NURYÊ REZENDE PRISINOTO

CONDUTAS CLÍNICAS ODONTOLÓGICAS EM PACIENTE IRRADIADO EM CABEÇA E PESCOÇO E DESCRIÇÃO DE CASOS DE APLICAÇÃO DE I-PRF EM ÁREAS DE OSTEORADIONECROSE

Clinical dental procedures in head and neck irradiated patient and description of cases of i-PRF application in osteoradionecrosis areas

Dissertação apresentada à Faculdade de Odontologia da Universidade de Uberlândia, para obtenção do Título de Mestre em Odontologia na Área de Clínica Odontológica Integrada

Uberlândia, 2022

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"Não deixemos passar despercebido o outro grande fato de que a ciência não apenas contribui a base da escultura, da pintura, da música e da poesia, mas de que ela própria é poética [...] É frequente aqueles que se dedicam a pesquisas científicas nos mostrarem que percebem não menos vividamente, mas de maneira mais vívida que outros, a poesia de seus temas".

Herbert Spencer

SUMÁRIO

RESUMO

A radioterapia é uma modalidade terapêutica utilizada para o tratamento de vários tumores. Apesar dos avanços nessa terapia, o tecido adjacente a lesões tumorais ainda recebe doses de radiação que podem afetar o seu potencial regenerativo. Otratamento odontológico pós-radioterapia deve ser realizado com planejamento adequado e pouca invasiva para oferecer previsibilidade e impedir a instalação de lesões de osteorradionecrose (ORN). Essas lesões são de difícil tratamento devido a sua fisiopatogenia que envolve o processo de fibrose induzida por radiação causando hipovascularização, hipóxia e hipocelularidade do tecido. Modalidades terapêuticas têm sido propostas para seu tratamento, porém ainda apresentam limitações e não há um tratamento estabelecido que ofereça processo curativo adequado. O objetivo desse trabalho é abordar o manejo odontológico do paciente irradiado em região de cabeça e pescoço e descrever casos de aplicação de fibrina rica em plaquetas injetável (i-PRF) em lesões de ORN. Esse trabalho foi dividido em dois objetivos: (1) Revisão de literatura com objetivo de descrever os procedimentos odontológicos realizados fora de ambiente hospitalar em pacientes pós-radioterapia onde demonstrou que o tratamento odontológico no paciente irradiado é possível de ser realizado, desde que seja feita avaliação minuciosa da saúde bucal e sistêmica do paciente, evitando-se realizar procedimentos invasivos; (2) Aplicação do protocolo de i-PRF em 5 lesões de ORNcom o objetivo avaliar o seu efeito no padrão do tecido mole adjacente a essas lesões e concluiu-se que o i-PRF pode servir como primeira tentativa menos invasiva paramelhorar o padrão de tecido mole, porém ainda são necessários mais estudos queavaliem seu efeito no tratamento de lesões de ORN. De uma forma geral, esse estudo demonstrou que a radioterapia é um fator complicador na manutenção da saúde oral e, protocolos de tratamento específicos para esses pacientes precisam ser aplicados ou desenvolvidos para o tratamento odontológico não ser o gatilho para ocorrência deORN. Essas lesões são de difícil tratamento, e a utilização do i-PRF pode ser um agente facilitador no preparo para cirurgias ressectivas, porém ainda carece de maiores evidências.

Palavras chaves: Osteorradionecrose; Fibrina rica em plaquetas; Tratamento odontológico; Radioterapia.

ABSTRACT

Radiotherapy is a therapeutic modality used for the treatment of various tumors. Despite advances in this therapy, tissue adjacent to tumor lesions still receives doses of radiation that can affect its regenerative potential. Post-radiotherapy dental treatment should be performed with proper planning and minimally invasive to provide predictability and prevent the onset of osteoradionecrosis (ORN) lesions. These lesions are difficult to treat due to their pathophysiology, which involves the process of radiation-induced fibrosis causing tissue hypovascularization, hypoxia and hypocellularity. Therapeutic modalities have been proposed for its treatment, but they still have limitations and there is no established treatment that offers an adequate curative process. The objective of this work is to approach the dental management of the patient irradiated in the head and neck region and to describe cases of injection of injectable platelet-rich fibrin (i-PRF) in ORN lesions. This work was divided into two objectives: (1) Literature review with the objective of describing the dental procedures performed outside the hospital environment in post-radiotherapy patients, which demonstrated that dental treatment in irradiated patients is possible, as long as it is performed thorough assessment of the patient's oral and systemic health, avoiding invasive procedures; (2) Application of the i-PRF protocol in 5 ORN lesions with the aim of evaluating its effect on the soft tissue pattern adjacent to these lesions and it was concluded that i-PRF can serve as a first less invasive attempt to improve the soft tissue pattern, but further studies are needed to assess its effect in the treatment of ORN lesions. In general, this study demonstrated thatradiotherapy is a complicating factor in the maintenance of oral health, and specific treatment protocols for these patients need to be applied or developed so that dental treatment is not the trigger for the occurrence of ORN. These lesions are difficult to treat, and the use of i-PRF can be a facilitating agent in the preparation for resective surgeries, but further evidence is still lacking.

Keywords: Osteoradionecrosis; Platelet-rich fibrin; dental treatment; Radiotherapy.

1. INTRODUÇÃO E REFERENCIAL TEÓRICO

O tratamento radioterápico é amplamente utilizado para o controle docrescimento, tratamento curativo ou paliativo de diversos tipos de tumores. Seu mecanismo de ação básico consiste em causar quebras moleculares e danos a diversas estruturas celulares levando a morte celular (Alterio *et al.,* 2019). Apesar dos avanços relacionados a esse tipo de tratamento, visando que a radiação ionizante atinja apenas o tecido tumoral, o tecido saudável adjacente ao tumor ainda pode receber doses de radiação, o que pode alterar microarquitetura e vascularização, prejudicando o seupotencial regenerativo (Sroussi *et al.,* 2017; Jasmer *et al.,* 2020).

A cavidade oral é exposta a grandes doses de radiação ionizante quando essa terapia é utilizada para tratar os tumores na região de cabeça e pescoço, dessa forma, alguns pacientes podem desenvolver efeitos agudos e crônicos da radiação ionizante nos tecidos orais (Chronopoulos *et al.,* 2018; Baudelet *et al.,* 2019; Beaumont *et al.,* 2021). Dentre as possíveis alterações, as mais comuns são: mucosite, alterações de quantidade e qualidade salivar, trismo, perda de paladar, disfagia, infecções oportunistas e ORN, sendo essa última considerada o efeito tardio mais grave da radiação (Sroussi *et al.,* 2017; Baudelet *et al.,* 2019). Além disso, as alterações de quantidade e qualidadesalivar, tornam o desenvolvimento de periodontite e cárie de radiação mais propícios nesses pacientes, uma vez que alterações salivares podem estimular a ocorrência de disbiose microbiana, diminuição da capacidade de tamponamento de pH e da atividade de regularização da mineralização desse fluido e consequentemente dificuldade de higienização pelo paciente (Jensen *et al.,* 2019; Piret *et al.,* 2021).

Os procedimentos odontológicos realizados em pacientes irradiados são passíveis de serem realizados após a radioterapia, porém é necessário planejamento adequado para que haja previsibilidade em qualquer tratamento oferecido com plano de manutenção estabelecido (Jawad *et al.,* 2015; Kawashita *et al.,* 2020; Piret *et al.,* 2021). A reabilitação desses pacientes é de grande importância para devolver qualidade devida, e a escolha do procedimento adequado deve ser baseada em avaliação minuciosada saúde bucal e sistêmica do paciente, evitando-se realizar procedimentos invasivos nesse período, uma vez que, procedimentos odontológicos realizados em áreas que receberam doses de radiação podem ser um fator desencadeador de lesões de

osteorradionecrose, que são complexas e de difícil tratamento (Chronopoulos *et al.,* 2018; Kawashita *et al.,* 2020; Piret *et al.,* 2021).

A ORN consiste em necrose do óssea devido a fibrose induzida por radiação, que compromete sua microarquitetura e vascularização (Aarup-Kristensen *et al.,* 2019). A hipovascularização, hipóxia e hipocelularidade que ocorrem nesse tecido o torna menos competente nos processos regenerativos e a lesão permanece sem cicatrizaçãopor 3 meses ou mais caso não haja intervenção. Além disso, pode haver perda de integridade da mucosa, expondo o osso necrótico ao meio bucal, que torna propício a contaminação da ferida (Chrcanovic *et al.,* 2010; McCaul *et al.,* 2014; Aarup-Kristensen*et al.,* 2019; Dziegielewski *et al.,* 2020). Diversos tratamentos têm sido propostos para essa lesão, como a ressecção cirúrgica, ozonioterapia, oxigenação hiperbárica,fotobiomodulação e protocolos medicamentosos (Rivero *et al.,* 2017; Vahidi *et al.,* 2020), porém ainda há fatores limitadores relacionados a esses tratamentos, que vão desde questões logísticas onde há necessidade de acessibilidade a grandes centros de referência para tratamento oncológico e até questões individuais relacionadas a capacidade de suportar o uso de medicações sistêmicas por tempo prolongado. Além disso, é importante ressaltar que a ORN é uma lesão altamente redicivante (REF), e um procedimento de ressecção cirúrgica pode piorar o quadro clínico dessa lesão. De fato, ainda não há um tratamento estabelecido que seja eficaz para a maioria dos casos, e tratamentos que visem estimular os processos de angiogênese, pelo menos teoricamente,são os que poderiam oferecer condições mais propicias para o processo de cicatrização dessas lesões (Lopez-Jornet *et al.,* 2016; Miron *et al.,* 2017).

A fibrina rica em plaquetas (PRF) é um concentrado sanguíneo de última geração. Desde que foi proposto pela primeira vez, vem sendo amplamente utilizada no campo médico e odontológico para auxiliar no processo regenerativo de vários tipos de lesões (Choukroun *et al.,* 2001). Seu mecanismo de ação básico consiste em acelerar a cicatrização do tecido devido a quantidade de células e fatores de crescimento que estimulam a angiogênese do local, tornando propício os processos de proliferação, diferenciação e atividade celular (Chen *et al.,* 2019; Thanasrisuebwong *et al.,* 2019; Law *et al.,* 2020). Além disso, vários tipos de PRF podem ser obtidos a depender do protocolo de centrifugação aplicado, o que varia a concentração de células e fatores de crescimento dentro desse produto (Choukroun *et al.,* 2001; Miron *et al.,* 2019).

Algumas vantagens relacionadas a sua utilização são a sua biocompatibilidade imunológica, sua apresentação física e seu custo reduzido quando comparado a outros tipos de tratamento (Miron *et al.,* 2017).

O i-PRF, por se encontrar em estado líquido, pode ser modulado e aplicado em tecido mole adjacente as lesões de ORN. Além disso, devido à baixa força de centrifugação aplicada para a produção desse concentrado, há uma presença maior de células e fatores de crescimento que ficam contidas na porção superior do tubo (Miron *et al.,* 2017). Um estudo clínico demostrou que a utilização do i-PRF melhorou a qualidade do tecido queratinizado após cirurgias de recobrimento de recessões gengivais (Ozsagir *et al.,* 2020) e esse efeito poderia ser benéfico ao se executar cirurgias de ressecções de tecido ósseo necrótico, porém, a utilização do i-PRF para tratamento de lesões de ORN ainda carece de maiores evidências cientificas.

2. PROPOSIÇÃO

Essa dissertação de mestrado foi dividida em dois objetivos:

(1). Abordar tópicos importantes sobre procedimentos odontológicos realizados em pacientes após radioterapia, descrevendo efeitos biológicos da radiação ionizante no tecido ósseo com foco em protocolos de atendimento clínico

(2) Avaliar o efeito do protocolo de fibrina rica em plaquetas injetável (i-PRF) no tratamento inicial de lesões de ORN em pacientes submetidos à radioterapia de cabeça e pescoço em relação ao padrão do tecido mole queratinizado e na qualidade de vida dos pacientes.

3. CAPÍTULOS

3.1. CAPÍTULO 1.

Artigo submetido para BRAZILIAN JOURNAL OF ORAL SCIENCES

Clinical dental management of the head and neck irradiated patient: Topics of interest for clinicians

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Resumo

Objetivo: Abordar tópicos importantes sobre procedimentos odontológicos realizados em pacientes após radioterapia, descrevendo efeitos biológicos da radiação ionizante no tecido ósseo com foco em protocolos de atendimento clínico. Procedimentos invasivos e não invasivos pós-tratamento radioterápico na região de cabeça e pescoço serão abordados por meio de evidências científicas visando auxiliar o clínico na tomada de decisão do momento adequado para exodontias, manejo periodontal e procedimentos de prevenção da osteorradionecrose.

Material e Métodos: Foram selecionados na base de dados MEDLINE (PubMed) trinta e três estudos, sendo incluídos estudos originais e revisões. Não foi aplicada restrição de ano de publicação. O idioma foi restrito ao inglês, e os seguintes termos foram usados: radioterapia, osteorradionecrose, tratamento dentário. Foram selecionados estudos de osteorradionecrose envolvendo manejo clínico de pacientes irradiados, com ênfase em diretrizes e protocolos atualizados.

Conclusões: Procedimentos odontológicos pós radioterapia podem ser realizados, porém devem ser os menos invasivos possíveis. Recomenda-se elaboração de plano de manutenção que mantenha as condições de saúde e reduza necessidade de tratamentos complexos e invasivos.

Palavras-Chaves: Câncer de cabeça e pescoço. Radioterapia. Osteorradionecrose

Abstract

Background: To discuss important topics regarding the dental procedures performed in patients before, during and after the radiotherapy treatment. The biological effects of ionizing radiation on bone tissue focusing on clinical care will be described. Theinvasive and not invasive procedures after radiotherapy treatment in the head and neck region will be addressed using scientific evidences to determine the appropriate moment

for tooth extractions, periodontal management, and preventive procedures for osteoradionecrosis.

Material and Methods: Thirty-three studies including original studies and reviews were selected in MEDLINE database (PubMed). No year of publication restriction was applied. Language was restricted to the English, and the following Medical Subject Heading terms were used: radiotherapy, osteoradionecrosis, dental management. Studies of osteoradionecrosis involving clinical management of irradiated patients, with anemphasis on updated guidelines and protocols were selected

Conclusions: The dental procedures should and can be performed before, during but also after radiotherapy. However, the clinical procedures should be less invasive as possible. A maintenance plan that reduces the necessity for major and more invasive treatments after radiotherapy is recommended.

Key words: Head and neck cancer. Radiotherapy. Osteoradionecrosis.

Introduction

Radiotherapy (RTX) treatment is widely used to treat various types of head and neck cancers[1]. The purpose of RTX is to control the growth or elimination of the tumor[1], reducing the possibility of recurrence and improving the patient's quality of life[1]. RTX treatment is indicated as a palliative protocol of incurable cancers[1]. Despite of the benefits of this therapy, some patients frequently are involved with adverse effects caused by ionizing radiation[2,3]. The main complications associated with RTX are: mucositis, xerostomia, changes in salivary quality and quantity, opportunistic infections, tissue fibrosis, sensory dysfunctions such as dysgeusia, increased periodontal disease progression, caries and osteoradionecrosis (ORN)[4]. These intercurrences can have acute manifestation, during the treatment, or chronic manifestation after the completion of the treatment[4].

The clinical characteristic of ORN is bone necrosis due to hypoxia, hypovascularization and hypocellularity[5], with loss of mucosal integrity, associated or not with oral environment bone exposure[2]. The ORN is the most serious adverse effect of RTX, compromising the tissue integrity and health of the oral structures. The ORN incidence ranges from 5 to 30% of patients who have undergone head and neck RTX[3].

The incidence of RTX has decreased with the use of the most modern radiation techniques[3].

Several risk factors are associated with the development of the ORN, such as smoking, periodontal disease, alcohol abuse, intensity and duration of radiation[2]. Controlling the risk factors is important to minimize the development of ORN. The approaches proposed for the treatment of ORN involve non-invasive techniques such as maintaining the quality of oral hygiene, the use of antibiotic therapy, and also extensive surgical procedures to remove the necrotic bone[2]. The high uncertainty rate of the infection control is a factor that must be considered for choosing the ideal treatment[2].

The knowledge about the manifestations caused by ionizing radiation in the oral cavity has great importance for clinicians. Many professionals still have doubts regarding the treatment planning and the management of patients involved with RTX. Therefore, this study aimed to describe and clarify the dental procedures performed by clinicians in cancer patients before, during and after RTX treatment.

Materials and methods

Thirty-three studies were included in this review. twenty-one these studies were original researches while twelve were reviews. These studies were searched in the MEDLINE databases (PubMed). All selected through the focus on the management of irradiated patients in the head and neck region. No publication year restriction was applied. The language was restricted to English, and the following Medical Subject Heading terms were used: radiotherapy, osteoradionecrosis, dental management. Studies on osteoradionecrosis involving clinical management of irradiated patients, with an emphasis on updated guidelines and protocols, were selected.

1. Dental procedures before and during RTX treatment

Before starting RXT, the professional must perform all necessary adequacy of the oral environment[1]. Caries lesions treatment, subgingival scaling, endodontic treatments or tooth extraction that could be the focus of infection should be performed[2]. These procedures should be performed at least two weeks before to start the RTX treatment[2]. The prevention of ORN is based on elimination of the oral cavity infectious conditions at the pre-RXT phase, as well as to prevent the invasive procedures during

and after RXT treatment[6]. Monitoring the quality of oral hygiene should be also always performed, since the development of ORN is also associated with poor oral hygiene[6].

During the irradiation period, mucositis, opportunistic infections such as candidiasis, salivary gland dysfunctions such as xerostomia and taste alterations are frequently reported by patients[7]. During the RTX, invasive dental procedures are not recommended[2]. Prior monitoring the patient oral conditions should be performed[2], except in cases the occurrence of an emergency, then the invasive procedures arenecessary for maintaining the patient's safety and health.

2. Dental procedures after RTX treatment

Post- RXT patients may have chronic complications such as ORN, xerostomia and trismus[7]. The irradiated patients may need dental care requiring the performance of various dental procedures, such as tooth restorations, endodontics, rehabilitation, among others[8,9]. It is important that clinicians understand the consequences of RTX on the mucosa, bone tissue and dental tissue to prevent the installation of ORN and failure of clinical procedures[10].

Ionizing radiation produces hypoxia, hypocellularity and hypovascularization that can alter the regenerative potential of the soft and hard tissues[2, 11, 12]. Changes in tooth and bone structure can occur due to degradations in amine components that can mechanically alter enamel[13, 14], dentin[10], and bones[12, 13, 15]. The effect of ionizating radiaton on the salivary flow and the xerostomia reduce the protection of this fluid against pathogens and enhance the friction on the mucosa during the oral chewing that could be the trigger for the occurrence of the mucositis lesions[16].

2.1. Extractions

Post-RTX extraction is an important risk factors for the development of the ORN[17], then this procedure should be avoided during this period[3]. A safety period for the development of the ORN is inconclusive[3, 10]. The tooth extractions performed during post-RTX can result on ORN, due the invasive procedure in bone and mucosa tissues, which can compromise the microarchitecture and vascularization [3, 5, 10, 17].

A retrospective study evaluated 32 patients with tooth extraction after RTX and showed the ORN in 12.1% (9 patients)[17]. The patients with ORN received higher radiation dose (62.0 Gy vs. 37.4 Gy) and longer treatment time until extraction (41.2 months vs. 28.2 months) than the groups of patients without ORN. The recent

systematic demonstrates that the presence of risk factors such as smoking, radiation dose and duration of treatment are more predictable aspects in decision-making when performing dental extractions than the time after RTX[3].

The possibility of occurrence of ORN after tooth extraction is a possible and uncertain complication. If necessary, the extraction should be performed less traumatically possible, avoiding large flaps and osteotomies in order to improve the healing process[2]. Adjunct therapies, such as photobiomodulation, ozonetherapy, PENTOCLO protocol, hyperbaric chambers, may also be indicated, as early intervention may reduce the risk of ORN[18].

2.2 Restorative treatment

In irradiated patients increased the risk of developing dental carious lesions due to multiple factors [19, 20]. The development of carious lesions after RTX treatment can occur mainly from three months after irradiation and can lead to a severe oral health impact[13, 20, 21]. These effects can occur due to the degradation of the organic components of dentin and enamel, which stimulate the increasing of its rigidity, making less efficient to support occlusal forces, which leads to the tooth wear [21, 22]. The reduction or qualitative alteration of salivary flow turns the patients as a greater risk for developing dental caries due the limited pH buffering function promoted by saliva, as well as the dryness of the oral mucosa that makes oral hygiene procedures more uncomfortable[16, 22].

The rapid progression of the carious lesions on enamel and dentin and the structural substrate changes make the restorative protocols a major challenge due the poorly adhesive interaction with the dental substrate [10, 22, 23]. It has been indicated the use of the neutral fluor application periodically[21, 24]. In patients with xerostomia and high risk of radiation carious lesions and poor adherence to preventive fluoride therapy, the use of conventional and resin modified glass ionomer cement are more effective in protecting recurrent carious lesions[8].

2.3 Surgical and non-surgical periodontal treatment

Periodontal disease occurs due to an imbalance between the periodontal microbiota and the host response, and the process of oral dysbiosis may be responsible in part for the disease progression[6]. RTX can be an important agent for periodontal microbiota dysbiosis due to reduced salivary flow, which is associated with less efficient oral hygiene[25]. RTX induced fibrotic effects on connective tissues make

periodontal tissues less competent in regenerative processes due to reduced oxygenation found especially in terminal-type circulation[26]. These effects together increase the host's susceptibility to present more aggressive periodontal disease, increasing the risk of tooth loss after RTX treatment[27].

Due to the risks of ORN after tooth extraction, a personalized treatment and maintenance plan must be indicated considering the periodontal health status and systemic conditions pre-RXT[6]. The treatments must be completed as soon as possible before RTX, being the full-mouth scaling technique is indicated[25, 27]. Periodontal therapy for head and neck cancer implemented before, during and after treatmentsresults in a significant improvement on periodontal health, but this therapy should be maintained, otherwise periodontal disease continues its progression[6, 26].

2.4 Endodontic treatment

Due to the increased carious lesions activity in patients after RTX, endodontic treatment should be necessary to avoids more aggressive procedures such as extraction [9, 19]. However, some factors such as the reduction of the dental pulp oxygenation the structural tooth fragilization can complicate the diagnosis and reduce the endodontic treatment success[9, 19]. Pulp oxygenation levels are reduced after 4-6 months, which can impair pulp diagnosis by promoting a negative sensitivity response in vital pulps and directing unnecessary endodontic interventions[19]. It is necessary to await at least 6 months after the radiotherapy to perform the sensibility pulp tests. The endodontic treatment associated with RTX, can increase the tooth structural weakening[19]. Resin composite restorations are recommended to direct restorative material for restoring the endodontically treated teeth, strongly avoiding the use of the amalgam[28]. It is also important and recommended to replace amalgam restorations prior to RTX treatment[28].

2.5 Rehabilitation for edentulous regions using prostheses and implants

Most irradiated patients mainly seek treatment for edentulous regions, usually as a result of multiple tooth extractions performed before RTX treatment[10]. Oral rehabilitation is important to improve the patient’s quality of life[29]. It is essential that the clinicians understand the procedures that should be avoided in this post-radiation period[30]. Treatments with partial or complete dentures must be carefully performed. The patient follow-up is essential so mismatched dentures can cause damage to the mucosa can generate trauma that predisposes ORN[29, 31].

It is not well established the safer rehabilitation procedure for post- RTX patients[30]. When fixed prostheses are indicated, it should be taking in consideration that the tooth substrate after the RTX become more fragile, reducing the predictability of this treatment[10]. Another alternative for oral rehabilitation is the use of dental implants supported prostheses without interfering with compromised mucous membranes and teeth[30, 31]. The installation of implants prior to RTX is safer procedure with high success and survival levels[31]. The installation of implants after the RTX period present a slightly higher level of complication compared with the implants installed in the general population[30]. The innovations on macrostructure and microstructure implants surface, and on the implant installation techniques guided by surgery without flap opening, can make the rehabilitation of post-radiotherapy patients increasingly safer and more predictable, but this clinical procedures still requires further investigations.

Discussion

The treatment of head and neck cancer is an extremely challenging condition for maintain the patient's quality of life. The patients tend to resist to the highly aggressive treatments such as extensive surgery to remove the tumor, the RTX protocol, and in many situations to perform multiple tooth extractions prior to the RTX[3]. During and after the period of active treatment, therapeutic planning aiming proper oral rehabilitation is necessary in order to limit the acute and chronic damage caused by cancer treatment[2]. It is important to recognize that the effects of RTX are cumulative, and the indication of the dental procedures must consider the limitations imposed by thealterations on the dental and bone caused by irradiation, avoiding as much as possible the occurrence of ORN.

To avoid this complication, has been suggested not performing dental extraction due the ORN[17]. Bone tissue intervention should ideally be performed before RTX[3]. This indication is based on the progressive process of connective tissue fibrosis that reduces the vascularization, cellularity and oxygenation of oral tissues, especially bone tissue, which can impair the repair processes[5, 10, 11, 26]. The bone tissue has the slower regenerative potential than soft tissues[2, 5, 12, 26]. During the healing phase, especially the post-extraction alveolar repair occurred by second intention, makes this tissue more

susceptible to contamination and subsequent development of necrotic lesions, which are difficult to treat[2].

There is an important relationship between the occurrence of cancer in the head and neck region and poor periodontal conditions, since the risk factors are shared[25, 27]. It is expected that patients indicated for RTX treatment may have more severe and active periodontal disease than the general population[27]. Periodontal treatment after RTXshould be performed as quickly and less aggressively as possible, avoiding surgical procedures to access root surfaces[6 ,27]. Supportive periodontal therapy should be performed at least every 3 months to prevent disease progression that the risk of tooth loss[4]. It is recommended that teeth with a questionable periodontal prognosis should be removed at least 14 days prior to initiation of RTX[26].

If the treatment plan and preventive procedures before RTX are indicated for the teeth maintenance. Special attention is essential due the changes in the protein portion on the dentin, enamel and at the cementoenamel junction substrate. Associated with the salivary flow reduction the developing radiation carious lesions is increased[13, 20]. The adhesive systems efficiency is reduced in forming prober hybrid layer to dentin substrate and the different restorative materials[10]. Thus, restorative materials that allow the continuous release the fluoride, such as conventional or resin modified glass ionomer cements should be chosen, reducing the recurrent carious lesions, and the dependence on the bonding interface promoted by adhesive systems[10]. More extensive carious lesions with pulp involvement may indicate endodontic therapy, that will furtherweaken the tooth structure affected by RTX[32].

The dosage used and the time elapsed of the RTX should be taken in consideration during the planning of the rehabilitation of the edentulous areas[26]. It has been described that muco-supported prostheses must be well adapted to avoid trauma to the mucosa, as this tissue is also fragile and can more easily lose its integrity and exposethe adjacent bone tissue[29]. The denture-supported dentures planning must consider the quality of the remaining abutment teeth, avoiding involving teeth with large restorations with endodontic treatment as abutments[9, 19]. Teeth with a history of periodontal disease are more susceptible to disease progression after RTX and should also be avoided as support for protheses[4].

The security of the implant placement in patients after the RTX are inconclusive. It has been described that the rehabilitation with dental implants has been indicated as a good alternative to rehabilitate patients after RTX and has shown relatively good levels of clinical survival[31]. It has been also showed that the bone tissue surgery may present higher risk factor for the ORN installation[31]. Indeed, the myriad of protocols of RTX impairs a properly documentation regarding the safety for implants placement in these patients[17].

Technological advances may improve the outcomes of the oral treatment in the RTX patients. The advances in the mechanical of the restorative materials associated with adhesive procedures, and preventive protocols may improve the treatment complication related with the carious lesions[9, 28]. The implants design and microstructure advantages, as well as the use of less traumatic surgeries may enhancethe oral rehabilitation predictability[33]. In addition, the dental therapy may become more safety as much the RTX protocols become more focused on injuries[30]. The dental treatment after RTX is possible to be performed, but they should be less invasive as possible.

In conclusion, the dental procedures before, during and after RTX should be performed, however they should be always less invasive as possible. However, the type complexity of the treatment is patient and moment dependent. A maintenance plan performed before, during and after RTX is strongly recommended to reduce the necessity for major and more invasive treatments after radiotherapy.

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3.2. CAPÍTULO 2.

Artigo a ser submetido para INTERNATIONAL JOURNAL OF CLINICAL ONCOLOGY

Original article: Effect of i-PRF on gingival tissue quality in osteoradionecrosis lesions: Description of series cases

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Summary

This study evaluated an autogenous blood concentrate (i-PRF) protocol in the healing of soft tissue in the vicinity of the ORN lesions in patients undergone head and neck radiotherapy. Four patients who had five ORN lesions were treated. The i-PRF was applied weekly for 4 weeks on the lesions and the soft tissues features were evaluated through clinical analysis at baseline and at 7, 15, 30, 60 and 90 days after the first session of i-PRF application. Extension of the bone lesions were evaluated through radiographic analyses, with the patient-centered related outcomes were evaluated by the application of the quality of life questionnaires at baseline and 90 days after the first treatment session. Of the 5 treated lesions, 2 closed completely and 3 remained open. Lesions that did not close showed an increase in necrotic tissue exposure. No changes were noted in the radiographic appearance of the lesions. There were also no impacts onthe quality of life of patients. It can be concluded that the application of i-PRF has the potential to promote good outcomes in the treatment of ORN, but its success rate is relatively moderate and its impact on the quality of life of these patients appears to be null.

Keywords: Blood concentrates, osteoradionecrosis, radiotherapy

Introduction

Osteoradionecrosis (ORN) is a serious complication resulting from the radiotherapy treatment widely used for the treatment of several types of head and neck cancers (Chrcanovic *et al.,* 2010; McCaul *et al.,* 2014). The ORN presents as clinical characteristic the exposition of bone tissue associated with the loss of skin and mucosa integrity that persists with no healing for at least 3 months (Chrcanovic *et al.,* 2010; McCaul *et al.,* 2014; Dziegielewski *et al.,* 2020). This condition occurs due to fibrosis on connective tissues induced by ionizing radiation that induces hypoxia, hypocellularity, and tissue hypovascularization (Chrcanovic *et al.,* 2010; Dziegielewski *et al.,* 2020). The main risk factors for the development of ORN are the size andlocation of the tumor (Raggio *et al.,* 2018), tooth extractions (Reuther *et al.,* 2003; Lajolo *et al.,* 2021), radiation dose used in the treatment (Chrcanovic *et al.,* 2010; Dziegielewski *et al.,* 2020), smoking habit (Moon *et al.,* 2017), presence of infections (Sroussi *et al.,* 2017), association with medications (Lopez-Jornet *et al. ,* 2016), low immunity (Chronopoulos *et al.,* 2018), and periodontal disease (Chrcanovic *et al.,* 2010;Irie *et al.,* 2018).

Ideally, patients who will undergo radiotherapy treatment in the head and neck region should have risk factors identified and modulated in such a way as to prevent the occurrence of ORN (Sroussi *et al.,* 2017). However, it is not always possible to control all these factors and the occurrence of ORN is moderate within these patient groups (Chronopoulos *et al.,* 2018). ORN has a significant impact on the quality of life resulting from clinical symptoms that involve spontaneous and chronic pain, dysphagia and in some cases can lead to facial deformation (Chrcanovic *et al.,* 2010; Chronopoulos *et al.,* 2010; Sroussi *et al.,* 2017; Chronopoulos *et al.,* 2017; Sroussi *etal.,* 2017; Chronopoulos *et al.,* 2018) and this impact is even more important because it affects patients who are already debilitated by cancer treatment.

The standard treatment proposed for ORN is surgical resection of the lesions, however it has been verified that this procedure has high failure rates, as demonstrated in a previous clinical study in which the treatment of 120 patients with chronic ORN lesions promoted success in the closure of the ORN injury in 55 patients (Dai *et al.,* 2015). For this reason, several therapeutic modalities have been proposed for the treatment of ORN as an adjunct to the surgical debridement of these lesions, with

surgical resections associated with the use of adjuvant agents such as systemic antibiotics (McCaul *et al.,* 2014; Rice et al., 2014; Rice *et al .,* 2015; Costa *et al.,* 2016), photobiomodulation therapy (Ribeiro et al, 2018), hyperbaric chambers (Sultan *et al.,* 2017) and ozone therapy (McCaul *et al.,* 2014; Rice *et al.,* 2015). The search for therapeutic protocols for the treatment of ORN is still necessary (Costa *et al.*, 2016; Raggio *et al.,* 2018).

Platelet-rich fibrin (PRF) is a concentrate of autologous growth factors, and since it was first proposed, it has been used in the medical and dental field to aid in tissue regeneration (Choukroun *et al.,* 2001). The mechanism of action of PRF consists of accelerating tissue regeneration through stimulation of angiogenesis and the presence of growth factors that promote the processes of proliferation, differentiation and cellular activity in connective tissues (Thanasrisuebwong *et al.,* 2019; Law *et al.,* 2020). It is a material obtained by collecting the patient's own blood, other relevant advantages are related to its use, such as absolute biocompatibility and its reduced cost compared to other types of treatment (Miron *et al.,* 2017).

Various types of PRF can be obtained depending on the centrifugation protocol applied, and this can vary the number of cells and growth factors, as well as the physical presentation and manipulation of the blood infiltrate (Miron *et al.,* 2019). Among the possible ways of presenting the PRF, the use of i-PRF stands out, which, because it is in a liquid state, can be modulated and used in irregular bone defects (Miron *et al.,* 2017; Thanasrisuebwong *et al.,* 2019) that are characteristic of necrotic bone sites arising from ORN. The potential of using i-PRF to treat this type of injury lacks further scientific evidence.

An important condition for improving the management of the treatment of ORN lesions is the improvement of the local soft tissue conditions around these lesions. As it has been shown that the use of PRF improves the phenotype pattern of keratinized tissues (Ozsagir *et al.,* 2020), the use of this blood concentrate, at least theoretically, canimprove the conditions of keratinized tissues and subsequently benefit the surgicaltreatment of these lesions. This study evaluated an autogenous blood concentrate (i- PRF) protocol in the initial treatment of ORN lesions in patients undergoing head and neck radiotherapy.

Material and Methods

The protocol of these case series was submitted and approved by the Human Research Ethics Committee of the Federal University of Uberlândia (CAAE: 38301120.4.0000.5152). This study was conducted in accordance with the human research concepts determined by the Declaration of Helsinki.

Inclusion and exclusion criteria

Patients with ORN lesions of both genders and who had given consent to participate in this research project were included in this study. Patients with blood dyscrasias, decompensated diabetics and patients in the active phase of radiotherapy were not included in this study.

Treatment with i-PRF and clinical analysis

To produce i-PRF, blood was collected from patients using 2 tubes of 13 ml, without any additive, specific for i-PRF synthesis according to the Choukroun protocol. These tubes were positioned in a horizontal centrifuge, in order to maintain the balance for centrifugation for 3 minutes (for women) and 4 minutes (for men), with a speed of 700 rpm. After the centrifugation, it was possible to observe an orange colored area in the tube (i-PRF) and the rest of the blood material just below. The tubes were carefully opened to avoid homogenization of the material. With a 3 ml syringe (Injex®, Brazil) and an 18G x 1/2 hypodermic needle (Injex®, Brazil), i-PRF was collected from the tubes, which was injected into all the soft tissue adjacent to the lesion through a needle 30G X 1/2 hypodermic (Injex®, Brazil). This procedure was performed once a week for 4 consecutive weeks. Patients were evaluated at baseline and at 7, 15, 30, 60, and 90 days after the first application of i-PRF. Panoramic radiographs were performed at baseline and 90 days after the 1st application of i-PRF.

Quality of life analysis

To analyze the impact of treatment on the quality of life, patients were asked to answer two questionnaires related to general quality of life (QLQ-C30) and related to oral health (QLQ-H&N35) in cancer patients. The QLQ-C30 questionnaire consisted of 30 questions divided into 17 domains, while the QLQ-H&N35 questionnaire had 35 questions divided into 18 domains. Both questionnaires were developed by the European Organisation for Research and Treatment of Cancer (EORTC). These questionnaires were evaluated according to the Likert scale: 1 = never, 2 = sometimes, 3

= often, 4 = always. The answers to these questionnaires for statistical purposes were considered as a percentage, with scale 1 being considered as 25%, scale 2 as 50%, scale 3 as 75% and scale 4 as 100%. The last 5 questions of the QLQ-H&N35 questionnaire were dichotomous, with the value 0 being considered as 0% and the value 1 being considered as 100%. The last two questions of the QLQ-C30 questionnaire were numbered from 1-7 with the number 1 being considered as 14.28% and the value 7 as 100%. Patients received these questionnaires at baseline and 90 days after starting ORN treatment with i-PRF.

Statistical analysis

Quality of life data from this study were exposed through descriptive and frequency statistics among the four patients who were treated with this protocol. Statistical analysis of quality of life questionnaires was performed using the Wilcoxon test. All statistical tests were applied at the 95% confidence level. The GraphPad Prism 8.4 software (San Diego, CA, USA) was used for the statistical analysis of this study.

Results

During the period from February to December 2021, five ORN lesions were diagnosed in 4 patients. Of this total, three patients were men and one was a woman and two of them were smokers. ORN lesions were detected due to tooth extraction (3 lesions), ill- fitting prosthesis (1 lesion) and dental implant placement (1 lesion). All the lesions presented an improvement in the soft tissue continue without altering the aspect of the bone lesions that continues to be confined to the alveolar bone. Furthermore, the patients did not perceived a relevant improvement in the quality of life after the beginning of treatment of the lesions (Table 1).

Clinical case 1

Patient LJ, male, 61 years old, smoker, was attended the clinic of our institution with the presence of an ORN lesion in the mandible on the right side. This patient had a history of metastatic carcinoma to cervical lymph nodes from an occult primary site. Patient underwent chemotherapy and radiotherapy (39 sessions; Dose of radiation of 70.2 Gy) at the right side on the subclavian and cervical portion of the head and neck region. The lesion started after extraction of tooth 44. This lesion has been diagnosed after a period

of one year and two months after the end of radiotherapy. The extraction procedure was performed in the same center and it was indicated due to the periodontal condition of the remnants associated with smoking and poor hygiene of the patient.

Regarding the clinical analyses, the presence of necrotic tissue that was exposed to the oral environment was verified, the degree of healing was very poor in all evaluation periods. In addition, there was no closure of the flap and the size of the lesionincreased after the 90-day period compared to the initial period. The patient did not report edema, but he felt pain associated with the injury that was controlled after taking analgesics during the first week of starting the i-PRF interventions. There were also no differences in the radiographic appearance of the lesions in any of the index (Figure 1).

Clinical case 2

Patient MM, a 48-year-old female, non-smoker, who was previously treated for squamous cell carcinoma of stage 2 on the tongue, underwent radiotherapy (40 sessions;Dose of radiation of 72 Gy) at the lower portion of the face and subclavian portion atthe right side in the head and neck region, chemotherapy and surgical resection. The patient presented to the dental service with an ORN lesion in the region of teeth 45-46 which began with the installation of a dental implant that was performed 6 years afterthe treatment of the primary tumor. The patient had undergone the installation of 3 implants, and one of the implants (installed in the region of 36) was osseointegrated.The two implants installed in the region of 45 and 46 were associated with the formation of bone sequestration and ORN. The implant from the 46 region was lost and the ORN lesion associated with the 45 implant was treated by i-PRF. A stabilization of the condition was observed and it was possible to maintain the dental implant (Figure2).

Clinical case 3

Patient NM, male, 65 years old, had squamous cell carcinoma in the soft palate with stage 3, which was treated with radiotherapy (40 sessions; Dose of radiation of 72 Gy)at the left side on the subclavian and cervical portion of the head and neck region, and chemotherapy. ORN lesions associated with extraction of teeth 28 and 37 were noted in the clinical examination, which was performed 5 years after the radiotherapy procedure.

The patients was submitted to i-PRF applications and a stabilization of the lesion was noticed that, despite not having closed, remained in the same size and with an aspect of normality of the mucosa around the necrotic tissue. The patient did not report edema, but he felt persistent pain throughout the experimental period, which was controlled with the use of analgesics. He had limited mouth opening due to injuries, which made it impossible to take photographic images. There were also no differences in the radiographic appearance of the lesions in any of the index (Figure 3).

Clinical case 4

Patient AA, male, 55 years old, had a history of squamous cell carcinoma of the soft palate and tonsil/oropharynx pillar, with stage 4, which was treated with radiotherapy (39 sessions; Dose of radiation of 70.2 Gy) at the left side on the subclavian and cervical portion of the head and neck region, and chemotherapy. The same presented ORN in the region of the alveolar ridge in the second quadrant due to poorly adapted prosthesis. These lesions were treated with i-PRF and complete closure was noted at the end of follow-up. The patient did not report pain or swelling and presented adequate healing. There were also no differences in the radiographic appearance of the lesions in any of the index (Figure 4).

Discussion

The treatment of ORN lesions is a difficult condition to resolve due to reduced blood supply to the irradiated regions, which impairs the healing processes in these regions (Chrcanovic *et al.,* 2010; Chronopoulos *et al.,* 2018). The search for treatments aimed at accelerating the healing process in these areas aims to stimulate angiogenesis processes, which at least theoretically would have more promising conditions to reverse this pathological condition (Lopez-Jornet *et al.,* 2016; Miron *et al.,* 2017). In this study, an autogenous blood concentrate protocol (i-PRF) was tested and the results were promising since the soft tissues around the ORN lesions presented improvements in their tissue quality.

The i-PRF has been successfully applied in soft tissue repair processes (Kızıltoprak & Uslu, 2020) and accelerated bone formation in healthy patients (Gülşen & Dereci, 2019). These effects have been related to the presence of growth factors that

stimulated angiogenesis, migration, proliferation and cell activity (Thanasrisuebwong *et al.,* 2019). In this series of cases, i-PRF was not effective in promoting the healing process in all cases, and it is possible that factors such as the systemic condition of the evaluated patients and the severity of the lesions had a negative effect on the cases. However, it is worth mentioning that the lesions that presented improvement in the soft tissue healing may presented better prognostic after the ORN surgical treatment (Dai *et al.,* 2015; Silva *et al.,* 2016). Thus, the i-PRF can serve as a less aggressive first attempt to the patient for the treatment of this type of lesion, before the indication of resective surgical procedures.

An important feature observed in this study is that the majority of the ORN lesions stability from exposure of bone tissue. It has been reported that some lesions canbe contaminated by resistant microorganisms (Goyal *et al.,* 2017) that associated with tissue hypovascularization (Chronopoulos *et al.,* 2018) can be complicating agents inthe successful treatment of these lesions (Mendes *et al.,* 2020). In addition, the absence of granulation tissue associated with these lesions was noted, which is consistent with the lack of new vessels and an inflammatory process that collaborates with the healingof these lesions (Raggio *et al.,* 2018). All these factors are complicating factors for the treatment of ORN lesions to achieve clinically acceptable success.

An important fact noted in this study was the non-interference of the treatment of ORN lesions in the patients' quality of life. Bone necrosis lesions are not usually accompanied by painful processes, and it is likely that other side effects of radiotherapy have a greater impact on patients' quality of life, such as xerostomia, lesions with exposure of connective tissue, dental pain and mucositis (Sroussi *et al.,* 2017; Chieng *et al.,* 2021). Thus, it is possible that, in view of these other conditions, ORN lesions are not so challenging to reduce the quality of life of patients and their treatment is not noticed as having an impact in this aspect. Furthermore, the injuries treated in this study were not functionally debilitating to the point of promoting pathological fractures in the involved bones. However, it should be taken into account that most of the lesions in thisstudy did not close and that the sample size evaluated limits the inferences of our findings.

This description of cases has limitations that must be taken into account when evaluating our findings. The absence of a control group in which there is a comparison

of the i-PRF protocol makes it difficult to indicate whether there is any advantage of this treatment technique over the others. The use of autogenous material from unhealthy individuals is also a critical factor in this study, as the failures observed may be inherent to local factors of the lesion or to systemic factors, and the discernment of the cause of these failures is not possible to be precisely determined in this study. Finally, treatments of necrotic lesions are complex and the prevention of these events is the most effective way of managing patients who have risk factors for the occurrence of these lesions, thus, it is necessary to understand in the future whether the i-PRF protocol would be more beneficial in preventing the occurrence of ORN lesions associated with oralsurgeries

It can be concluded that the application of i-PRF has the potential to promote good results in the treatment of ORN, but its success rate is relatively low and its impacton the quality of life of these patients appears to be null.

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Table 1: Description of the mean(median)±standard deviation of the score of EORTC QLQ-C30 and QLQ-HN35 before and 90 days after the treatment of the ORN lesions by the use of i-PRF.

Parameter	Baseline	90 days	p value
Global health status/QoL	33.70(31.25) ± 9.11	35.93(33.03) ± 9.74	0.250
Physical function	36.25(37.50) ± 10.31	41.25(37.50) ± 17.97	>0.999
Role Function	34.13(31.73) ± 11.25	35.57(36.54) ± 7.10	0.625
Emotional fuction	34.38(31.25) ± 10.83	35.94(31.25) ± 14.77	>0.999
Congnitive function	37.50(31.25) ± 17.68	37.50(31.25) ± 17.68	>0.999
Social funcion	29.17(29.17) ± 4.80	37.50(33.33) ± 14.43	0.500
Fatigue	31.25(25.00) ± 12.50	40.63(37.50) ± 6.25	0.250
Nausea/Vomiting	34.38(25.00) ± 18.75	34.38(25.00) ± 18.75	>0.999
Pain	40.63(37.50) ± 18.75	37.50(37.50) ± 10.21	>0.999
Dyspnoea	25.00(25.00) ± 0.00	31.25(25.00) ± 12.50	>0.999
Insomnia	31.25(25.00) ± 12.50	31.25(25.00) ± 12.50	>0.999
Appetite loss	37.50(25.00) ± 25.00	31.25(25.00) ± 12.50	>0.999
Constipation	25.00(25.00) ± 0.00	31.25(25.00) ± 12.50	>0.999
Diarrhoea	31.25(25.00) ± 12.50	25.00(25.00) ± 0.00	>0.999
Financial problems	37.50(37.50) ± 14.43	31.25(25.00) ± 12.50	>0.999
General Healthy	82.14(85.71) ±7.14	78.57(78.57) ± 8.25	>0.999
Quality of life	89.28(85.71) ± 7.14	85.71(85.71) ± 16.50	>0.999
HN- Pain	39.06(40.63) ± 5.98	39.06(37.50) ± 16.44	>0.999
HN- Swallowing	31.25(28.13) ± 8.83	32.81(31.25) ± 7.86	>0.999
HN- Senses	34.38(31.25) ± 11.97	34.38(31.25) ± 11.97	>0.999
HN-Speech	25.00(25.00) ± 0.00	28.13(25.00) ± 6.25	>0.999
HN- Social eating	34.38 (34.38) ± 3.60	31.88(31.25) ± 6.16	>0.999
HN-Social contact	32.81(28.13) ± 11.83	25.00(25.00) ± 0.00	0.500
HN-Sexuality	34.38(31.25) ± 11.97	31.25(25.00) ± 12.50	>0.999
HN-Teeth	50.00(50.00) ± 20.41	37.50(25.00) ± 25.00	0.750
HN-Opening mouth	37.50(37.50) ± 14.43	37.50(25.00) ± 25.00	>0.999
HN-Dry mouth	50.00 (50.00) ± 0.00	75.00(75.00) ± 20.41	0.250
HN-Sticky saliva	50.00(50.00) ± 20.41	62.50(62.50) ± 32.27	>0.999
HN-Cough	37.50(37.50) ± 14.43	34.38(31.25) ± 11.97	>0.999
HN-Felt ill	25.00(25.00) ± 0.00	37.50(37.50) ± 14.43	0.500
HN-Pain killers	50.00 (50.00) ± 57.74	75.00 (100.00) ± 50.00	>0.999

HN-Nutritional supplements	50.00(50.00) ± 57.74	50.00(50.00) ± 57.74	>0.999
HN-Feeding tube	0.00(0.00) ± 0.00	0.00(0.00)± 0.00	>0.999
HN-Weight loss	25.00(0.00) ± 50.00	50.00(50.00) ± 57.74	>0.999
HN-Weight gain	0.00(0.00) ± 0.00	0.00(0.00) ± 0.00	>0.999

Figures

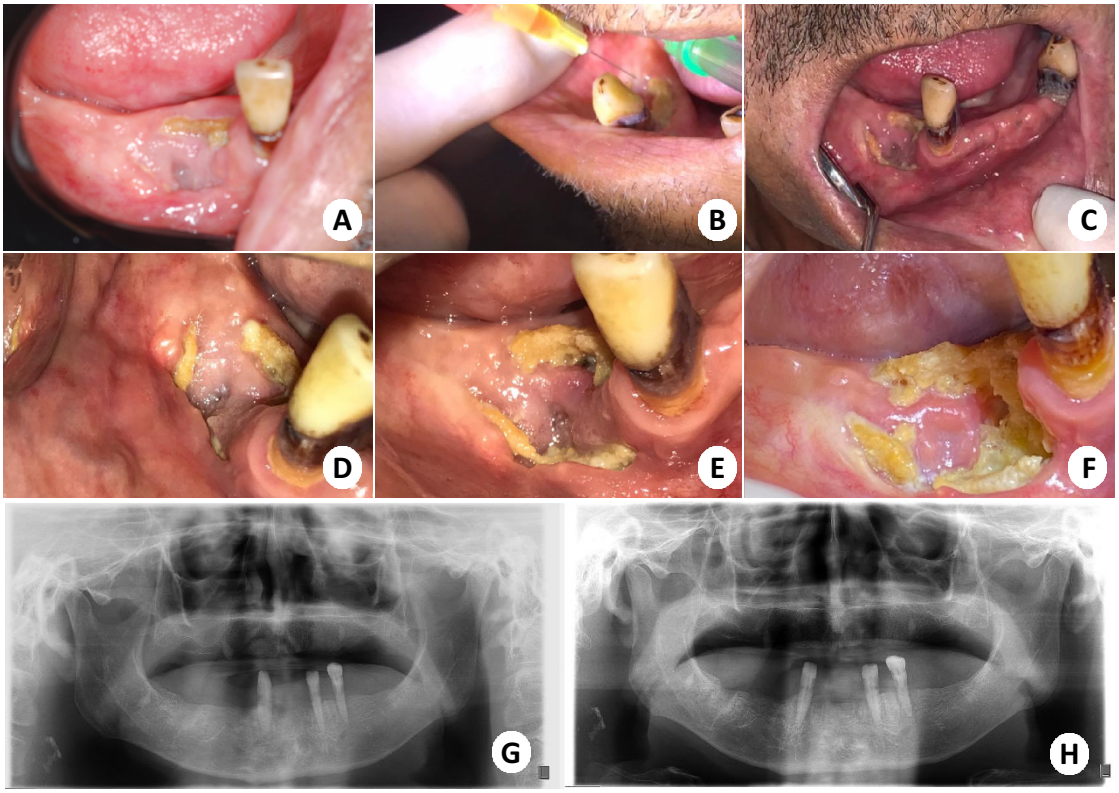

Figure 1: (A) Initial condition of the injury - Baseline period **(B)** Application of i-PRF within 7 days **(C)** 15 days after the first application of i-PRF **(D)** 30 days after the first application of i-PRF **(E)** 60 days after the first application of i-PRF **(F))** 90 days after the first application of i-PRF **(G)** Initial panoramic radiograph at baseline **(H)** Final panoramic radiograph at 90 days.

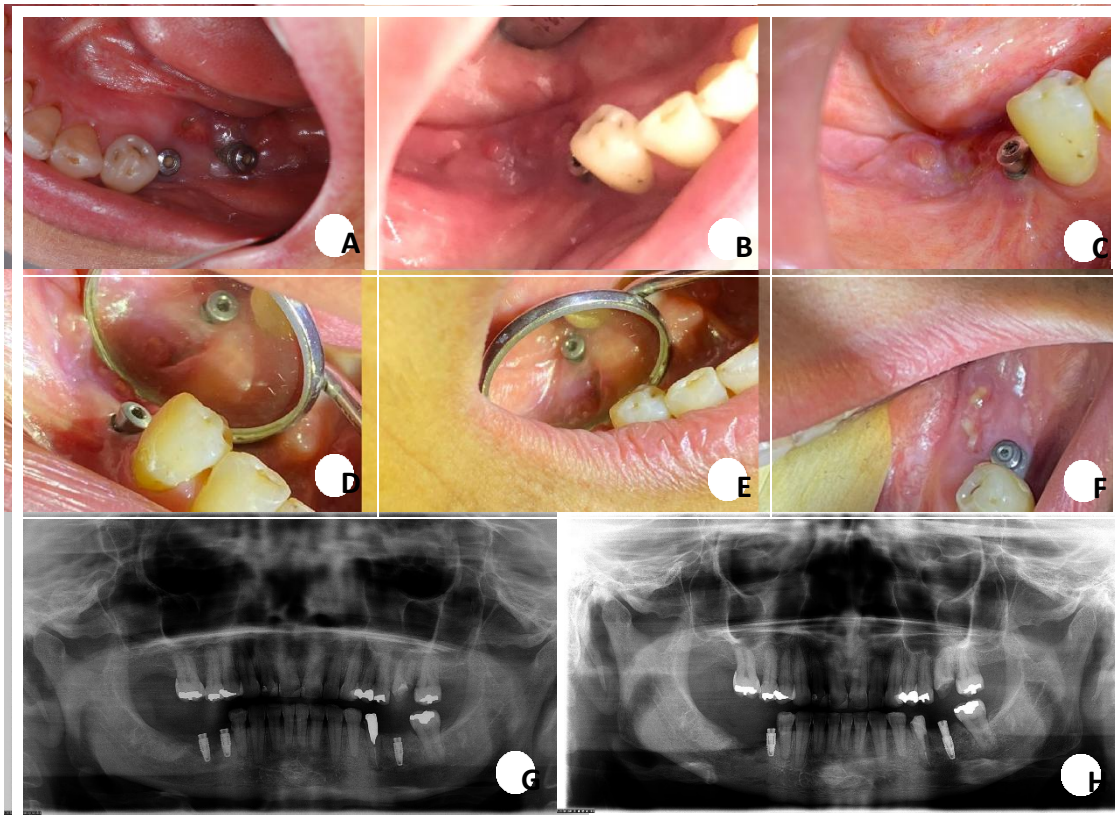

Figure 2: (A) Initial condition of the injury - baseline period **(B)** 7 days after first application **(C)** 15 days after first application of i-PRF **(D)** 30 days after first application of i-PRF **(E)** 60 days after first application i-PRF **(F)** 90 days after the first application of i-PRF **(G)** Initial panoramic radiograph - baseline **(H)** Final panoramic radiograph - 90-day period.

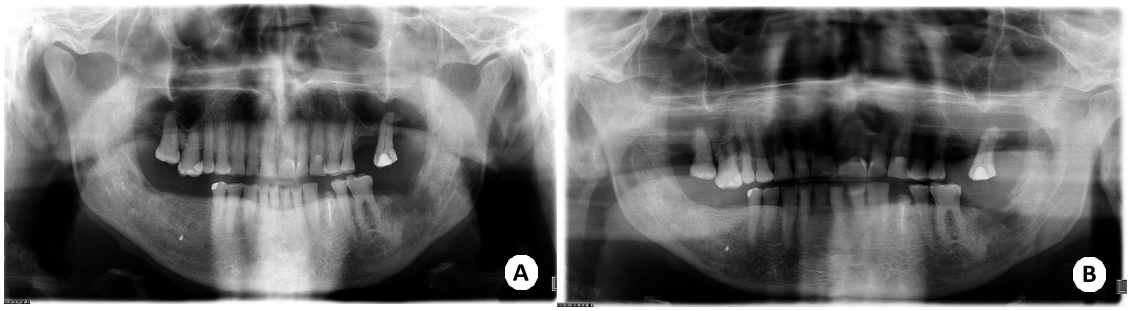

Figure 3: (A) Initial panoramic radiograph at baseline before tooth extraction; **(B)** Final panoramic radiograph within 90 days of starting treatment of ORN lesions with i-PRF.

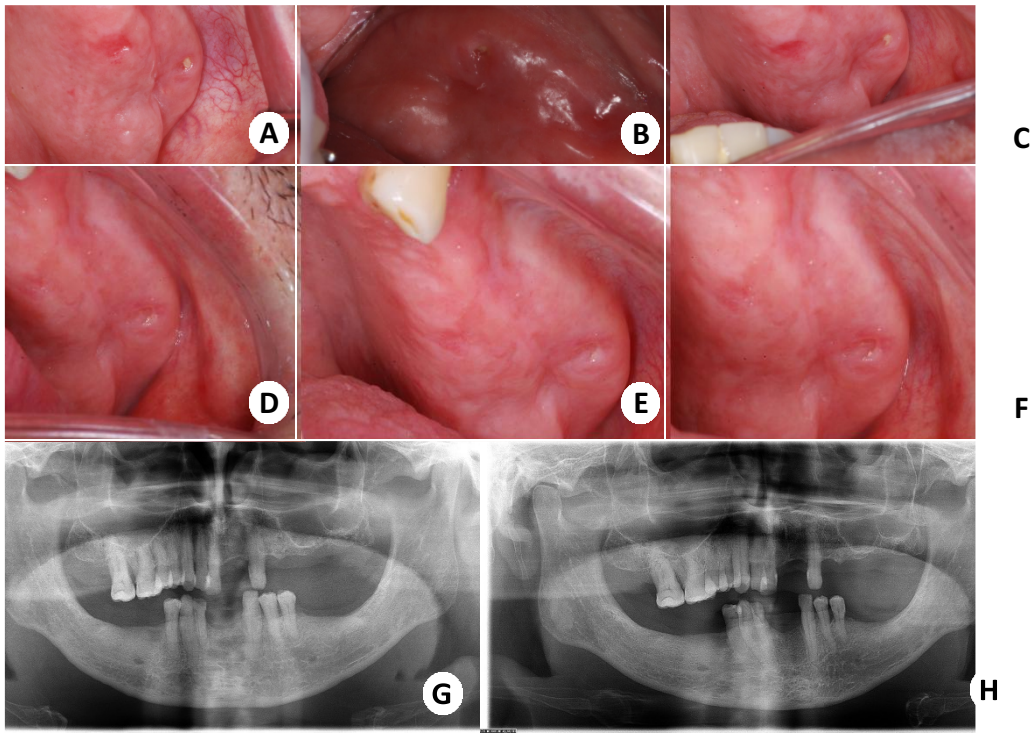

Figure 4: (A) Initial condition of the injury - baseline period **(B)** 7 days after first application **(C)** 15 days after first application of i-PRF **(D)** 30 days after first application of i-PRF **(E)** 60 days after first application i-PRF **(F)** 90 days after the first application of i-PRF **(G)** Initial panoramic radiograph - baseline **(H)** Final panoramic radiograph - 90-day period.

4. CONSIDERAÇÕES FINAIS

De uma forma geral, essa dissertação demonstra que o tratamento oncológico por radioterapia na cabeça e no pescoço é um importante fator de risco para ocorrência de lesões de manejo complexo e, devido a isso, um protocolo terapêutico pré-radioterapia deve ser aplicado para reduzir a necessidade de tratamento após a radioterapia. Porém, caso o tratamento odontológico seja necessário o mesmo deve ser executado de forma mais conservadora possível. Além disso, demonstrou a baixa previsibilidade do tratamento de lesões de ORN apesar do concentrado sanguíneo utilizado (i-PRF) ter potencial de melhorar o tecido mole ao redor dessas lesões e, pelo menos teoricamente, beneficiar o resultado clínico de futuras intervenções cirúrgicas nessas lesões.

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ANEXO: Carta de aprovação do Comitê de ética em Pesquisa

Pesquisador: Priscilla Barbosa Ferreira Soares
Área Temática:
Versão: 2
CAAE: 38301120.4.0000.5152
Instituição Proponente: FACULDADE DE ODONTOLOGIA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.394.121

Apresentação do Projeto:
Trata-se da versão 2 do projeto de pesquisa, após respostas de pendências referentes ao parecer 4.351.118, de 20 de Outubro de 2020.

Nas palavras dos autores, nos termos do documento <PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1613550.pdf>:

A osteorradionecrose (ORN) é uma complicação importante decorrente do tratamento radioterápico utilizado amplamente para tratamento de câncer de cabeça e pescoço. A ocorrência dessa lesão afeta a qualidade de vida de forma significativa devido as suas características clínicas e a sua sintomatologia dolorosa. Infiltrados sanguíneos, tais como o plasma rico em fibrina tem sido utilizado para acelerar o reparo tecidual em condições clínicas diversas devido aos estímulos na angiogênese e presença de fatores de crescimento que estimulam processos de proliferação, diferenciação e atividade celular nos tecidos conjuntivos. Dentre esses infiltrados, destaca-se a utilização da Fibrina rica em plaquetas injetável (iPRF) que, por se apresentarno estado líquido, pode ser modulado e utilizado em defeitos ósseos irregulares que são característicos de sítios pósremoção de osso necrótico decorrentes da ORN. O objetivo desse estudo será de avaliar o efeito do i-PRF na cicatrização de lesões de osteorradionecrose em pacientes submetidos a radioterapia. Serão selecionados 40 pacientes com lesões de ORN que serão aleatoriamente

2 – grupo experimental: pacientes com lesões de ORN tratadas pelo debridamento cirúrgico associado ao uso do i-PRF.

Todos os pacientes atendidos receberão prescrição medicamentosa e orientações pós-cirúrgica. Os pacientes serão avaliados em relação ao reparo das lesões de ORN por análises clínicas e radiográficas. Adicionalmente, serão executadas análises em relação ao efeito dos diferentes tratamentos de ORN sobre a qualidade de vida dos pacientes pela aplicação do questionário OHIP14 (Qualidade de vida relacionada com a saúde oral).

Critério de Inclusão:

Serão incluídos neste estudo pacientes com lesões de osteorradionecrose que sejam maiores de idade de ambos os gêneros e que forneçam consentimento para participação neste projeto de pesquisa.

Critério de Exclusão:

Serão excluídos desse estudo pacientes com discrasias sanguíneas, diabéticos descompensados, pacientes que fizeram uso de antibióticos nos últimos 3 meses e pacientes que estejam em fase ativa de tratamento radioterápico.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar o efeito do IPRF na cicatrização de lesões de osteorradionecrose em pacientes submetidos a radioterapia de cabeça e pescoço.

Objetivo Secundário:

2. Avaliar o efeito do i-PRF na cicatrização de tecido mole em lesões de osteorradionecrose em pacientes submetidos a radioterapia;

3. Avaliar o impacto do tratamento de lesões de osteorradionecrose com i-PRF na qualidade de vida do paciente.

Avaliação dos Riscos e Benefícios:
Conforme o protocolo:

Riscos:

Por se tratar de um procedimento cirúrgico, podem ocorrer complicações tais como inchaço, dor, sangramento, dificuldade de falar nos primeiros dias, hematomas, infecções e alterações na sensibilidade das áreas operadas. Como forma de amenizar a ocorrências dessas complicações, os pesquisadores irão prescrever medicações que controlam a dor, e previnem as infecções. Os riscos da coleta de sangue incluem infecção por agentes externos ao corpo, hematoma, edema e dor no local. Para minimizar esses riscos, esse procedimento será feito por profissional treinado e todos os materiais estéreis. Ressaltamos quea equipe de trabalho tem experiência com esse tipo de procedimento cirúrgico e que esse fato deverá também reduzir as chances das complicações acontecerem.

Benefícios:

O benefício será uma contribuição coletiva, com novo tratamento que busca melhores resultados clínicos na cicatrização da gengiva e do osso em pacientes que desenvolveram osteoradionecrose após a radioterapia na região de cabeça e pescoço.

Comentários e Considerações sobre a Pesquisa:
RESPOSTAS DAS PENDÊNCIAS APONTADAS NO PARECER ANTERIOR

1. Solicita-se esclarecimentos sobre quais os participantes farão uso de tratamento antibiótico, considerando que há informações dúbias ou conflitantes sobre este tópico (pelo que se entendo

medicamentosa, o que não seria ético, se o antibiótico for dado somente no grupo controle.

Resposta: A alteração foi feita no projeto e no TCLE. Para melhor esclarecimento,
todos os participantes, independente dos grupo, receberão medicamento pós cirúrgico. Ressalto que a prescrição medicamentosa é um procedimento padrão para todos os pacientes que passam por cirurgia no serviço PROCEDE - Programa de Cuidados Específicos às Doenças Estomatológicas.

PENDÊNCIA 1 ATENDIDA.

2. O TCLE apresenta a seguinte frase: "Será prescrito antibiótico por 7 dias (Amoxicilina 500mg + metronidazol 250 mg). Serão prescritos analgésicos (Dipirona Sódica ou Paracetamol) e antiinflamatórios (Nimesulida), bem como bochechos com antissépticos (Clorexidina a 0,12%)". O TCLE também apresenta a frase: " Você não terá nenhum gasto nem ganho financeiro por participar na pesquisa. " ENTRETANTO, o documento "ORÇAMENTO" não prevê o gasto com compra de antibióticos, nem com analgésicos, nem com antiinflamatórios, nem com antissépticos.

Resposta: Os medicamentos prescritos são oferecidos pelo SUS. Os pacientes são rotineiramente orientados a pegarem os medicamentos em qualquer farmácia das UAIs (Unidade de Atendimento Integrado) de Uberlândia. Por precaução os pesquisadores irão adquirir esses medicamentos para doação caso falte nas farmácia das UAIs. Esse custo foi inserido na tabela de orçamento. Não iremos prescrever o anti-inflamatório não esterioidal por causa de possíveis interações medicamentosas.

PENDÊNCIA 2 ATENDIDA, ficando em conformidade com a resolução 510/16 que diz que " As pesquisas devem ter seu orçamento discriminado e não devem onerar o SUS com procedimentos extras àqueles necessários ao atendimento ao paciente."

3. O TCLE contém termos de difícil compreensão para o participante da pesquisa, o que contraria as resoluções 466 e 510 do CNS (necrose óssea; radioterapia; osteorradionecrose; condição

Resposta: Foi feita a modificação dos termos para que ficasse mais compreensível.

PENDÊNCIA 3 ATENDIDA.

4. O TCLE não informa ao participante, que o protocolo de pesquisa prevê a aplicação de questionário ou questionários de qualidade de vida. O participante precisa ter ciência de todas as etapas da pesquisa, para que possa decidir se deseja participar ou não.

Resposta: Foi feita a alteração incluindo todos os termos que serão respondidos pelo paciente.

PENDÊNCIA 4 ATENDIDA.

5. BENEFÍCIOS DO ESTUDO: Nas palavras dos pesquisadores: "Os benefícios consistem em:
você será acompanhado durante toda fase de cicatrização após o procedimento cirúrgico, e será incluído em um programa de manutenção e cuidados de saúde bucal que é específico para tratamento de pacientes com histórico de radioterapia na região da cabeça e do pescoço (PROCEDE – Programa de Cuidados Específicos às Doenças Estomatológicas)." O CEP-UFU solicita esclarecimentos se os pacientes, que NÃO são participantes de pesquisa, têm acesso ao programa "PROCEDE".

Resposta: A titulo de esclarecimento ao parecerista. Todos os pacientes com diagnóstico de câncer de cabeça e pescoço, que necessitam de tratamento odontológico, são encaminhados para o serviço PROCEDE - Programa de Cuidados Específicos às Doenças Estomatológicas. O tratamento odontológico é oferecido antes e após a cirurgia de remoção do câncer e a radioterapia. Independente do pacienteparticipar ou não da pesquisa ele já é atendido no PROCEDE. Os pesquisadores responsáveis pelapesquisa irão recrutar os pacientes com quadro de osteoradionecrose que já são atendidos e acompanhados no serviço PROCEDE. Os benefícios consistem em novo tratamento que buscam melhores resultados clínicos na cicatrização da gengiva e do osso em pacientes que desenvolveram osteoradionecrose após a radioterapia na região de cabeça e pescoço. Essa colocação foi alterada no projeto e no TCLE.

6. O projeto detalhado e o documento "PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1010000.pdf" citam: " ... parâmetros a serem avaliados por escores (Classificações de Notoni, Store e Epstein; OHIP14; Escala de Landry)". ENTRETANTO, somente o questionário "OHIP14" foi incluído no protocolo de pesquisa, não tendo sido encontradas as descrições de Classificações de Notoni, Store e Epstein; SF-36; Escala de Landry, nem esclarecimentos sobre se serão aplicadas ou não e, se sim, como serão aplicadas aos participantes da pesquisa.

Resposta: Como descrito no projeto as Classificações de Notoni, Store e Epstein são utilizados, pelos pesquisadores, para obter os scores para analise do tamanho, localização, aspecto clínico e prognóstico das lesões de ORN. A Escala de Landry, também usada pelos pesquisadores, é utilizada para avaliar o grau de cicatrização. São referencias usadas pelo pesquisador durante a análise clinica antes e após tratamento. Nesse momento não há nenhum questionamento ao paciente. O que será aplicado ao paciente é apenas o questionário "OHIP14" relacionado a qualidade de vida antes e após o procedimento e a escala de VAS sobre sensação dolorosa e edema pós cirurgia.

PENDÊNCIA 6 ATENDIDA.

7. O TCLE contém a frase: "coleta do seu sangue para produção deste material que será aplicado na lesão de osteorradionecrose. Para essa coleta utilizaremos dois tubos de 9ml". O CEP-UFU solicita que isto seja explicado de maneira clara ao participante, em linguagem acessível, de forma que ele possa decidir se deseja participar ou não, tendo clareza do que significa "2 tubos de 9mL de sangue".

Resposta: A alteração foi feita para que ficasse mais compreensível.

PENDÊNCIA 7 ATENDIDA.

8. O protocolo de pesquisa cita, inclusive no TCLE, a frase: "Todo protocolo terapêutico será

caso haja outro grupo de pesquisadores. Além de link de currículo lattes, se for o caso.

Resposta: Obrigada pelo questionamento. Quando utilizamos o termo equipe médica nos referimos aos pesquisadores envolvidos no projeto. Removemos essa frase para não haver erro na comunicação.

PENDÊNCIA 8 ATENDIDA.

9. No projeto de pesquisa, tanto o detalhado quanto o <PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1613550.pdf>, diz que "O processo de randomização será baseado no uso de uma tabela online de randomização." ENTRETANTO, no TCLE, a informação que consta é "Essa seleção e inclusão nos grupos será feita através de um sorteio simples". O CEP-UFU solicita esclarecimentos sobre como será feita a aleatorização dos participantes e informa que deve ser a mesma em todos os documentos do protocolo de pesquisa.

Resposta: A randomização será feita através de uma tabela online do site chamado random.org, todavia havíamos colocado sorteio simples no TCLE para que ficasse mais fácil para o paciente entender.

PENDÊNCIA 9 ATENDIDA.

10. O TCLE não descreve o risco relacionado à coleta de sangue e o que será feito para minimizá-lo.

Resposta: Alteração foi realizada. “Os riscos da coleta de sangue incluem infecção por agentes externos ao corpo, hematoma, edema e dor no local. Para minimizar esses riscos, esse procedimento será feito por profissional treinado e todos os materiais estéreis.”

PENDÊNCIA 10 ATENDIDA.

Resposta: Foi acrescido a frase "Em nenhum momento você será identificado, porém existe o risco de ter o seu sigilo exposto, mas isso será minimizado através da colocação de códigos no seu prontuário."

PENDÊNCIA 11 ATENDIDA.

12. A sigla i-PRF é citada 16 vezes no <PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1613550.pdf>, 18 vezes no projeto detalhado, 1
vez no título, 6 vezes no TCLE. O CEP-UFU solicita esclarecimentos. O que significa i-PRF?

Resposta: Foi feita a correção necessária para que ficasse mais compreensível. i-PRF significa "Fibrina rica em plaquetas injetável"

PENDÊNCIA 12 ATENDIDA.

13. O Índice OHIP – 14 está previsto como questionário de qualidade de vida. O CEP-UFU solicita esclarecimentos sobre como será aplicado. Pelo pesquisador? O participante o responderá? No próprio documento não há descrição do significado da siga OHIP-14. Adequar.

Resposta: O ideal é que o questionário seja preenchido, a próprio punho, pelo paciente. Caso não seja possível os pesquisadores responsáveis se comprometem a fazerem a leitura e preencherem o formulário. O significado de OHIP-14 já foi acrescido no projeto.

PENDÊNCIA 13 ATENDIDA.

Considerações sobre os Termos de apresentação obrigatória:

Parecer baseado nos seguintes documentos apresentados:

PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1613550.pdf 07/11/2020 18:40:30
Analise_cicatrizacao_clinica.pdf 07/11/2020 18:39:32
Carta_resposta_ao_parecerista.pdf 07/11/2020 18:37:21

TCLE.pdf 07/11/2020 18:35:44
Projeto_iPRF.pdf 07/11/2020 18:35:01
Termo_de_Compromisso_Equipe.pdf 14/09/2020 19:00:51
Folhaderosto.pdf 08/09/2020 08:31:05
Curriculo_Priscilla.pdf 07/09/2020 19:19:45
curriculonurye.pdf 07/09/2020 19:15:21
Declar_FOUFU.jpg 16/08/2020 16:59:14

Conclusões ou Pendências e Lista de Inadequações:
As pendências apontadas no parecer consubstanciado número 4.351.118, de 20 de Outubro de 2020, foram atendidas.

De acordo com as atribuições definidas na Resolução CNS 466/12, Resolução 510/16 e suas complementares, o CEP manifesta-se pela aprovação do protocolo de pesquisa proposto.
O protocolo não apresenta problemas de ética nas condutas de pesquisa com seres humanos, nos limites da redação e da metodologia apresentadas.

Data para entrega de Relatório Parcial ao CEP/UFU: Dezembro de 2021.
Data para entrega de Relatório Parcial ao CEP/UFU: Dezembro de 2022.
Data para entrega de Relatório Parcial ao CEP/UFU: Dezembro de 2023.
Data para entrega de Relatório Final ao CEP/UFU: Dezembro de 2024.

* Tolerância máxima de 06 meses para atraso na entrega do relatório final.

Considerações Finais a critério do CEP:

OBS.: O CEP/UFU LEMBRA QUE QUALQUER MUDANÇA NO PROTOCOLO DEVE SER INFORMADA IMEDIATAMENTE AO CEP PARA FINS DE ANÁLISE E APROVAÇÃO DA MESMA.

O CEP/UFU lembra que:

b- poderá, por escolha aleatória, visitar o pesquisador para conferência de relatório e documentação pertinente ao projeto.

c- a aprovação do protocolo de pesquisa pelo CEP/UFU dá-se em decorrência do atendimento as Resoluções CNS 466/12, 510/16 e suas complementares, não implicando na qualidade científica do mesmo.

Orientações ao pesquisador :

• O participante da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 466/12 e 510/16) e deve receber uma via original do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado.

• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS 466/12), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa que requeiram ação imediata.

• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS 466/12). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

• Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, destacando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprobatório do CEP, para serem juntadas ao protocolo inicial (Res.251/97, item III.2.e).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação

pelo Pesquisador		18:37:21	Ferreira Soares	
Outros	OHIP_14.pdf	07/11/2020 18:37:07	Priscilla Barbosa Ferreira Soares	Aceito
Outros	Escala_vas_2.pdf	07/11/2020 18:36:44	Priscilla Barbosa Ferreira Soares	Aceito
Outros	Escala_vas_1.pdf	07/11/2020 18:36:22	Priscilla Barbosa Ferreira Soares	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	07/11/2020 18:35:14	Priscilla Barbosa Ferreira Soares	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_iPRF.pdf	07/11/2020 18:35:01	Priscilla Barbosa Ferreira Soares	Aceito
Declaração de Pesquisadores	Termo_de_Compromisso_Equipe.pdf	14/09/2020 19:00:51	Priscilla Barbosa Ferreira Soares	Aceito
Folha de Rosto	Folhaderosto.pdf	08/09/2020 08:31:05	Priscilla Barbosa Ferreira Soares	Aceito
Outros	Curriculo_Priscilla.pdf	07/09/2020 19:19:45	Priscilla Barbosa Ferreira Soares	Aceito
Outros	curriculonurye.pdf	07/09/2020 19:15:21	Priscilla Barbosa Ferreira Soares	Aceito
Declaração de Instituição e Infraestrutura	Declar_FOUFU.jpg	16/08/2020 16:59:14	Priscilla Barbosa Ferreira Soares	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

[redacted]