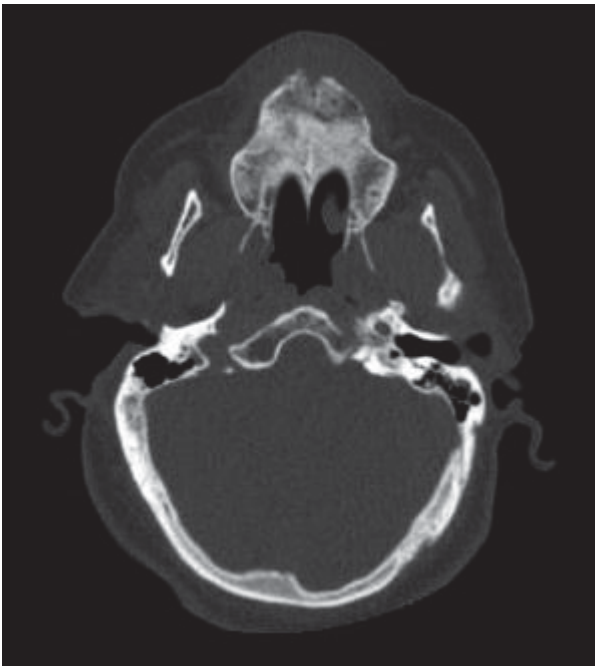


Figure 2 - Computed tomography (CT) examination revealed osteonecrosis in the premaxillary region, with an ill-define

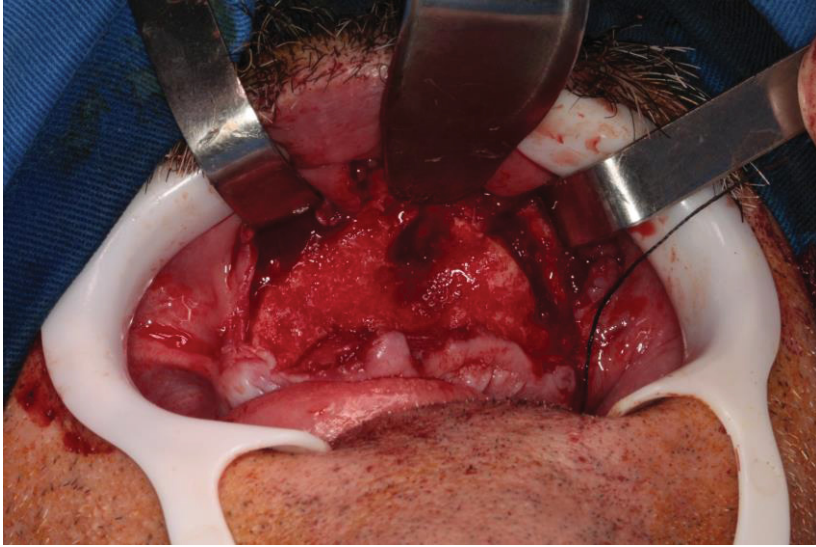


Figure 3 - Surgical bed after curettage of necrotic bone with removal of anterior nasal spine.



Figure 4 - PRF membrane after compression by using PRF box.



Figure 5 - Application of fibrin rich in leukocytes and rich in platelets on the surgical bone bed.

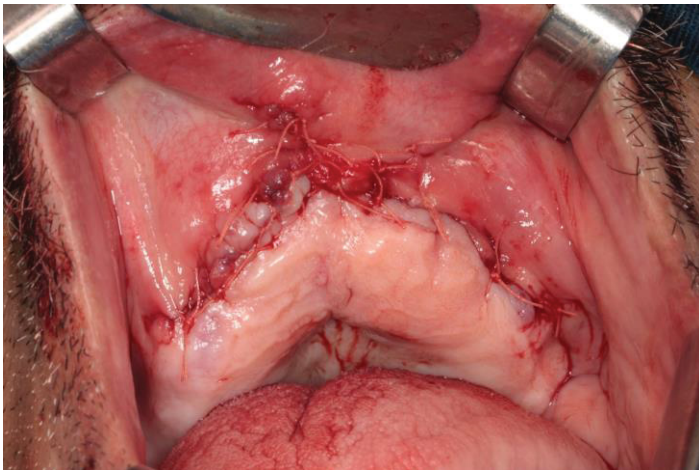


Figure 6 - Immediate post-operative after closure with use of absorbable suture.



Figure 7 - Post-operative with the formation of healthy tissue.



Figure 8 - Computed Tomography (CT) of the patient showed the regeneration of the necrotic bone in 24 months follow-up.

### 3 ARTIGO 2

#### DIFFERENT FORMS OF TREATMENT FOR OSTEONECROSIS OF THE JAWS RELATED TO THE USE OF MEDICATIONS: INTEGRATIVE REVIEW

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#### ABSTRACT

**Background:** Medication-related osteonecrosis of the jaws is a serious complication of bone-modifying agents and angiogenesis inhibitors agents. Its aetiology is not fully understood and is currently experiencing a considerable increase in the incidence of this complication in dental practice.

**Objective:** Review in the available literature the most effective treatments reported until now. **Design**

**and Settings:** An integrative review of the literature was carried out looking for articles on MRONJ treatments. **Methods:** Articles such as case reports, clinical research and systematic reviews on MRONJ treatments, published on the last ten years, indexed in PubMed, Medline and Scielo databases were selected after inclusion and exclusion criteria were applied. Type of treatment, time of follow-up and resolution were analyzed.

**Results:** After the assessment of 816, nine articles were included. The most frequent treatments reported in the literature were laser, ozone, L-PRF, teriparatide, hyperbaric oxygen, surgical treatments such as guided debridement, necrotic bone resection, and also non-surgical treatments. **Conclusion:** MRONJ surgical treatment is more effective even when early approach is conducted and L-PRF is a greater adjuvant of surgical treatment decreasing the post-op recurrence of bone exposure and increasing quality of newly formed mucous tissue.

**KEYWORDS:** Osteonecrosis; Therapeutics; Bisphosphonates

## INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) is diagnosed when there is a bone exposure or an intra or extraoral fistula that persists for more than 8 weeks with current or previous antiresorptive or antiangiogenic therapy without a history of radiotherapy in the area, or obvious metastatic disease.<sup>6</sup>

MRONJ was first reported in 2003, but its pathophysiology has not been fully understood.<sup>5,9</sup> The medications cause inhibition of osteoclastic bone resorption and remodeling, as well as inhibition of angiogenesis leading to soft tissue toxicity, and immune dysfunction.<sup>2</sup> Bisphosphonates are the most frequent medications associated with this complication. The high concentration of bisphosphonates after administration is believed to lead to apoptosis of osteoclasts in the alveolar process and decrease the tissue response to bacterial invasions, due to its influence on the immune system<sup>2</sup>. In addition to these factors, bisphosphonates can be released from the bone through acidification of the medium, which can be caused by an oral infection or during dentoalveolar surgery, contributing to osteonecrosis<sup>9</sup>. As the disease progresses, it can lead to severe spontaneous pain, purulent drainage, gingival ulceration with exposed bone, extra or intraoral fistula, and pathological fracture, with a consequent significant reduction in quality of life<sup>4,5</sup>. The MRONJ is associated with cumulative doses, duration of treatment, and type of medication administered.<sup>3</sup> The main risk factors for the development of MRONJ include dental trauma, tooth extraction, tobacco use, and concomitant inflammatory periodontal disease.<sup>10</sup> For diagnosis and staging, radiographic exams must be included. Diffuse sclerosis, cortical erosions, and extraction alveoli that do not heal may be the first signs of MRONJ seen on panoramic radiographs, for example. When in more advanced stages, thickening of the hard lamina, osteolysis, pathological fractures, and formation of bone sequestration are observed.<sup>9</sup>

There is no gold standard treatment so far. Some therapies, medications, and surgical techniques were reported in the literature, but the success rate differs in the literature. This integrative literature review aims to review MRONJ treatments reported and to assess which treatments have obtained the highest success rates.

## METHODS

For this integrative review, a search was carried out in the PubMed / Medline and Scielo databases, selecting articles in English and Portuguese. The descriptors and their combinations used for the search were "osteonecrosis"; "treatment"; "MRONJ". The inclusion criteria defined for the selection of articles were articles with at least 10 patients, articles published and indexed in the referred databases in the last ten years, articles where the main subject were the treatment of MRONJ, systematic reviews, articles published in periodic with high scientific rigor, and articles in which the complete resolution criterion for MRONJ was the presence of normal mucosa without any sign of

exposed bone. Clinical case reports with less than 10 patients, animal studies and laboratory analysis as well as studies related to the prevention of MRONJ were disregarded. Also, to complete and ensure the accuracy of the literature review, an additional manual search was performed in the references of the articles included in the study to find possible studies that were of interest to the research

## **RESULTS**

The search in the databases resulted in 816 articles found using the descriptors and their combinations. After applying the inclusion and exclusion criteria, nine articles were included. The treatments reported as well as other information found in the articles are shown in Table 1. The most frequent treatments reported in the literature were laser, ozone, L-PRF, teriparatide, hyperbaric oxygen, surgical treatments such as guided debridement, necrotic bone resection, and also non-surgical treatments.

The treatment that reported success in most cases were bone debridement with closure in several layers with about 95.2% resolution rate, followed by surgery with necrotic bone resection, with about 89.3% of success. Studies using laser surgery reported rates as high as 100% resolution in stage 1 MRONJ and 83% in stage 2.

On the other hand, the treatments that showed the lowest success rates were non-surgical treatments with around 33%. Among these treatments are hyperbaric oxygen treatment with a success rate of 26.7%, laser treatment 45.3% and ozone treatment 57.8%.

## **DISCUSSION**

MRONJ is a complex complication and there is still no gold standard protocol for the management and treatment of this condition, despite a large number of articles available in the literature. This fact is probably due to the lack of standardized clinical studies that demonstrate the success or failure of the different therapies available. This study aimed to analyze the literature in search of reports that showed successful treatments for MRONJ.

MRONJ's approach should be multidisciplinary and include an appropriate dental evaluation before starting anti-resorptive or anti-angiogenic drugs to reduce local risk factors.<sup>2</sup> Therefore, MRONJ treatment is challenging because management depends on the stage of the disease and may include conservative approaches, such as oral and antibiotic rinses or minimally invasive ones such as sequestrectomy, debridement and also major surgical intervention such as resection, as well as the discontinuation of the antiresorptive agent<sup>10</sup>. Other adjunct forms of treatment, such as leukocyte-rich fibrin, ozone therapy, hyperbaric oxygen therapy, therapy to low-intensity laser, have been reported in the literature.

It is possible to find several different therapeutic approaches in the literature with a high heterogeneity between designs and protocols, which led to some limitations in this review. Nonetheless, many strategies have shown success in healing the mucosa.

The assessment of the studies showed that when treatment option did not consider the stages of the disease, the non-surgical therapy showed less efficacy for the total healing of the mucosa. Surgical treatment and treatment with L-PRF provided the best results, reaching up to 92% of MRONJ's complete resolution. Laser surgeries also showed promising results in different stages of the disease.

In order to evaluate surgical treatment, we divided in three categories: conservative surgery, extensive surgery and laser surgery considering the stages of the disease. Rupel et al. (2014) demonstrated that conservative surgical procedures had lower success rates in advanced disease stages. On the other hand, for extensive surgery, regardless of the stage of the disease, the results exceed 80% in the complete resolution of the lesion.

In general, better results were achieved when surgical treatments were performed such as bone debridement and closure in several layers, necrotic bone resection and fluorescence- guided surgery. Among these, bone debridement and closure in several layers showed the highest rate of complete resolution, 90.4%. On the other hand, in a study by FLIEFEL.et al. (2015), which addressed the technique of guided debridement, the results were not as favorable, with about 48% of success rate<sup>12</sup>. Once again, the lack of standardization of studies and even of the surgical techniques used, lead to a difficulty in establishing the best level of scientific evidence for MRONJ treatment.

The same occurred in laser surgeries, using the ErCrYSGG and Er: YAG lasers which excellent results were observed when the stages of the disease were analyzed separately, rates of 100%, 83%, 100% for stages 1, 2 and 3, respectively. RUPEL et al. (2014). Other study showed different results with 45.5% of cases with complete lesion resolution, however it did not distinguish the stages of MRONJ and also did not inform which type of laser was used in the surgeries, again making it difficult to compare.

Regarding the L-PRF technique as a complement to surgery, the healing results are very similar and positive when compared to different studies, in which the rates of complete resolution exceed 75% in all studies observed KIM et al. (2014), PARK et al.(2017), CURI et al. (2011).

L-PRF techniques showed little variation among studies, and some presented the association of the use of L-PRF with BMP-2. Although, high resolution rates are observed in the different studies evaluated.

## CONCLUSION

Surgical approach to MRONJ lesions appears to be the most effective in all stages of the disease. In addition, among the surgical techniques reported, laser surgery presented the best results.

However, more randomized and controlled studies are needed to confirm this statement since there is a great variety of laser used and can influence these results. L-PRF used as an adjunct to surgery shows more constant and good results in the complete resolution of MRONJ. Conservative treatment protocols may control the disease while the patient is not fit for surgical treatment.

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**Table 1.** Studies reporting MRONJ treatment, included in the analysis.

Treatment	Papers	Number of cases	Total Resolution	Partial Resolution	Treatment failure	Follow-up
L-PRF	KIM et al., 2014	34	26 (77%)	6 (18%)	2 (6%)	6 months
	PARK et al., 2017	55	51 (92.3%)	N/I	N/I	4 months
	CURI et al., 2011	25	20 (80%)	N/I	N/I	36 months
Surgical Treatment	EGUCH et al., 2017	28	25 (89.3%)	None	3 (10.7%)	6 months
	FLIEFEL et al., 2015 *	25	12 (48%)	10 (40%)	2 (8%)	N/I
	VOSS et al., 2012	21	19 (90.4%)	N/I	1 (4.7%)	16 months
	OTTO et al., 2016	54	47 (87%)	5 (9.3%)	1 (1.9%)	N/I
	RUPEL et al., 2014 *	513	427	N/I	N/I	N/I
	FLIEFEL et al., 2015 <sup>1</sup> *	776	301 (39.2%)	N/I	22 (2.9%)	N/I
Non-Surgical Treatment	EGUCH et al., 2017	24	8 (33%) ok	None	16 (66.7%)	6 months
	ALTAY et al., 2014	11	7 (63.7%)	N/I	N/I	15.5 months
	FLIEFEL et al., 2015 *	160	93 (57.8%)	27 (16.8%)	8 (5.0%)	N/I
	FLIEFEL, R et al., 2015 *	45	12 (26.7%)	8 (17.8%)	N/I	N/I
	FLIEFEL et al., 2015 *	27	22 (81.5%)	5 (18.5%)	0 (0%)	N/I
	RUPEL et al., 2014 *	77	18 (19%)	N/I	N/I	N/I
	FLIEFEL et al., 2015 *	322	146 (45.3%) ok	18 (5.6%)	37 (11.5%)	N/I

N/I: Not informed

\* Information from studies that were included on a systematic review

#### 4 ARTIGO 3

### EFFICACY OF FIBRIN-RICH PLATELETS AND LEUKOCYTES (L-PRF) IN TISSUE REPAIR IN SURGICAL ORAL PROCEDURES IN PATIENTS USING BISPHOSPHONATES – CASE-CONTROL STUDY

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#### ABSTRACT

Medication-related Osteonecrosis of the Jaws (MRONJ) is a complication that develops in patients who use or have used anti-resorptive or anti-angiogenic medications for the treatment of bone metabolic disease and bone metastases. Clinically, MRONJ is characterized by the appearance of an inflammation in soft tissues and exposure of necrotic bone tissue in mandible or maxilla, for a period of eight weeks, in patients with no history of head and neck radiotherapy that were being or are being treated with anti-resorptive and/or antiangiogenic agents. The Fibrin rich platelets and leukocytes (L-PRF) membrane has been used as an alternative for MRONJ prevention. The aim of this study was to evaluate the use of L-PRF in prevention and treatment of bone necrosis. The patients included had MRONJ diagnosis confirmed after clinical and radiographic examination and patients whose only therapeutic option was dental extraction. Twenty patients were included in the study and were divided in three groups. Two patients were removed from the study due to previous history of pentoxifylline and tocopherol use. The result of surgical treatment was successful in 57% in group 1, 100% in group 2 and 80% in group 3. L-PRF is a autologous biomaterial that allows the release of growth factors for a prolonged time, resulting in an acceleration of healing, reducing the risk contamination, edema, postoperative pain. Although it can be a great ally in the prevention and treatment of MRONJ.

Key-words: Bisphosphonate-Associated Osteonecrosis of the Jaw; Platelet-Rich Fibrin; Treatment Outcome;

## INTRODUCTION

Bisphosphonates (BPs) are the most used antiresorptive medication in the management of cancer-related conditions, such as the prevention of bone metastatic malignancies, and are also used for the treatment and prevention of osteoporosis<sup>1</sup>. In 2003, the first case of osteonecrosis of the jaws as an adverse effect of these medications was reported in cancer patients<sup>2</sup>.

Over the years, other classes of non-BP drugs (antiresorptive or antiangiogenic medications) have been related to clinical features of bone exposure in the jaw<sup>3</sup>. Based on that, in 2014 the Association of Oral and Maxillofacial Surgeons (AAOMS) renamed the complication as 'medication-related osteonecrosis of the jaw' (MRONJ)<sup>4</sup>.

BPs act to decrease local vascular support and regulating bone metabolism, thereby reducing the action of osteoclasts and decreasing angiogenesis affecting bone remodeling and deposition of physiological bone matrix<sup>5</sup>. Therefore, an interruption or discontinuation of bisphosphonate medication (drug holidays) does not lead to the desired therapeutic effect<sup>6</sup>.

One of the most discussed and controversial aspects of this complication are the risk factors, which are most commonly associated with bisphosphonates therapy, such as invasive dental treatment, concomitant illness and harmful habits. These risk factors can be classified into three groups: 1. Risk factors related to the medication (type of medication, dose, frequency and treatment duration), 2. Risk factors associated with dental disease and/or dental procedures (dental extraction, denture placement, implant placement, local infection or bone/tissue trauma, and periodontal procedures (periosteum damage) and 3. Other risk factors (age, gender, type of oncological disease, tobacco and alcohol use and corticosteroids)<sup>7</sup>.

The clinical diagnosis of MRONJ follows three mandatory conditions: presence of bone exposure area or persistent intra- or extra-oral fistula for eight weeks or more in patients without history of radiation therapy who were or are being treated with antiresorptive and/or antiangiogenic agents<sup>4</sup>.

MRONJ can be challenging to treat and can cause significant pain and reduced quality of life<sup>8</sup>. Many studies have established that preventive oral care methods combined with effective oral health practices are associated with a lower rate of MRONJ<sup>9</sup>. When it comes to treatment there is no definitive standard care and the most effective treatment is still controversial. Treatment options are classified into conservative, surgical, and adjuvant non-surgical therapies, and they can be used in combinations<sup>10</sup>. AAOMS describes that the first choice of treatment is a conservative approach including local debridement and disinfection with antimicrobial rinses and/or systemic antibiotic therapy, and when the conservative treatment has no response the surgical therapy, such as bone debridement, sequestrectomy, or resection is recommended<sup>4</sup>. Nowadays several publications have reported that in all stages of the necrosis, surgical treatment is more effective than conservative therapy, proving the success of early-stage surgical therapy<sup>11</sup>.

Autologous platelet concentrates have been used in the oral and maxillofacial field for more than 20 years, and in 2007 they were used for the first time in MRONJ<sup>12</sup>. The base of L-PRF is a 3- dimensional fibrin network with embedded thrombocytes, leukocytes, and stem cells, also includes a wide variety of growth factors, cytokines, and proteins<sup>13</sup>.

The aim of this study was to evaluate the effects of L-PRF on patients suffering from MRONJ or patients in need of dental surgical procedures. The objective was to assess the prevention and the treatment of MRONJ with L-PRF-supplemented surgical therapy with the prognosis of traditional surgical therapy in terms of healing and recurrence.

## **MATERIALS AND METHODS**

### **Ethical considerations**

The procedures employed followed the ethical standards of the 1975 Declaration of Helsinki revised in 2000. The research was submitted and approved by the Ethics Committee in Research of the Erasto Gaertner Hospital and registered in the National System of Ethics in Research – SISNEP under the number 27354919.8.0000.0098.

The patients underwent surgical treatment at the Department of Oral and Maxillofacial Surgery at Erasto Gaertner Hospital, in Curitiba, Brazil, after signing a free and informed consent form, including the release of image rights and the use of

their data for scientific publication. The treatment was conducted by calibrated local residents assisted by the principal author.

### **Research participants**

Patients were included in the study after attending a routine consultation at the Department of Oral and Maxillofacial Surgery at the Erasto Gaertner Hospital. Inclusion criteria were diagnosis of MRONJ or need of tooth extraction in patients under oncological treatment (Prostate and Breast Cancer or Multiple Myeloma) with bisphosphonates (Alendronate Sodium or Zoledronic Acid); patients able to undergo surgical treatment (ASA-1 or ASA-2); patients able to sign an informed consent form. The diagnosis of MRONJ was confirmed in all patients after clinical examination, including history, oral and radiographic exam (panoramic radiography and/or computed tomography).

The exclusion criteria were other types of cancer; cancer patients for prostate/breast cancer or multiple myeloma who were not in use of Alendronate Sodium or Zoledronic Acid; patients with history of radiation therapy in the head and neck area; patients with previous history of use of pentoxifylline and tocopherol.

Patients were divided randomly into three groups: Group 1: Control; Group 2: Prevention (patients without diagnosis of MRONJ but needed for tooth extraction) and Group 3: Treatment (patients with diagnosis of MRONJ in any stage).

### **L-PRF production**

Blood samples were collected from each patient with a 21 G vein needle (BD, Brazil), in 9 mL glass red top blood collection tubes (BD, Brazil). After collection, the blood was immediately centrifuged (DT4000, Daiki), with a force of approximately 400g for 12 minutes, at 2700rpm. At the end of the procedure, the clot (L-PRF) was removed from the collection tubes and implanted into the operated site after the surgeon applied a light pressure on the L-PRF clot with L-PRF box (Supremo Instrumentais, Caieira, São Paulo, Brazil), to remove the excess of serum and obtain a L-PRF membrane.

### **Surgical procedures**

Oral antibiotic treatment with amoxicillin 500mg and metronidazole 400mg was initiated seven days before surgery and continued every 8 hours for seven more days

after the procedure. Oral rinse with 0,12% Chlorhexidine gluconate alcohol-free was prescribed twice a day, for one minute. All surgical procedures were performed by trained residents in the presence of a third dental surgeon, who was in charge of data collection. The following information was collected: age, gender, medications in use, duration of anti-resorptive therapy, surgical site, tooth extracted, degree of mobility of the extracted tooth, the state of the tooth (decayed, broke, rooted), and postoperative follow-up (7, 15, 30, 90, 180 days).

None of the patients interrupted the use of antiresorptive medication. Local anesthesia was induced by 2% lidocaine with 1:100.000 epinephrine in 3 groups. Group 1 (Control): Patients who had an indication for surgical treatment of MRONJ or when tooth extraction was the only treatment option. All patients received the same techniques and treatments already recognized in the world literature but did not receive L-PRF membranes at the surgical site.

Group 2 (Prevention): Patients that presented a condemned tooth in which the only treatment option was extraction.

Group 3 (MRONJ Treatment): Patients diagnosed with MRONJ with indication of surgical treatment.

For group 1 and 2, patients underwent minimally invasive tooth extractions, with the least possible trauma to bone tissue and gingival mucosa. After curettage and irrigation of the surgical alveolus with 0.9% saline solution, L-PRF membranes were inserted, filling the entire surgical alveolus, and 3-0 nylon sutures were performed.

In order to access the surgical site, a mucoperiosteal flap was elevated (when necessary) and mobilized to facilitate tension free-closure. Necrotic bone was removed with rotating burs (and abundant irrigation with 0,9% saline solution to avoid heating the remaining bone) and the bone surface underwent surgical debridement of the necrotic bone. Any sharp edge was removed. The extent of the resection was based on the preoperative computed tomography or panoramic radiography findings and intra-operative appearance of the bone vitality (bleeding) at the resected area.

The amount of L-PRF membranes used was left to the surgeon's decision and it was personalized for each case as needed, depending on the extension of the surgical bone defect. The suture was performed with a nylon suture (3-0 size).

A pasty liquid diet was prescribed for two weeks, painkillers for 3-5 days after surgery. The suture was removed within 15 days and the patients received regular clinical and radiographic follow-up until 6 months after surgery.

The outcomes considered a success were well-healed soft tissue at the treated site and disappearance of any symptoms. The occurrence of postsurgical complications, such as infection or persistent painful symptoms, and bone exposure recurrence was considered as unsuccessful.

## **RESULTS**

### Clinical evaluation

Twenty patients were included in the study. The mean age of the participants was 61,9 years (range 41-91 years); 8 (40%) were male. The mandible was the site most frequently involved (11/55% cases). The patients' features and the data collected from all participants are presented in table 1.

Table 1 - Data collected from all groups

	Patients	Age (years)	Sex	Underlying disease	Location of Lesion/Teeth Extraction	Outcomes
Group 1	#1	57	Female	Breast Cancer	Mandible	No MRONJ
	#2	56	Male	Multiple Myeloma	Maxilla	No MRONJ
	#3	77	Male	Prostate Cancer	Mandible	No MRONJ
	#4	66	Female	Breast Cancer	Mandible	Recurrence
	#5	41	Female	Breast Cancer	Maxilla	No MRONJ
	#6	49	Female	Breast Cancer	Mandible	Recurrence
	#7	70	Female	Breast Cancer	Mandible	No recurrence
Group 2	#1	70	Male	Multiple Myeloma	Maxilla	No MRONJ
	#2	73	Male	Prostate Cancer	Maxilla	No MRONJ
	#3	41	Female	Breast Cancer	Mandible	No MRONJ
	#4	56	Male	Multiple Myeloma	Mandible	No MRONJ
	#5	62	Female	Breast Cancer	Mandible	No MRONJ
	#6	51	Female	Breast Cancer	Maxilla	No MRONJ
	#7	57	Female	Breast Cancer	Maxilla	No MRONJ
	#8	57	Female	Breast Cancer	Mandible	No MRONJ
Group 3	#1	68	Male	Multiple Myeloma	Maxilla	Recurrence
	#2	66	Male	Multiple Myeloma	Maxilla	No recurrence
	#3	91	Male	Prostate Cancer	Mandible	No recurrence
	#4	73	Female	Breast Cancer	Mandible	No recurrence
	#5	57	Female	Breast Cancer	Maxilla	No recurrence

All patients took intravenously zoledronic acid every month. The mean duration of medication therapy before MRONJ occurrence was 10,2 months (range 8-36 months). The outcome of the surgical treatment was successful in 57% in group 1, 100% in group 2 and 80% in group 3. The mean follow-up was 6 months. The clinical evaluation showed excellent soft tissue healing from first follow-up, without bone exposure and signs of infections in the groups 2 and 3. In group 1 the healing process was slow with a variety of complications (post-op pain and suture dehiscence with inflammation and infection), including bone re-exposure. In groups 2 and 3 total soft tissue closure was achieved by 4 weeks. In group 1 the healing process took 8-12 weeks, when achieved. Local pain was not reported by patients

within the first week post-surgery and no postoperative complications occurred throughout the follow-up period in the groups who received the L-PRF membranes.

To assess success, we considered complete closure of bone exposure without recurrence during the entire follow-up period. We also consider success when there was suture dehiscence in the mediate postoperative period with posterior epithelization. In addition, the absence of local inflammatory/infectious processes and pain were taken into account.

For Group 2, we observed a fast-healing process with formation of granulation tissue within the first 7 days after surgery and an even faster healing after the removal of the sutures on the 15th day after the procedure. We also noticed a lower rate of postoperative pain and edema when compared to the control group.

In group 3, patients already had some stage of bone necrosis, in addition to pain complaints and presence of local suppuration. None of these patients had an extra-oral fistula. The tissue repair and healing process in this group was slower, taking up to 12 weeks for complete healing when there was no recurrence of bone exposure as it was shown in some cases. Pain complaints and postoperative edema were not reported by the evaluated patients. Full recovery occurred in more than 50% of patients in this group.

## **DISCUSSION**

The direct clinical effect of use L-PRF in the surgical treatment of MRONJ is an early epithelization of the surgical sites<sup>14</sup>. In our study, we evaluated that the best results were seen in Group 2, where patients did not present bone necrosis, when compared to Group 3. Group 3, although showed a slow healing process, full recovery was considered high. This can be explained by the fact that the research took place within a specialized service of oral and maxillofacial surgery, in a cancer hospital that has broad experience in treating this kind of complication associated do cancer therapy.

A systematic review published recently found that application of PRF for the treatment of MRONJ with complete recovery was found in 92.8%<sup>15</sup>. Other authors also show that the healing results are very similar and positive with rates of complete resolution exceeding 75% in all studies<sup>16,17,18, 19, 20</sup>.

Our study had some limitations. First, we had a limited sample, that was affected by SARS-COV-2 pandemic that reduced the face-to-face appointments, with longer periods between appointments. This led to a reduce number of patients included in the study, and to a concern about early diagnosis and prevention of this complication. Also, not all patients were able to perform the radiographs at the desired frequency, however, we understand that in successful cases, mucosal healing is related to the condition of healthy and non-necrotic bone. On the other hand, sample randomization and standardization were important to minimize research bias.

All patients included in the sample presented MRONJ-risk associated intravenous use of Zoledronic Acid<sup>®</sup> as well poor teeth condition and although recommendation is to avoid oral surgical procedures, sometimes it is the only option for some cases. Thus, this study demonstrated that adjuvant treatments such as L-PRF can be very usefull to prevent and treat medication-related osteonecrosis of the jaws.

MRONJ is a well-recognized complication of drug therapies for bone metabolic disease or cancer. Antiresorptive drugs, such as bisphosphonates and denosumab are been used in low and high-doses and, a recent literature review identified a range of other medications classified as tyrosine kinase inhibitors, monoclonal antibodies, mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators and immunosuppressants that have been implicated in MRONJ in addition to the drugs already mentioned<sup>21</sup>. Many studies have investigated the mechanism of MRONJ development and various therapeutic methods have been proposed but still poorly understood<sup>22,23</sup>.

Radiographically, osteonecrosis caused by different types of antiresorptive drugs are very similar, but the panoramic radiography (PR), computed tomography (CT) and magnetic resonance imaging (MRI) are considered important examinations in the general evaluation of the lesions, the latter two being important in assessing the limits of disease. Also, MRI as well as bone scintigraphy (BS), may be useful in detecting subclinical osteonecrosis when the bone is not exposed. However, BS has no specificity and low resolution<sup>24</sup>.

Surgical treatment is considered to be the most standard treatment of MRONJ, although some differences exist in the treatment approach depending on the stage<sup>25</sup>. Complete removal of the necrotic bone, until bone appears healthy in terms of

structure with perioperative antibiotic treatment, infection control and smoothing of the sharp bone edges before tension-free sutures are generally considered the most appropriate approach for successful recovery<sup>26</sup>.

In order to improve wound healing and reduce the rate of recurrence, local therapeutic measures are becoming increasingly popular based on surgical debridement combined with local application of platelet-rich blood products such as platelet-rich fibrin and leukocytes (L-PRF)<sup>6</sup>.

Platelet concentrate refers to an autologous concentration of human platelets obtained by centrifuging blood. It results in a high concentration of several protein growth factors secreted actively by platelets<sup>27</sup>. L-PRF has been used for regenerative procedures in various fields of medicine, including dentistry and reconstructive surgery in order to deliver high concentrations of autologous growth factors directly to wounds<sup>28</sup>. Not only acts as a three-dimensional fibrin scaffold but also contains numerous autologous cells, such as platelets, macrophages, and neutrophils. Growth factors are released by platelets include platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor  $\beta$  (TGF-  $\beta$ ), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF)<sup>29</sup> and seems to persist for at least 14 days due a slowly and naturally polymerizes during centrifugation<sup>30</sup>.

The lack of epithelization exposes the bone to the oral microbial population, which can result in recurrent and persistent infections<sup>29</sup>. Thus L-PRF contains numerous immune cells, which may inhibit infectious. Recently studies shown that membranes obtained by horizontal centrifugation may exert greater antibacterial effects<sup>31</sup>.

## **CONCLUSION**

L-PRF is cheap, safe, autologous, and easy to prepare treatment option for MRONJ and may reduce the risk of delayed recovery in tooth extracted patients undergoing intravenous bisphosphonate therapy. Moreover, L-PRF may be useful in preventing and treat MRONJ in patients receiving intravenous bisphosphonates. Further clinical trials are needed to stablish whether the use of L-PRF could significantly reduce the incidence of MRONJ in oncological and non-oncological

patients after oral surgery procedures, improve healing and quality of life in patients requiring oral surgical treatment.

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## 5 CONCLUSÕES

Ainda não existe um consenso a respeito do melhor tratamento para as ONAM, mas os tratamentos cirúrgicos mesmo em estágios iniciais parecem ter melhores resultados quando comparados a tratamentos conservadores.

L-PRF pode ser mais efetivo na prevenção das osteonecroses induzidas por medicamentos quando utilizada no tratamento de necroses ósseas já instaladas. Estudos com amostras maiores talvez possam reforçar os resultados encontrados nesta pesquisa.

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## APÊNDICE 1 – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nós, Dra<sup>a</sup> Juliana Lucena Schussel e Guilherme Klein Parise, pesquisadores da Universidade Federal do Paraná, estamos convidando o(a) Sr(a). a participar de um estudo intitulado “Eficácia da Fibrina rica em Plaquetas e Leucócitos (L-PRF) no reparo tecidual em procedimentos odontológicos cirúrgicos em pacientes em uso de bifosfonatos – Estudo caso-controle” (Iremos criar através do seu sangue uma membrana para auxiliar na cicatrização da sua cirurgia). Essa pesquisa é importante para conseguirmos diminuir o risco de complicações após a sua cirurgia ou para tratarmos a complicação e sabermos se a membrana que iremos criar a partir do seu sangue é capaz de ajudar na cicatrização da sua cirurgia. Caso você participe da pesquisa, será necessário coletar sangue para confecção da membrana e realização de exames pré-cirúrgicos, como radiografia e/ou tomografia e exames de sangue para identificarmos qualquer problema com relação à sua coagulação sanguínea e estado de saúde geral. Para tanto você deverá comparecer no Ambulatório de Odontologia do Hospital Erasto Gaertner para realização de consultas, exames, procedimento cirúrgico e retornos para acompanhamento pós-operatórios. Estes retornos de acompanhamento serão realizados a cada 7 dias e após completado o processo cicatricial a cada 30 dias por aproximadamente 6 meses. É possível que o(a) Sr(a) experimente algum desconforto, principalmente relacionado a coleta de sangue e/ou ao procedimento cirúrgico, como dor, falta de sensibilidade no lábio ou na língua, dificuldade para falar ou engolir, manchas arroxeadas no braço ou no rosto, infecção, inchaço, ânsia de vômito, entre outros. Os benefícios esperados com essa pesquisa são: 1. Melhora da cicatrização; 2. Prevenção da “morte” do osso; 3. Tratamento da “morte” do osso. No entanto, nem sempre você será diretamente beneficiado com o resultado da pesquisa, mas poderá contribuir para o avanço científico.

Os pesquisadores Dra<sup>a</sup> Juliana Lucena Schussel e Guilherme Klein Parise, responsáveis por este estudo poderão ser contatados no Departamento de Estomatologia da Universidade Federal do Paraná localizada na Avenida Prefeito Lothário Meissner, 632 – Jardim Botânico, Curitiba/PR, 80210-170 ou pelo telefone celular através do número [REDACTED] ou também pelo e-mail [REDACTED] ou [REDACTED].

Neste estudo será utilizado um grupo controle. Isto significa que você poderá receber o tratamento com a membrana do seu sangue ou não.

A sua participação neste estudo é voluntária e se você não quiser mais fazer parte da pesquisa poderá desistir a qualquer momento e solicitar que lhe devolvam o termo de consentimento livre e esclarecido assinado. A sua recusa não implicará na interrupção de seu atendimento e/ou tratamento, que está assegurado.

As informações relacionadas ao estudo poderão ser conhecidas por pessoas autorizadas (médico, dentista, etc.). No entanto, se qualquer informação for divulgada em relatório ou publicação, isto será feito sob forma codificada, para que a **sua identidade seja preservada e seja mantida a confidencialidade.**

As despesas necessárias para a realização da pesquisa não são de sua responsabilidade e pela sua participação no estudo você não receberá qualquer valor em dinheiro. Você terá a garantia de que problemas decorrentes do estudo serão tratados no Hospital Erasto Gaertner junto ao ambulatório de Odontologia.

Quando os resultados forem publicados, não aparecerá seu nome, e sim um código. Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo “Eficácia da Fibrina rica em Plaquetas e Leucócitos (L-PRF) no reparo tecidual em procedimentos odontológicos cirúrgicos em pacientes em uso de bifosfonatos – Estudo caso-controle” Eu discuti com a Dra. Juliana Lucena Shussel sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

---

Assinatura do paciente/representante legal

Data \_\_\_\_/\_\_\_\_/\_\_\_\_

\_\_\_\_\_  
Assinatura da testemunha

Data \_\_\_\_/\_\_\_\_/\_\_\_\_

\_\_\_\_\_  
Assinatura do Pesquisador

Data \_\_\_\_/\_\_\_\_/\_\_\_\_

**APÊNDICE 2 – FICHA DE COLETA DE DADOS**

Código de Ficha: \_\_\_\_\_

- 
1. Sexo: [Masculino] [Feminino]
  2. Idade do paciente: \_\_\_\_\_
  3. Data de Nascimento: \_\_\_\_\_
  4. Iniciais do paciente: \_\_\_\_\_
  5. Prontuário: \_\_\_\_\_
  6. Raça: [Leucoderma] [Feoderma] [Melanoderma] [Xantoderma]
  7. Comorbidades: \_\_\_\_\_
  8. Medicamento utilizado: [Alendronato de Sódio] [Ácido Zoledrônico] [Ambos]
  9. Tempo de utilização do bifosfonato: \_\_\_\_\_
  10. Forma de administração do bifosfonato: \_\_\_\_\_
  11. Queixa principal do paciente: \_\_\_\_\_
  12. Diagnóstico definitivo: \_\_\_\_\_
  13. Estadio clínico: \_\_\_\_\_
  14. Motivo da intervenção cirúrgica: [Extração dentária] [Osteonecrose]
  15. Local da Intervenção cirúrgica:
    - a) Mandíbula posterior
    - b) Mandíbula anterior
    - c) Maxila posterior
    - d) Maxila anterior
  16. Dente extraído:
    - a) Incisivos
    - b) Caninos
    - c) Pré-Molares
    - d) Molares
  17. Grau de mobilidade do dente extraído:
    - a) Grau I
    - b) Grau II
    - c) Grau III
  18. Integridade do elemento dentário:

- a) Hígido
  - b) Cariado
  - c) Em estado de raíz
19. Extensão da necrose óssea (em mm) \_\_\_\_\_
20. Há proximidade ou envolvimento da área necrótica com o canal mandibular:  
[Sim] [Não]

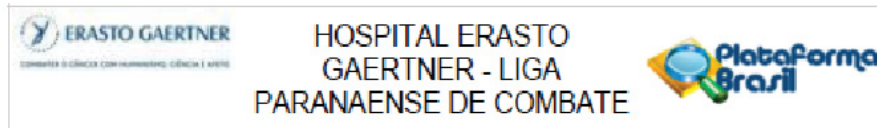
21. **Período pós operatório:**

- a) 7 dias: Exposição óssea [Sim] [Não] [NSA]
  - Deiscência de sutura [Sim] [Não]
  - Perda da membrana [Sim] [Não] [NSA]
  - Aspecto de infecção [Sim] [Não]
  - Aspecto de inflamação [Sim] [Não]
  - Higiene do Local [Boa] [Regular] [Ruim]
  - Tecido de Granulação [Sim] [Não] [NSA]
  
- b) 15 dias: Exposição óssea [Sim] [Não] [NSA]
  - Deiscência de sutura [Sim] [Não]
  - Aspecto de infecção [Sim] [Não]
  - Aspecto de inflamação [Sim] [Não]
  - Higiene do Local [Boa] [Regular] [Ruim]
  - Tecido de Granulação [Sim] [Não] [NSA]
  
- c) 30 dias: Exposição óssea [Sim] [Não] [NSA]
  - Deiscência de tecido [Sim] [Não]
  - Aspecto de infecção [Sim] [Não]
  - Aspecto de inflamação [Sim] [Não]
  - Higiene do Local [Boa] [Regular] [Ruim]
  
- d) 90 dias: Exposição óssea [Sim] [Não] [NSA]
  - Deiscência de tecido [Sim] [Não]
  - Aspecto de infecção [Sim] [Não]
  - Aspecto de inflamação [Sim] [Não]
  - Higiene do Local [Boa] [Regular] [Ruim]

- e) 180 dias: Exposição óssea [Sim] [Não] [NSA]  
Deiscência de tecido [Sim] [Não]  
Aspecto de infecção [Sim] [Não]  
Aspecto de inflamação [Sim] [Não]  
Higiene do Local [Boa] [Regular] [Ruim]

22. Observações: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

## ANEXO A – PARECER CONSUBSTANCIADO DO CEP DO HOSPITAL ERASTO GAERTNER



### PARECER CONSUBSTANCIADO DO CEP

#### DADOS DO PROJETO DE PESQUISA

**Título da Pesquisa:** Eficácia do L-PRF no reparo tecidual em procedimentos odontológicos cirúrgicos em pacientes em uso de bifosfonatos - estudo caso-controle

**Pesquisador:** Juliana Lucena Schussel

**Área Temática:**

**Versão:** 2

**CAAE:** 27354919.8.0000.0098

**Instituição Proponente:** LIGA PARANAENSE DE COMBATE AO CANCER

**Patrocinador Principal:** Financiamento Próprio

#### DADOS DO PARECER

**Número do Parecer:** 4.132.757

##### **Apresentação do Projeto:**

As informações elencadas nos campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram retiradas do arquivo Informações Básicas da Pesquisa.

A osteonecrose dos maxilares induzidas por medicamentos é uma complicação do tratamento de diversos tipos de cânceres, sendo os mais

comuns, o câncer metastático de mama e próstata. Até então não existe na literatura mundial um protocolo seguro para o tratamento odontológico

destes pacientes. As membranas de fibrina em rica em plaquetas vêm crescendo muito dentro da odontologia devido seus fatores de crescimento e

de neovascularização. Com isso objetivamos verificar a eficácia da utilização dessas membranas na cicatrização e no reparo ósseo dos pacientes

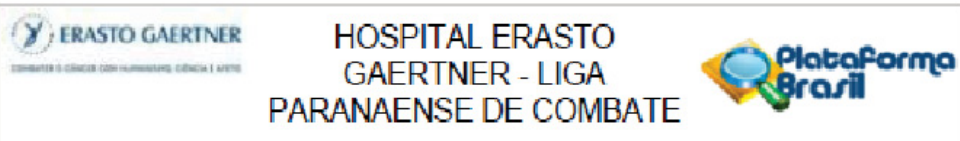
com osteonecrose dos maxilares ou em pacientes com alto risco para desenvolvimento da complicação.

Os pacientes serão selecionados a partir da necessidade de extrações dentárias depois de diversas tentativas de outras formas terapêuticas de

manutenção do elemento dentário, ou da necessidade de remover fragmentos ósseos necrosados e expostos na cavidade bucal. Visto que hoje

ainda não existe uma maneira de realizar este tipo de procedimento de maneira segura, e

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Continuação do Parecer: 4.132.757

impossibilitados de evitar a ocorrência da necrose óssea após um procedimento de extração dentária e nem de evitar a progressão da necrose após curetagem do tecido necrosado, o paciente será questionado se gostaria de participar da pesquisa utilizando as membranas de L-PRF visto que elas têm se mostrado eficientes em diversas pesquisas odontológicas.

**Objetivo da Pesquisa:**

**Objetivo Primário:**

Avaliar a eficácia da utilização de membranas de L-PRF na prevenção e no tratamento das necroses ósseas de mandíbula e maxila induzidas por bifosfonatos

**Objetivo Secundário:**

-Avaliar as medicações utilizadas-Elaborar um protocolo de prevenção de necrose óssea após cirurgias odontológicas-Elaborar um protocolo de tratamento de necroses ósseas em maxila e mandíbula-Verificar a eficácia do L-PRF

**Avaliação dos Riscos e Benefícios:**

As informações apresentadas não alteram o perfil de riscos e benefícios apresentados na avaliação inicial do projeto de pesquisa.

**Comentários e Considerações sobre a Pesquisa:**

Respostas à pendências prévias apresentadas de modo satisfatório.

**Considerações sobre os Termos de apresentação obrigatória:**

Termos obrigatórios e considerações apresentados satisfatoriamente.

**Conclusões ou Pendências e Lista de Inadequações:**

O projeto está de acordo conforme itens acima analisados, sem lista de inadequações.

**Considerações Finais a critério do CEP:**

Diante do exposto, este Comitê de Ética em Pesquisa, de acordo com as atribuições definidas na Resolução CNS nº 488 de 2012 e na Norma Operacional nº 001 de 2013 do CNS, manifesta-se pela aprovação do projeto de pesquisa.

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Continuação do Parecer: 4.132.757

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1485039.pdf	20/05/2020 11:52:18		Aceito
Outros	Declaracao_Coordenadora_Geral_HEG.pdf	20/05/2020 11:50:33	Guilherme Klein Parise	Aceito
Outros	Respostas_Pendencias.pdf	20/05/2020 11:40:34	Guilherme Klein Parise	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_revisado.pdf	20/05/2020 11:38:31	Guilherme Klein Parise	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_revisado.pdf	20/05/2020 11:39:17	Guilherme Klein Parise	Aceito
Folha de Rosto	Folha_de_Rosto.pdf	20/12/2019 11:12:53	Guilherme Klein Parise	Aceito

**Situação do Parecer:**

Aprovado

**Necessita Apreciação da CONEP:**

Não

CURITIBA, 03 de Julho de 2020

Assinado por:  
Jeanine Marie Nardin  
(Coordenador(a))

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## ANEXO B – NORMAS PARA ESTRUTURAÇÃO DA DISSERTAÇÃO NO FORMATO ALTERNATIVO



MINISTÉRIO DA EDUCAÇÃO E DO DESPORTO  
UNIVERSIDADE FEDERAL DO PARANÁ  
SETOR DE CIÊNCIAS DA SAÚDE  
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

### ESTRUTURA DA DISSERTAÇÃO

Orientação Normativa: (aprovada no Colegiado do Programa de Pós-graduação em Odontologia/UFPR)

- 1- As dissertações de mestrado do Programa de Pós-graduação em Odontologia podem ser elaboradas no formato tradicional ou alternativo. O orientador e o aluno decidirão qual formato adotar.
- 2- Os artigos que fizerem parte da dissertação no formato alternativo devem ser elaborado dentro das normas de um periódico com Qualis B2 ou superior para a área odontológica (consultar a lista do WebQualis com a classificação dos periódicos, disponível no site <http://www.capes.gov.br/avaliacao/quali>).
- 3- Tanto no formato tradicional como alternativo, deverão ser seguidas as orientações da série Normas para Apresentação de Documentos Científicos, 2ª edição, 2007, da Editora da UFPR.
- 4- Na dissertação com formato alternativo o item *Introdução* deve ser desenvolvido de forma mais extensa, expondo o tema e fazendo referência à literatura científica que traga contribuições significativas diretamente relacionadas ao assunto. As principais idéias devem ser demonstradas e fundamentadas na literatura. A formulação clara do tema investigado e a justificativa da pesquisa devem ser incluídos.
- 5- Na dissertação com formato alternativo o item *Capítulos* ou *Capítulo* é a parte da dissertação onde devem ser inseridos os artigos de autoria do candidato que serão enviados para publicação, escritos no idioma exigido pela revista, sempre com cópia em Português.
- 6- Na dissertação com formato alternativo o item *Discussão* ou *Considerações gerais* é o espaço que permite estabelecer argumentos que evidenciem relações entre os artigos apresentados nos Capítulos, dando liberdade ao aluno para ampliar suas reflexões, sempre baseado dentro do contexto e do estado da arte. É opcional.
- 7- Na dissertação com formato alternativo o item *Conclusões* deve apresentar o fechamento das idéias correspondentes aos objetivos, tentando responder a pergunta (hipótese) formulada. Pode ser apresentada na forma de tópicos ou de texto corrido. A conclusão deve ser apresentada de forma lógica e clara.
- 8- Na dissertação com formato alternativo as normas das revistas para as quais os artigos foram escritos devem fazer parte do item *Apêndice*.

Quadro 1 – Elementos estruturais das dissertações em formato tradicional e alternativo				
		Tradicional	Alternativo	
Elementos Externos		Capa	Capa	Obrigatório
		Lombada	Lombada	Obrigatório
Elementos Internos	Pré-textuais Textuais	Folha de rosto	Folha de rosto	Obrigatório
		Termo de aprovação	Termo de aprovação	Obrigatório
		Dedicatória	Dedicatória	Opcional
		Agradecimento	Agradecimento	Opcional
		Epígrafe	Epígrafe	Opcional
		Resumo em português	Resumo em português	Obrigatório
		Abstract (Resumo em Inglês)	Abstract (Resumo em Inglês)	Obrigatório
		Lista de ilustrações	Lista de ilustrações	Opcional
		Lista de tabelas	Lista de tabelas	Opcional
		Lista de abreviaturas e siglas	Lista de abreviaturas e siglas	Opcional
		Lista de símbolos	Lista de símbolos	Opcional
		Sumário	Sumário	Obrigatório
		Introdução	Introdução	Obrigatório
		Objetivos	Objetivos	Obrigatório
	Revisão da literatura	Capítulos: (artigos)	Obrigatório	
	Material e métodos		Obrigatório	
	Resultados		Obrigatório	
	Discussão	Discussão ou considerações gerais	Obrigatório na tradicional e optativa na alternativa	
	Conclusão	Conclusão	Obrigatório	
	Pós-textuais	Referências	Referências	Obrigatório
Glossário		Glossário	Opcional	
Apêndice		Apêndice	Opcional na tradicional e obrigatório na alternativa	
Anexo		Anexo	Opcional	
Índice		Índice	Opcional	