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Original Article

Radiographic Bone Evaluation after Periodontal Full Mouth Disinfection Treatment in Women Undergoing Chemotherapy or Hormone Therapy with Tamoxifen

Rahyza Inacio Freire de Assis[1], Manoelito Ferreira Silva-Junior[2], Marciel Silva dos Santos[3], Teresa Cristina Rangel Pereira[4], Alfredo Carlos Rodrigues Feitosa[4], Sergio Lins de Azevedo-Vaz[4]

[1]Master student, School of Dentistry, State University of Campinas, Piracicaba, SP, Brazil.
[2]PhD student, School of Dentistry, State University of Campinas, Piracicaba, SP, Brazil.
[3]DDS, MSc in Dentistry, Federal University of Espírito Santo, Vitória, ES, Brazil.
[4]Professor, Federal University of Espírito Santo, Vitória, ES, Brazil.

Author to whom correspondence should be addressed: Rahyza Inácio Freire de Assis, Rua Pedro Chiarini, 419, apto 54, Vila Independência, Piracicaba, SP, Brasil. 13416-330. Phone: (19) 99910-9966. E-mail: rahyzaifa@gmail.com.

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Abstract

Objective: To radiographically evaluate the alveolar bone level after periodontal full mouth disinfection (FMD) treatment in women during chemotherapy (CHE) and hormone therapy with Tamoxifen (TAM). **Material and Methods:** This is an uncontrolled clinical trial with a convenience sample of women in antineoplastic treatment (CHE and TAM) and non-surgical periodontal FMD treatment. The Radiographic examination consisted of four bitewing radiographs and six periapical radiographs of the upper and lower anterior teeth, acquired according to the parallelling standard technique at three times: before (T0), 3 (T3) and 6 (T6) months after periodontal treatment. The alveolar crest level in the interproximal area of each tooth was measured by two calibrated observer using magnifying glass and digital caliper. Statistical analysis was performed for evaluation of the three times in each experimental group using the Friedman test ($p < 0.05$) and between groups, the Mann Whitney test ($p < 0.05$). **Results:** Overall, 14 women undergoing treatment for breast cancer participated in this study. A follow-up loss of five (35.71%) women occurred during the study and the final sample size was composed of nine women divided into two groups: CHE ($n = 4$) and TAM ($n = 5$). A total of 330 sites were evaluated: 126 (CHE) and 204 (TAM). The alveolar bone level showed statistically significant reduction after 6 months of FMD therapy ($p < 0.05$), but there was no difference between antineoplastic treatment type ($p > 0.05$). **Conclusion:** Patients undergoing chemotherapy and hormone therapy with Tamoxifen showed better alveolar bone levels after six months of periodontal FMD treatment. The current antineoplasic therapy did not influence the results obtained with periodontal treatment.

Keywords: Breast cancer; Chemotherapy; Tamoxifen; Dental Radiography.

Introduction

Inflammation is a common feature of many chronic diseases such as periodontal disease and cancer [1,2]. Breast cancer is the most prevalent malignancy and the leading cause of death among women worldwide [3]. The breast cancer rates are high in developed countries and are on the rise in developing countries [4]. Systemic treatment for breast cancer is constantly expanding and can be accomplished by surgery, radiotherapy, chemotherapy, biological agents and hormone therapy [5].

The current antineoplastic treatment modalities have undesirable side effects. Hormone therapy works by reducing estrogen levels, because some tumors have positive estrogen receptors and are particularly stimulated by estrogen or even progesterone. Since most tumors have positive estrogen-like receptors, hormone therapy is considered effective and less toxic in the clinical management of patients with breast cancer [6]. This type of treatment basically works with two types of drugs that have different mechanisms of action and side effects: Tamoxifen and Aromatase Inhibitors. While Tamoxifen has a tendency to maintain bone mass in postmenopausal women [7], aromatase inhibitors work by suppressing serum estrogen levels [6] and therefore are associated with negative indicators of periodontal disease [8]. Chemotherapy is associated with premature ovarian failure, which causes a decrease in bone mineral density [9,10] and can affect the periodontal condition of patients.

Although the effects of chemotherapy and Tamoxifen on body bone mass are relatively well defined, little information is available in literature about the effects of these drugs during periodontal treatment. Periodontal therapy aims at reestablishing the health of periodontal tissues, including alveolar and cortical bone tissue. Treatment of periodontal disease is a major challenge because inflammation is generated by bacterial biofilms, which is highly resistant to antimicrobial agents and host response. The removal of bacteria from the periodontal pocket can be accomplished by surgical therapy and / or non-surgical therapy (scaling and root planning), with or without the use of associated pharmacologic agents [11,12]. Traditional non-surgical therapy involves removal of subgingival plaque by scaling and root planning, where sessions are divided according to sextants [13]. However, during the interval between sessions, treated periodontal pockets can be reinfected by untreated pockets. In 1995, a new approach was proposed in a single stage: the full-mouth disinfection (FMD) protocol associated with the use of antiseptics and has achieved significant improvements in clinical outcomes such as reduced bleeding on probing, probing depth and changes in the clinical attachment level [14].

Considering a reduction in bone density in women submitted to chemotherapy and bone maintenance in hormonal treatment with Tamoxifen, it is believed that the type of antineoplastic treatment can interfere in periodontal treatment. Given the above, the aim of this study was to radiographically evaluate the interproximal bone level after periodontal Full-Mouth Disinfection (FMD) treatment in women under anticancer treatment by chemotherapy (CHE) and hormone therapy with Tamoxifen (TAM).

Material and Methods

Study Design

Uncontrolled clinical trial was conducted between months of September 2013 and June 2014 at the Federal University of Espírito Santo (UFES), Vitória-ES, Brazil.

Sample Selection and Clinical Examinations

The universe elected comprised women with breast cancer in antineoplastic treatment at the Mastology Service of the Cassiano Antonio Moraes University Hospital (HUCAM) of UFES and Santa Rita de Cássia Hospital (HSRC), located in Vitória-ES. Sampling was done by convenience and recruitment took place from August to October 2013 on HUCAM and HSRC for further verification as for the study eligibility criteria.

Selected patients had to meet the following inclusion criteria: have at least one not contiguous periodontal interproximal site with probing depth (PD) and clinical attachment level (CAL) greater than or equal to 5 mm, age between 35 and 75 years. Exclusion criteria were: smokers, hypertensive, pregnant women, those with diabetes mellitus, previous history of cancer, completed chemotherapy and / or radiotherapy, cardiovascular diseases or other systemic diseases that could compromise the host response or require prophylactic medication for clinical examination and periodontal treatment. Patients with extensive prosthetic restorations, periodontal treatment history or antibiotic therapy in the past six months were also excluded, as well as those allergic to chlorhexidine.

For sample selection, one examiner was previously trained by a Periodontics teacher of the UFES Dentistry course (benchmark) for the performance of the initial periodontal clinical examination, PD and CAL measurement. The intra-rater Kappa value showed almost perfect agreement (> 0.80) for both clinical parameters [15]. In addition, a medical history was made in the initial consultation to verify the eligibility criteria and antineoplastic therapy in progress.

Experimental Stage

A total of 14 patients were selected for the study and were equally divided into experimental groups (CHE = 7; TAM = 7). All were submitted to the same type of periodontal therapy associated with the cause using FDM technique, performed by experienced and trained operator. Subsequently, tongue cleaning was performed, followed by application of 1% chlorhexidine gel for 5 minutes into periodontal pockets, removing the excess thereafter. Patients also received oral hygiene instructions during the sessions. To assist in therapy, mouthwash with 0.12% chlorhexidine gluconate was used for 7 days in order to control microorganisms present in the dental plaque.

X-ray Examinations

An experienced and properly trained operator performed the technical radiographic procedures in all patients in the sample. Patients were submitted to four bitewing radiographs

(region of molars and premolars on both sides) and six periapical radiographs (region of the upper and lower central incisors and lateral incisors and upper and lower canines from both sides), according to the parallelism technique. Rinn-XCP type positioners were used (DentsplyRinn, Elgin, IL, USA) for the parallelism technique. Radiographs were performed using Timex 70E device (Gnatus, Ribeirão Preto, São Paulo, Brazil), operating at 70kVp and 7mA, with exposure time in the molar region equal to 0.63 seconds, 0.5 seconds for the region of pre-molars and anterior upper teeth and 0.4 seconds for lower anterior teeth. Radiographic films 1.2 were used (standard periapical), with E sensitivity (Ektaspeed, Eastman Kodak, Rochester, NY). Films were manually processed according to the time-temperature method in processing tanks installed in a darkroom room available in the institution. Patients attended to performed radiograph examinations in three different times: before periodontal therapy (T0), 3 (T3) and 6 months (T6) after.

Training and Calibration of Evaluators

Using x-rays of individuals who do not participate in the sample, two researchers were trained and calibrated by a Dental Radiology teacher of UFES (benchmark). In an environment with low light, the alveolar bone level of proximal areas (mesial and distal) of each tooth was measured by two reviewers independently. For this, X-rays were fixed to a cold-light light box and adapted in black masks. Measurements of enamel-cementum junction to the bone crest were made using a digital caliper and magnifying glass with magnification of 1.3x, as performed in previous [16,17].

After the training of evaluators, 60% of the sample was evaluated by both and the Intraclass Correlation Coefficient (ICC) was calculated for inter-observer reproducibility in order to verify their calibration and consistency in the evaluation of radiographs. The ICC value was equal to 0.89 (CI 95% = 0.87-0.91), indicating excellent reproducibility according to the interpretation scale [18] (<0.4, poor, 0.4 - 0.75, satisfactory; > 0.75, excellent). Thus, only data collected by one of the evaluators were considered for the study.

Data Collection

After training and calibration, X-ray examinations were coded in order to allow blind assessments regarding the group of patients (CHE and TAM) and study times (T0, T3 and T6). Evaluations followed the same system adopted in the training and calibration and all interproximal sites were evaluated.

Statistical Analysis

Data were tabulated in Microsoft Office Excel 2007 spreadsheets (Microsoft Corporation, Redmond, WA, USA). The study outcome was the level of alveolar bone crest evaluated in three study times (T0, T3 and T6) in women under antineoplastic treatment (CHE and TAM). The BioStat 5.0 software (Institute for Sustainable Development of Mamirauá, Tefé, AM, Brazil) was used for data analysis, adopting a 5% significance level for all tests.

Initially, a descriptive analysis was performed in order to obtain the mean and standard deviation (SD) of the alveolar bone level values in the three study times for each experimental group. In addition, mean and SD of bone level differences for each group were calculated in three situations: T3-T0; T6-T0 and T6-T3. The Kolmogorov-Smirnov test was used to verify the data distribution normality. The mean alveolar bone values were submitted to the Friedman test and to compare the difference between means of groups, the Mann Whitney test was performed.

Ethical Aspects

The study protocol was approved by the Ethics Committee of the Federal University of Espirito Santo (CEP / CCS / UFES) under protocol No. 07/08/2013 352,550.

Results

Of the 14 women initially selected for the study, there was a follow-up loss of five (35.71%) patients, four for not returning to sessions and one for not tolerating the parallelism technique. The final sample consisted of nine patients, four in the CHE group and five in the TAM group, with mean age of 51 years, ranging from 42 to 59 years.

The ICC values for the intra-observer reproducibility were 0.94 (CI 95% = 0.90-0.96) and 0.96 (CI 95% = 0.93-0.97), respectively for evaluators 1 and 2, indicating excellent concordances.

Table 1 shows the mean and SD values of the alveolar bone level of all sites measured in the three study times for both experimental groups. A reduction in the alveolar bone level regardless of antineoplastic treatment between the third and sixth month after periodontal FMD treatment was observed ($p < 0.05$) (Table 1).

Table 1. Mean and standard deviation (SD) of bone level values at baseline, 3 and 6 months after periodontal treatment in women of antineoplastic therapy for breast cancer. Vitória, ES, 2014.

Group	n	Bone Level		
		T0 Mean (SD)	**T3** Mean (SD)	**T6** Mean (SD)
CHE	126	2.60a (1.24)	2.59a (1.20)	2.28b (1.23)
TAM	204	1.89a (0.91)	1.84a (0.92)	1.58b (0.84)

Different letters show difference between mean bone level matched within the horizontal lines (Friedman test, $p < 0.05$). Note: n = sample size. T0 = Baseline (prior to periodontal therapy). T3 = 3 months after periodontal therapy. T6 = 6 months after periodontal therapy. SD = standard deviation. CHE = Chemotherapy Group. TAM = Tamoxifen group.

Table 2 shows the mean and SD values of the difference between alveolar bone levels for experimental groups at the three times. It was found that the antineoplastic therapy adopted did not influence the change in the alveolar bone level in any study time evaluated ($p > 0.05$).

For illustration of the radiographic follow-up after periodontal FMD treatment, Figure 1 shows increased radiopacity in the furcation region of tooth 16 and in the interproximal bone crest of the remaining teeth.

Table 2. Mean and standard deviation (SD) of bone level values at baseline, 3 and 6 months after periodontal treatment in women under antineoplastic therapy for breast cancer. Vitória, ES, 2014.

		Bone Level					
Group	**n**	**Difference T0-T3 Mean (DP)**	**p-value***	**Difference T3-T6 Mean (DP)**	**p-valor***	**Difference T0-T6 Mean (DP)**	**p-value***
CHE	126	0.01 (0.66)	0.2425	0.30 (0.57)	0.1949	0.31 (0.81)	0.3079
TAM	204	0.05 (0.63)		0.27 (0.46)		0.32 (0.63)	

* Mann Whitney test (p <0.05). Note: n = sample size. T0 = Baseline (prior to periodontal therapy). T3 = 3 months after periodontal therapy. T6 = 6 months after periodontal therapy. SD = standard deviation. CHE = Chemotherapy Group. TAM = Tamoxifen group.

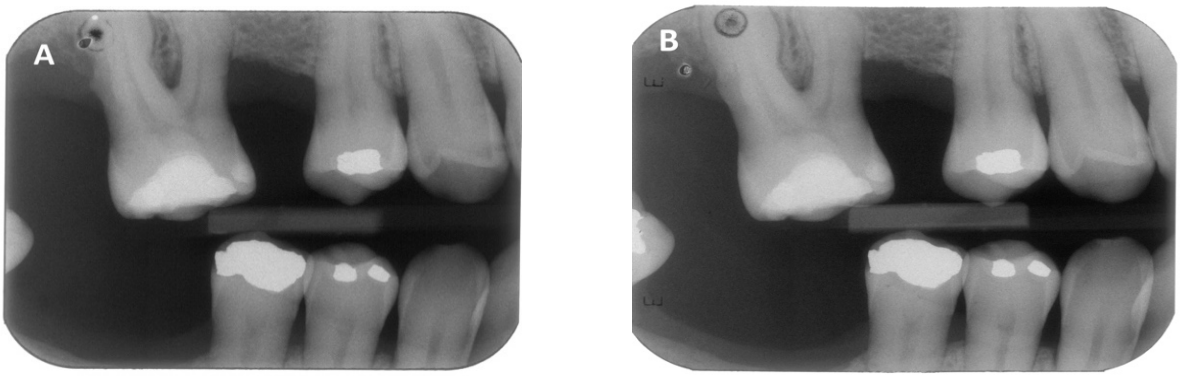


Figure 1. Interproximal radiography of the furcation region of element 16 of a CHE patient. A. Before periodontal treatment (T0). B. Six months after treatment (T6). Vitória-ES, 2014.

Discussion

In this study, women under antineoplastic treatment for breast cancer, chemotherapy or hormone therapy with Tamoxifen submitted to periodontal FMD treatment showed better level of alveolar bone crest after six months of treatment; however, no changes in the first three months of study were observed. However, no differences for bone level in relation to the type of anticancer treatment were found (CHE or TAM).

Periodontal disease is one of the most prevalent oral diseases in the world population [19]. It is a chronic inflammatory disease characterized by a greater severity of bone loss in support teeth [20,21]. Periodontal treatment aims at achieving good oral hygiene conditions by removing all soft or hard deposits and their retention factors to reestablish the health of periodontal tissues, including alveolar bone tissue [22]. Thus, it is known that scaling and root planing play an important role in improvement of clinical and microbiological parameters [23,24].

Scientific studies have shown that antineoplastic therapies cause significant effects on the female body. Bone loss has been one of the consequences induced by chemotherapy for the treatment of cancer in women at pre- and postmenopausal phases. In the pre-menopausal phase, the cytotoxic effects of chemotherapy can induce premature menopause about ten years earlier, as women over 40 are at increased risk of premature ovarian failure. Bone loss is caused by the effect of chemotherapy cytotoxicity on the bone cells such as osteoblasts and osteoclasts, and as a result, after the

completion of treatment, changes in bone density are primarily related to the negative effect on the function of ovaries [25].

Tamoxifen belongs to the class of Selective Estrogen Receptor Modulators (SERMS) and binds to estrogen receptors present in the tumor cells. This blockage prevents tumor growth and keeps estrogen levels in the body. This drug can be used in patients at pre- or post-menopausal stage and have a complex mechanism of action, which depends on the microenvironment in which it operates. Tamoxifen is known for its modest estrogenic effect, which maintains or increases density and bone mass in women at post-menopausal stage [7,8,25]. The antineoplastic therapy with tamoxifen five years after treatment showed modest gains in bone mass in the lumbar spine, without gains in the femoral neck region [26]. Although the effects of antineoplastic therapies in these bone regions are similar in other regions, as in the alveolar bone crests, few studies have addressed the radiographic aspects of bone magnitude in the periodontal region.

In this study, periodontal FMD therapy had lower alveolar bone level in the evaluated sites. However, it is impossible to conclude that there was a bone "gain" after completion of periodontal treatment. The results in the radiographic analysis showed difference of bone height observed at the final time (T6) compared to previous times (T0 and T3), both in CHE and TAM groups. One of the facts that could justify this supposed "gain" would be the higher bone density, which could result in better visualization of the bone crest, mainly in the area of angular bone defects. Figure 1 shows a repair the defect in the furcation region of tooth 16 in one of the patients evaluated (CHE group). The improvement of the alveolar bone condition after periodontal treatment infers the understanding of a possible stabilization of the periodontal disease, mainly due to a reduction in pathogens, factors that may contribute to the improvement and maintenance of the periodontal health of these patients.

At menopause, the main biological change is the end of ovulation, confirmed one year after the cessation of menstruation. After menopause, ovaries become inactive and there is minimal or no estrogen release [27]. It is noteworthy that at the beginning of this study, all patients selected were at the post-menopausal phase. Thus, hypothetically, CHE patients would be more prone to bone loss, while TAM patients would be prone to a slight increase in bone mass. This hypothesis was discarded by the study because there was no statistically significant difference in bone level among T0-T3 T3-T6 and T0-T6 time intervals in groups.

Although there is difference in the average initial bone level between CHE and TAM groups, it was possible to compare them. It is important to reveal that in case of chronic diseases such as periodontal disease, age seems to be an important aspect to be considered, since this disease has become more severe with aging. However, due to the small sample size, this factor was not considered in this study. Perhaps, this would explain the fact that the groups have started with different average bone levels, not necessarily the type of antineoplastic treatment adopted. In an attempt to reduce statistical errors, the difference in bone height in the respective times was used. In addition, the radiographic analysis was performed only after completion of all three radiographic

examinations (T0, T3, T6). At this stage, the radiographic records of each period were separately coded in order to blind evaluators regarding the identification of the subject, when it came to the type of antineoplastic treatment and the stage of participation in the study.

Still, it is important to point out some limitations of this study. The follow-up loss, typical of clinical studies, was considered high [28]. One possible explanation is related to the difficulty of working with a sample diagnosed with cancer in which, in addition to physical aspects, emotional aspects can justify the withdrawal of participation. Due to the side effects of anticancer treatment, FMD therapy has been chosen because it is less invasive and there is increased need for dental care of patients who were still in active period of antineoplastic treatment. Another important limitation relates to the use of conventional X-rays, which require a great working time, especially due to the phase of chemical radiographic processing. Moreover, difficulties have been found in standardizing the medication time of patients. Thus, further studies should use a larger sample size and follow-up times and preferably, the digital radiography technology.

Conclusion

Women undergoing chemotherapy and hormone therapy with Tamoxifen showed better alveolar bone level values after six months of periodontal FMD treatment, with no difference between types of antineoplastic therapies adopted.

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