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Treatment of osteoradionecrosis of the jaw with injectable platelet-rich fibrin (i-PRF): case series

Tratamento de osteorradionecrose dos maxilares com fibrina rica em plaquetas injetável (i-PRF): série de casos

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ABSTRACT

Objective: This study evaluated the use of autogenous blood concentrate (injectable platelet-rich fibrin) [i-PRF] for promoting soft tissue healing in osteoradionecrosis (ORN) lesions in patients who underwent head and neck radiotherapy. **Material and Methods:** This study included five ORN lesions in four patients who were treated with i-PRF (applied weekly for 4 weeks to the lesions). Soft tissue features were evaluated through clinical analysis at baseline and at 7, 15, 30, 60, and 90 days after the first session of i-PRF. Extension of the bone lesions was evaluated radiographically. Patient-centered related outcomes were evaluated using quality-of-life questionnaires at baseline and 90 days after the first treatment session. Quality of life data were analyzed using descriptive and frequency statistics and the Wilcoxon test. **Results:** Of the 5 treated lesions, 1 was completely closed and 3 remained open. The open lesions showed increased necrotic tissue exposure. No changes were observed in the radiographic appearance of the lesions. There was also no impact on the patient's quality of life. **Conclusion:** The results suggest that the majority of ORN lesions remained stable after the application of i-PRF, with a slight improvement in the quality of the mucosa around the lesions. Furthermore, it was observed that i-PRF did not compromise the quality of life of patients during treatment.

KEYWORDS

Head and neck neoplasms; Osteoradionecrosis; Platelet-rich fibrin; Quality of life; Radiotherapy.

RESUMO

Objetivo: Este estudo avaliou o uso de concentrado de sangue autógeno (fibrina rica em plaquetas injetável) [i-PRF] para promover a cicatrização de tecidos moles em lesões de osteorradionecrose (ORN) em pacientes submetidos a radioterapia de cabeça e pescoço. **Material e Métodos:** Este estudo incluiu cinco lesões de ORN em quatro pacientes tratados com i-PRF (aplicado semanalmente por 4 semanas nas lesões). As características do tecido mole foram avaliadas por meio de análises clínicas no início e aos 7, 15, 30, 60 e 90 dias após a primeira sessão de i-PRF. A extensão das lesões ósseas foi avaliada radiograficamente. Os resultados centrados no paciente foram avaliados usando questionários de qualidade de vida no início e 90 dias após a primeira sessão de tratamento. Os dados de qualidade de vida foram analisados usando estatísticas descritivas e de frequência, além do teste de Wilcoxon. **Resultados:** Das 5 lesões tratadas, 1 foi completamente fechada e 3 permaneceram abertas. As lesões abertas mostraram aumento na exposição de tecido necrótico. Não foram observadas mudanças na aparência radiográfica das lesões. Também não houve impacto na qualidade de vida do paciente. **Conclusão:** Os resultados sugerem que a maioria das lesões de ORN permaneceu estável após a aplicação de i-PRF, com uma discreta melhora na qualidade da mucosa ao redor das lesões. Além disso, observou-se que a i-PRF não comprometeu a qualidade de vida dos pacientes durante o tratamento.

PALAVRAS-CHAVE

Neoplasias de cabeça e pescoço; Osteorradionecrose; Fibrina rica em plaquetas; Qualidade de vida; Radioterapia.

INTRODUCTION

Osteoradionecrosis (ORN) is a serious complication of radiotherapy, that is widely used to treat several types of head and neck cancers [1,2]. The clinical presentation of ORN includes bone exposure associated with the loss of skin and mucosal integrity that persists for at least three months without healing [1-3]. This condition occurs because of radiation-induced hypoxia, hypocellularity, tissue hypovascularization and radiation-induced fibrosis [1-4]. The main risk factors for the development of ORN are the size and location of the tumor [5], tooth extractions [6], radiation dosage [1-3], smoking habits [7], presence of infections [8], medications [9], low immunity [10] and periodontal disease [1,11].

Ideally, when planning radiotherapy treatment in the head and neck region, patients should be risk assessed for ORN, and identified risks should be modulated to prevent the occurrence of ORN where possible [8,12]. However, it is impossible to control all risk factors 100% of the time [8,10]. The prevalence of ORN is up to 15% [10]. ORN has a significant impact on the patient's quality of life due to symptoms that involve spontaneous and chronic pain, dysphagia, and facial deformation [1,8,10]. This impact is even greater because patients have already been debilitated by cancer treatment [8].

The standard treatment for ORN is surgical resection of the lesion [10]. However, 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 successful ORN resolution in only 55 patients [13]. Consequently, therapeutic modalities, have been proposed for ORN treatment [2]. These are mainly adjunctive to surgical debridement of ORN lesions [2,14,15]. Or surgical resections and include systemic antibiotics [2], photobiomodulation therapy [14], hyperbaric chambers [15], and ozone therapy [2]. The continual search for alternative or complementary therapeutic protocols for ORN is necessary [5].

Platelet-rich fibrin (PRF) is a concentrate of autologous growth factors used in the medical and dental fields to aid tissue regeneration [16]. The mechanism of action of PRF involves accelerating tissue regeneration through the stimulation of angiogenesis by cytokines and growth factors, connective tissue proliferation, differentiation, and cellular activity [17]. It is a material obtained by collecting the patient's own blood, and hence, offers additional advantages, such as absolute biocompatibility and reduced cost, compared with other options [18].

Different centrifugation protocols result in specific types of PRF, distinguished by the quantity of cells and growth factors, as well as the physical presentation and manipulation of the blood infiltrate [19]. An injectable form of PRF is advantageous because as a liquid, it can be easily manipulated and applied to the typical irregular ORN bone defects [17,18]. Importantly, improving local soft tissue health around the ORN lesions is paramount in enhancing treatment outcomes [20]. Furthermore, the use of PRF improves the phenotypic pattern of keratinized tissues [21]. Hence, the use of this blood concentrate, at least theoretically, can improve the condition of keratinized tissues, and thus, provide surgical benefits.

To date, evidence supporting the use of i-PRF to treat ORN of the jaw is limited. Hence, this study aimed to evaluate an autogenous blood concentrate (i-PRF) protocol for the initial treatment of ORN lesions in patients who underwent head and neck radiotherapy.

MATERIAL & METHODS

Patients

This study enrolled patients with ORN of the jaw related to radiotherapy for head and neck cancer treatment, in the period from February to December 2021. The protocol was submitted and approved by the Human Research Ethics Committee of the Federal University of Uberlândia (CAAE: 38301120.4.0000.5152). ORN was diagnosed based on a long-standing (> 3 months) mucosal ulceration resulting in exposed bone in the irradiated field [10]. Management of the patient's jaw condition was performed in the Dental Hospital of the Federal University of Uberlândia, Brazil.

Treatment with i-PRF and clinical analysis

To produce i-PRF, blood was collected from each patient using two tubes of 13 ml (Tubos i-PRF+ | Process for PRF® (by Choukroun), Nice, France), without any additive, and i-PRF synthesis

was conducted according to the Choukroun protocol [16].These tubes were centrifuged for 3 minutes (for women) and 4 minutes (for men), at 700 rpm, at room temperature (Duo Quattro (by Choukroun) | PRF Process®, Nice, France). Following centrifugation, i-PRF can be seen as an orange upper phase. The tubes were carefully opened to prevent homogenizing 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 and immediately injected into all surrounding soft tissues of the patient's ORN lesion through a 30G X 1/2 hypodermic needle (Injex®, Brazil). This procedure was performed once a week for four consecutive weeks. Each patient was clinically evaluated at baseline and 7, 15, 30, 60, and 90 days after the first application of i-PRF. Panoramic radiographs were obtained at baseline and 90 after the first application of i-PRF.

The following clinical parameters were assessed: necrotic tissue (absence or presence), wound closure (yes or no), connective tissue exposition (in mm^2), pain sensation (VAS Scale numeric between 0-10 considering 0 no pain and 10 higher levels of pain), and healing degree using Landry´s scale, which evaluates four parameters (color of the mucosa, palpation, granulation tissue, and wound epithelization) qualified in a scale metric from 1 to 5 (1-very poor, 2 = poor, 3 = good, 4 = very good, 5- excellent).

Quality of life analysis

To analyze the impact of treatment on the quality of life, each patient was asked to answer two questionnaires, related to general quality of life (QLQ-C30) and oral health (QLQ-H&N35) [22]. The QLQ-C30 questionnaire consists of 30 questions divided into 17 domains, while the QLQ-H&N35 questionnaire consists of 35 questions divided into 18 domains. Questionnaires were evaluated on a Likert scale:1 = never, 2 = sometimes, 3 = often, and 4 = always. The answers to these questionnaires were considered as percentages for statistical purposes, with scale 1 being considered 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 a value of 0 being considered 0% and a value of 1 being considered 100%. The last two questions of the QLQ-C30 questionnaire were numbered from 1-7, with the number 1 being considered 14.28%, and the value 7 being 100%. Patients answered these questionnaires at baseline and 90 days after starting the i-PRF treatment.

Statistical analysis

Quality of life data were analyzed using descriptive and frequency statistics and the Wilcoxon test. All statistical tests were performed at the 95% confidence level. GraphPad Prism 8.4 software (San Diego, CA, USA) was used for statistical analysis.

RESULTS

Five ORN lesions were diagnosed in four patients (three male and one female) were included in this study. The sociodemographic data and information regarding the treatment of head and neck cancer patients included are presented in Table I. The mean age was 57.2 ± 7.4 years. Two patients were smokers (40%). None reported the present or past use of bone antiresorptive agents.

The ORN showed balanced incidence in this study, with 50% in maxillary lesions and 50% in mandibular lesions, as shown in Table II. All ORN lesions developed in the posterior region of the arch. The majority of ORN was related to tooth extractions (60%), followed by ill-fitting

Table I - Characteristics of patients with head and neck cancer who developed ORN included in the study

Patient	Gender	Age (Years)	Type of cancer	Tumor location	Treatment	Total Radiation	Comorbidities
1	M	61	CM	Cervical lymph nodes	CT + RT	7.200cGy	Smoker
2	F	48	SCC	Tongue	SUR + CT + RT	7.200cGy	NCP
3	M	65	SCC	Soft palate	CT + RT	7.200cGy	Hypertension
4	M	55	SCC	Soft palate and tonsils/ oropharyngeal pillars	CT + RT	7.200cGy	Hypertension

M: male; F: female; CM: Carcinoma metastatic; SCC: Squamous cell carcinoma; SUR: Surgery; CT: Chemotherapy; RT: Radiotherapy; NCP: No comorbidities present.

prosthesis (20%) and dental implant placement (20%). The results showed a large difference in post-radiation period among the patients (38.7 ± 31,9 months).

At baseline, all lesions were small (< 2 cm), presenting as ulcers and exposed bone spicules, and radiographically confined to the alveolar ridge. During follow-up, one lesion closed (10%) and the others remained open (Table III). No adverse effects were reported; only two patients reported pain in the affected area during the study, which was controlled with analgesic.

A slight improvement in the quality of the mucosa around the lesions was observed in three cases (60%) (Table IV). At the end of the assessments, two patients were classified as having poor wound healing, while another two showed good wound healing, according to the Landry and Howley scale [23].

Table II - Clinical information about ORN lesions of the patients included in this study

Patient	Location Max/Mand	Specific location	Causes	Pos-radiation time
1	Mand	Alveolar ridge	tooth extraction	14 months
2	Mand	Alveolar ridge	Tooth implant placement	6 years
3	Max and Mand	Alveolar ridge	Teeth extraction	5 years
4	Max	Alveolar ridge	Ill-fitting prosthesis	9 months

Max: Maxilla; Mand: Mandible.

Table III - Clinical data of the ORN lesions aspects and frequency of the clinical features in all the patients

Analysis/Period		7 days	15 days	30 days	60 days	90 days
Necrotic Tissue	**Present**	4	4	4	4	4
	Absent	1	1	1	1	1
Closening of the wound	**Close**	1	1	1	1	1
	Open	4	4	4	4	4
Area of the exposed connective tissue (mm^2) (mean ± SD)		31.60±33.37	32.10±29.58	39.00±40.68	52.80±47.93	96.80±116.90
VAS scale (mean ± SD)	**Pain**	2.80±2.58	3.00±2.82	2.00±2.44	3.60±3.57	2.40±3.28

SD: Standard deviation.

Table IV - Clinical data on the appearance of ORN lesions analyzed through the assessment of healing using the Landry scale

Analysis/Period	Case	7 days	15 days	30 days	60 days	90 days
Colour of the mucosa	**1**	0	0	0	0	0
	2	0	0	0	0	0
	3	1	1	1	2	2
	4	3	3	3	3	3
	5	1	1	1	1	1
Palpation	**1**	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	4	2	2	2	2	2
	5	3	3	3	3	3
Granulation tissue	**1**	5	5	5	5	5
	2	0	0	0	0	0
	3	0	0	0	0	0
	4	0	0	0	0	0
	5	0	0	0	0	0
Wound epithelialization	**1**	4	3	2	2	3
	2	0	1	1	1	0
	3	0	0	0	0	0
	4	1	1	2	2	2
	5	0	0	0	0	0

There was an overall modest and non-significant improvement in the quality of life after beginning treatment of the lesions (Table V). No radiographic changes were observed in any of the patients during the analyzed periods.

Clinical and radiographic follow-up of the cases

Figure 1 depicts the radiographs and clinical progression of patient 1 over the 90-day follow-up period.

Figure 2 shows the radiographic follow-ups over the 90-day monitoring period. The patient had limited mouth opening, which prevented photographic clinical recording.

Figure 3 shows the radiographic follow-ups over the 90-day monitoring period. The patient had limited mouth opening, which prevented photographic clinical recording (Figure 3).

Figure 4 displays the radiographic follow-ups and clinical analyses of patient 4.The ORN lesion

Table V - Description of the 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 mean (median) ± SD	90 days mean (median) ± SD	p value
QLQ-C30			
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
H&N35			
Pain	39.06(40.63) ± 5.98	39.06(37.50) ± 16.44	>0.999
Swallowing	31.25(28.13) ± 8.83	32.81(31.25) ± 7.86	>0.999
Senses	34.38(31.25) ± 11.97	34.38(31.25) ± 11.97	>0.999
Speech	25.00(25.00) ± 0.00	28.13(25.00) ± 6.25	>0.999
Social eating	34.38 (34.38) ± 3.60	31.88(31.25) ± 6.16	>0.999
Social contact	32.81(28.13) ± 11.83	25.00(25.00) ± 0.00	0.500
Sexuality	34.38(31.25) ± 11.97	31.25(25.00) ± 12.50	>0.999
Teeth	50.00(50.00) ± 20.41	37.50(25.00) ± 25.00	0.750
Opening mouth	37.50(37.50) ± 14.43	37.50(25.00) ± 25.00	>0.999
Dry mouth	50.00 (50.00) ± 0.00	75.00(75.00) ± 20.41	0.250
Sticky saliva	50.00(50.00) ± 20.41	62.50(62.50) ± 32.27	>0.999
Cough	37.50(37.50) ± 14.43	34.38(31.25) ± 11.97	>0.999
Felt ill	25.00(25.00) ± 0.00	37.50(37.50) ± 14.43	0.500
Pain killers	50.00 (50.00) ± 57.74	75.00 (100.00) ± 50.00	>0.999
Nutritional supplements	50.00(50.00) ± 57.74	50.00(50.00) ± 57.74	>0.999
Feeding tube	0.00(0.00) ± 0.00	0.00(0.00) ± 0.00	>0.999
Weight loss	25.00(0.00) ± 50.00	50.00(50.00) ± 57.74	>0.999
Weight gain	0.00(0.00) ± 0.00	0.00(0.00) ± 0.00	>0.999

SD: Standard deviation.

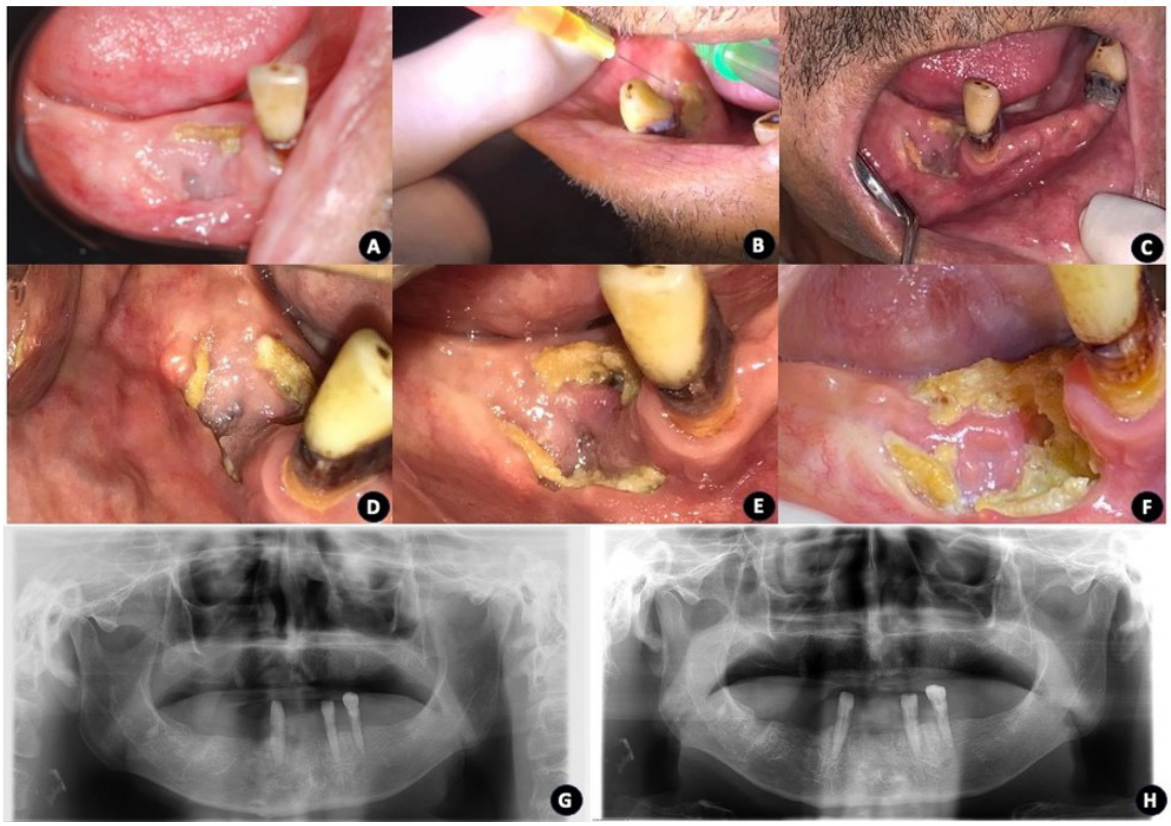

Figure 1 - Clinical condition of the ORN lesion in Patient # 1 at baseline (A) and within 7 days after the first application of i-PRF (with the needle of the second application) (B), 15 days (C), 30 days (D), 60 days (E), and 90 days of follow-up (F). Radiographic aspect at baseline (G) and at 90 days (H).

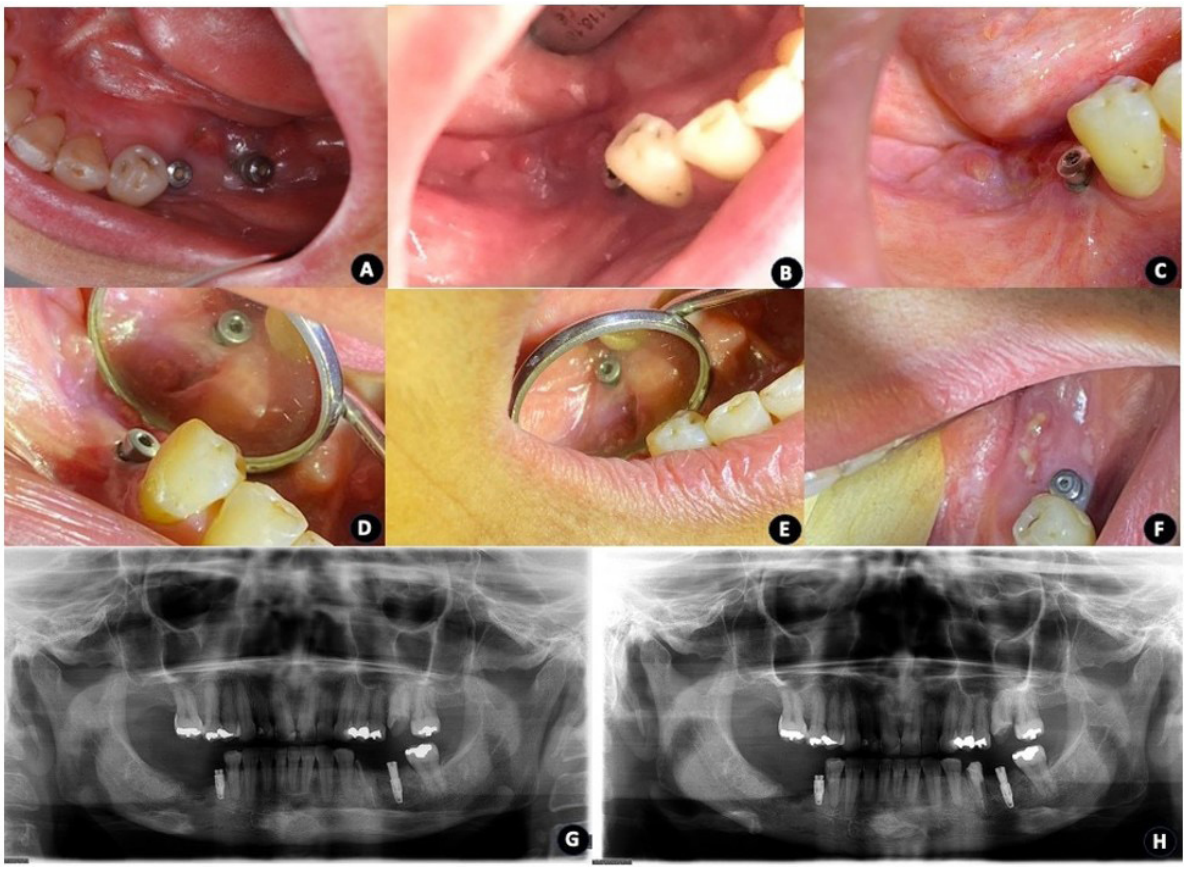

Figure 2 - Clinical condition of the ORN lesion in Patient # 2 at baseline (A) and within 7 days (B), 15 days (C), 30 days (D), 60 days (E), and 90 days after the first application of i-PRF (F). Radiographic aspect at baseline (G) and at 90 days (H).

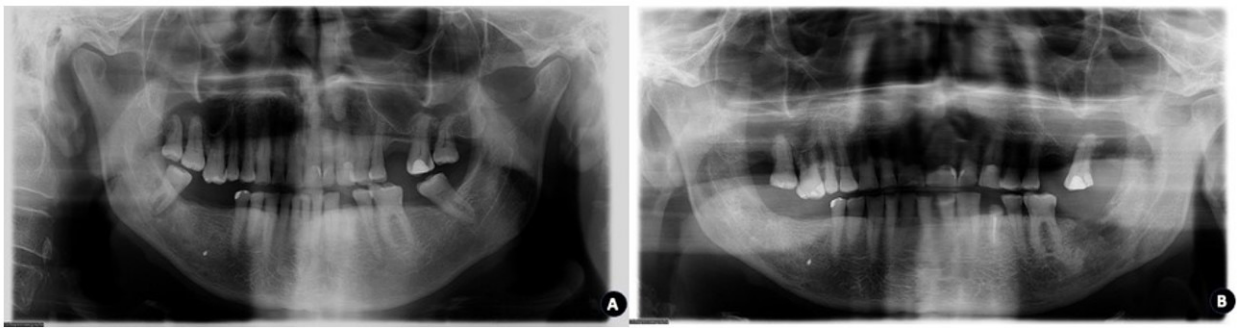

Figure 3 - Radiographic condition of the ORN lesion in Patient # 3 at baseline (A) and at the 90th day after application of i-PRF (B).

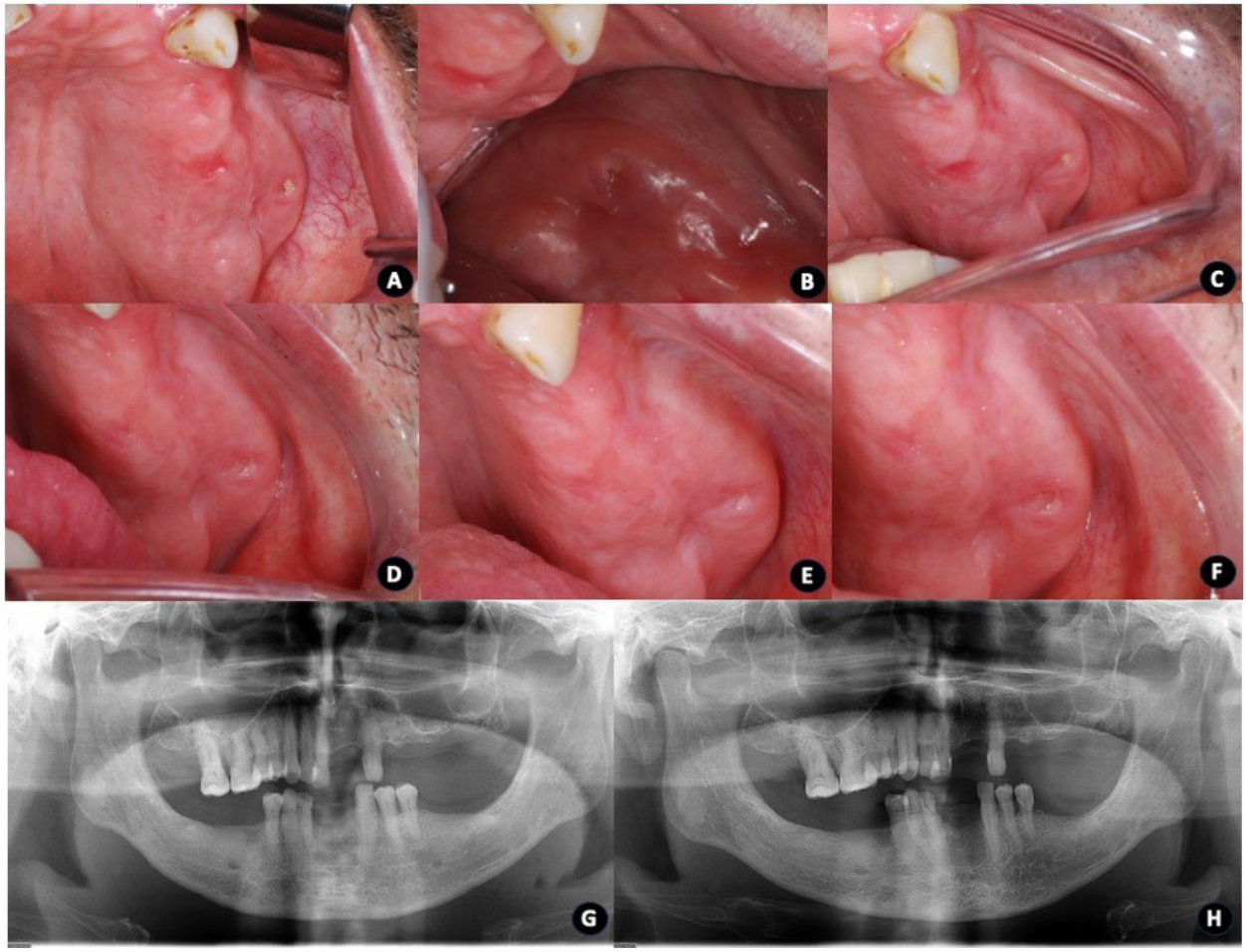

Figure 4 - Clinical condition of the ORN lesion in Patient # 4 at baseline (A) and within 7 days (B), 15 days (C), 30 days (D), 60 days (E), and 90 days after the first application of i-PRF (F). Radiographic aspect at baseline (G) and at 90 days (H).

was treated with i-PRF, and complete closure was noted at the end of follow-up.

DISCUSSION

ORN lesions are difficult to resolve because of the reduced blood supply to the irradiated bone, which impairs the healing process [1,10]. Generally, treatment aims to accelerate the healing process by stimulating angiogenesis. Theoretically, this provides conditions conducive to reversing this pathological condition [9,18]. In this study, treatment with i-PRF was tested. The results suggest potential improvement, with enhanced quality in the soft tissues surrounding the ORN lesions.

i-PRF has been successfully applied in soft tissue repair processes [24] and accelerates bone formation in healthy individuals [25]. These

effects are associated with the presence of growth factors that stimulate angiogenesis, migration, proliferation, and cell activity [17]. In this case series, i-PRF was not effective in promoting the healing process. A possible reason may be that negative effects of factors, such as systemic conditions and the severity of the lesions, were not counteracted. Nevertheless, soft tissue improvement may favor better outcomes after surgical treatment for ORN [13,26]. In particular, i-PRF may be used as a less aggressive initial treatment for ORN before considering resective surgery.

Importantly, the majority of ORN lesions remained stable after i-PRF application. A case with a small lesion six months after the last session of radiotherapy showed complete closure of the lesion during the analysis period. Early diagnosis, followed by appropriate treatment, prevents disease progression [20]. However, some lesions may be contaminated by resistant microorganisms [27], leading to further tissue hypovascularization [10], which in turn, complicates treatment success [28]. Furthermore, the absence of granulation tissue associated with these lesions was noted. This is consistent with the lack of new vessels and an inflammatory process that impairs healing [5].

One significant finding was that ORN treatment with i-PRF did not disrupt the patient's quality of life. Bone necrosis lesions are not usually accompanied by painful processes, and likely, other side effects of radiotherapy, such as xerostomia, lesions with exposure of the connective tissues, dental pain, and mucositis [8,29] impact the patient more significantly. Relative to these other conditions, ORN lesions do not adversely impact the quality of life of patients, and ORN treatment did not improve quality of life.

Patients included in this study did not experience pathological fractures of the involved bones. However, wound closure was not achieved in most of the lesions in this study, and therefore future deterioration is possible. Our sample size limits any inferences.

This study has some limitations. A control group to determine whether there is any advantage to this treatment technique over others was not included in this study. The sample size was small. However, ORN limits patient participation in clinical trials. A better study design approach may be to measure ORN as a clinical outcome after applying i-PRF for the prevention of ORN. After all, prevention is the most effective way of managing patients with risk factors for ORN. In the future, studies to investigate whether i-PRF is beneficial in preventing ORN development following oral surgery are warranted.

CONCLUSION

It can be concluded that the majority of ORN lesions remained stable after the application of i-PRF, with a slight improvement in the quality of the mucosa around the lesions. Additionally, it was observed that i-PRF did not compromise the quality of life of patients during treatment.

Author's Contributions

NRP: Conceptualization, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing. GJPLO: Formal Analysis, Validation, Writing – Original Draft Preparation, Writing – Review & Editing. ROA: Writing – Review & Editing. SVC: Writing – Original Draft Preparation, Writing – Review & Editing. LBL: Writing – Review & Editing. PBFS: Conceptualization, Methodology, Supervision, Writing – Review & Editing.

Conflict of Interest

The authors declare to have no conflict of interest.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of: Federal University of Uberlândia. This study protocol was reviewed and approved by Comitês de Ética em Pesquisa, approval number 38301120.4.0000.5152.

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