

An evaluation of a dentifrice containing salivary peroxidase elements for the control of gingival disease in patients with irradiated head and neck cancer

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Patients who have undergone irradiation for head and neck tumors commonly have xerostomia. Loss of the protective constituents normally found in saliva leaves patients at greater risk for development of significant dental pathologic disorders, including gingival and periodontal disease. Periodontal disease and tooth extractions are currently accepted as etiologic factors for the development of osteoradionecrosis. This double-blind crossover trial was conducted to assess the efficacy of a dentifrice containing salivary peroxidase elements in the reduction of gingivitis in a population of patients with irradiated cancer. Subjects were instructed to brush with the dentifrice provided. Plaque and gingival index values were obtained and statistically compared with baseline values. A weak positive effect was found between use of the dentifrice and a reduction in gingival inflammation. Patient compliance was a limiting factor in this treatment effect. The results suggest possible efficacy for the dentifrice in augmenting traditional measures of postradiation oral health maintenance. (*J Prosthet Dent* 1996;76:292-6.)

Oral health maintenance for patients who have undergone therapeutic irradiation for neoplasms of the head and neck is complicated by posttreatment regional tissue changes. These include damage to the salivary glands resulting in xerostomia. Xerostomia may significantly increase susceptibility to various odontogenic pathogens because normal, functioning saliva contains a number of nonspecific defense factors for counteracting intraoral bacterial activity and subsequent dental disease.^{1,2} It is an effective buffering agent and so can limit the acidic environment created by the resident microflora. The constant flow of saliva serves further to bathe and rinse the oral cavity. This action helps to reduce overall bacterial counts by washing away surface layers of microbial colonies to be ultimately neutralized in the gastrointestinal tract.

Finally, there exists in saliva a number of chemical and humoral factors that can inhibit the action and proliferation of oral bacteria (Table I). Manipulation of these naturally occurring factors could offer potential applica-

Table I. Immunoglobulin and nonimmunoglobulin factors in saliva

Immunoglobulins	Nonimmunoglobulins
Secretory immunoglobulin A	Lysozyme
Secretory immunoglobulin M	Lactoferrin
	Salivary peroxidase

tion in irradiated patients. One way this might be accomplished would be through the reintroduction of salivary system elements lost subsequent to postradiotherapy glandular damage.³⁻¹² An over-the-counter dentifrice is available (Biotene toothpaste, Laclede Research Laboratories, Gardena, Calif.). The manufacturer claims this dentifrice is effective in the control of plaque and plaque-induced gingivitis resulting from nonspecific xerostomia. This dentifrice contains lactoperoxidase and glucose oxidase, which are thought to be critical for the activation of the salivary peroxidase system. Additionally, sodium monofluorophosphate is included as an inhibitor of caries activity.

To date, no published studies specifically assessing in vivo efficacy of the product have been reported in irradiated patients. The purpose of this study was to evaluate the control of plaque accumulations and gingivitis through the use of this dentifrice in a population of patients with irradiated head and neck cancer.

THE SALIVARY PEROXIDASE SYSTEM

Peroxidases are found in a number of biologic fluids and in saliva.¹ Salivary peroxidase has a heterogenic pre-

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Table II. Distribution of tumor locations and radiation dose to lesions

Patient	Tumor location	Dose (Gy)
E.H.	Oral tongue	68
S.L.	Ethmoid and left maxillary sinus	70
R.T.	Nasopharynx	70
L.D.	Hodgkin's lymphoma	50
W.K.	Oral tongue	68
F.S.	Nasopharynx	70
T.N.	Nasopharynx	70
C.A.	Right tonsil	64
W.L.	Cervical node	60
F.M.	Floor of mouth	70
R.R.	Pharynx	60
W.C.	Pharynx	65
B.S.	Pharynx	60
J.E.	Larynx	65
R.A.	Floor of mouth	65
A.A.	Pharynx	60
J.S.	Floor of mouth	70
T.R.	Floor of mouth	70
W.H.	Nasopharynx	50

sensation that consists of numerous electrophoretically different subfractions of various molecular weights. It appears to be concentrated in the parotid gland, from which it is dispersed into whole saliva.

Salivary peroxidase has a tendency to bind and concentrate on dental plaque. This is advantageous in that it places the enzyme in greatest concentration at the site of desired activity. The antibacterial action of salivary peroxidase takes place as a result of the peroxidase-catalyzed oxidation of thiocyanate. This detoxification product of cyanide is found in parotid gland secretions and whole saliva.^{1,13} Hydrogen peroxide, which is endogenously available from a number of sources, acts as the oxidant in this reaction.^{1,14,15} The result is the generation of antimicrobial end products including hypothiocyanite and hypothiocyanous acid and other, short-lived, oxidation products.^{1,13,16-18} The mode of action for salivary peroxidase appears to include inhibition of bacterial enzymes containing essential thiol groups.

METHODS AND MATERIAL

A double-blind crossover trial was initiated. Sixty subjects were recruited from a population of patients with a history of radiotherapy for tumors of the head and neck. Of those recruited, 19 subjects (15 men and 4 women) completed the entire term of the study (Table II). Table III lists additional criteria for study entry. Prestudy plaque accumulations and gingival health were assessed for each subject by use of the plaque index (PI) and the gingival index (GI), as described by Silness and Loe.¹⁹⁻²¹ Index measures were made by visual inspection and the use of a standard periodontal probe at four sites for each tooth present.

Table III. Requirements for study entry

≥50 Gy minimum treatment dose
Salivary glands in treatment fields
Minimum of 16 teeth present
No current antibiotic therapy
Good hand dexterity

After these scores were recorded, a thorough dental prophylaxis was performed to establish an equivalent hygiene baseline for all subjects. Subjects were then randomly assigned to one of two groups. Those assigned to group 1 were provided with the following materials in sealed, coded packets: (1) tubes of the test dentifrice, (2) a 1.1% neutral sodium fluoride gel (Prevident neutral sodium fluoride, Colgate-Hoyt Laboratories, Canton, Mass.), and (3) a toothbrush. Subjects assigned to group 2 received packets equal in all respects to group 1 with the exception of being given a placebo dentifrice. Subjects were given both written and verbal instructions. These included brushing with the dentifrice two times a day with a modified Bass technique for 2 minutes according to the manufacturer's recommendations. Subjects were also instructed to apply the neutral sodium fluoride gel to the dentition, with the custom-made mouth trays provided, for 5 minutes each evening before retiring.

All subjects were then seen monthly over a period of 3 months for follow-up examinations during which time repeat PI and GI scores were obtained. On completion of follow-up month 3, all used and unused tubes of dentifrice were collected from each subject to be weighed for later analysis. After a thorough dental prophylaxis repeated to reestablish an equivalent baseline, each subject was reassigned to the alternate group of the study while the double-blind design was maintained. In this manner subjects served as their own controls. All previous instructions were repeated and packets with new tubes of dentifrice were provided. Subjects continued to be monitored at monthly intervals over a subsequent period of 3 months during which index measures were repeated.

All GI and PI scores obtained were statistically evaluated in the following manner. The four scores obtained per tooth at each visit were averaged because they were seen to be highly correlated. Thus for each visit subjects could have a maximum of 32 measurements for each index.

The effect of the test dentifrice on GI and PI index scores was examined separately with a mixed-effects analysis of variance model.²² In the model the effect of the test dentifrice was examined after the main effects of visit, subject, and tooth location and the interaction effects of subject by visit and subject by tooth were controlled for. The first interaction term was included in the model because there was no reason to expect each of

Table IV. Averaged numeric values: GI

Time	Group 1 (n = 10)*	Group 2 (n = 9)†
Baseline	0.939 ± 0.203	1.102 ± 0.263
1 month	0.626 ± 0.292	0.790 ± 0.262
2 months	0.676 ± 0.331	0.790 ± 0.270
3 months	0.666 ± 0.354	0.806 ± 0.311
4 months	0.612 ± 0.330	0.737 ± 0.265
5 months	0.621 ± 0.337	0.662 ± 0.309
6 months	0.647 ± 0.402	0.599 ± 0.329

Values are mean ± SD.

*Test dentifrice used months 1 to 3, placebo dentifrice used months 4 to 6.

†Placebo dentifrice used months 1 to 3, test dentifrice used months 4 to 6.

the subjects to respond in the same manner over time. The second was included to account for the different missing teeth patterns in each of the subjects. The statistical significance of the test dentifrice was examined with Satterwaite's approximate *F* test.²²

RESULTS

Table IV presents the mean GI values for all subjects at each trial interval with SDs. A weak positive effect on gingival index scores was noted with use of the test dentifrice during the treatment period with an average improvement in GI score of 0.098 compared with control values ($n = 19$, $F = 3.02$, degrees of freedom = 1.91, $p = 0.086$). Although not significant at the 5% level, this suggests some improvement in subject gingival health in response to the test dentifrice. The means and SDs of the average gingival index for each subject at baseline and 3- and 6-month intervals when broken down by the order in which each received the test treatments agrees with the results of the analysis of variance. Table V lists the mean PI values for all subjects at each trial interval with SDs. No statistically significant response was revealed in plaque reduction between the treatment and control periods in this population ($n = 19$, $F = 1.25$, degrees of freedom = 1.90, $p = 0.27$).

To assess subject compliance with study instructions, all tubes of dentifrice returned by the subjects were weighed and compared with the known weight for sample tubes. From this, the amount of dentifrice used by each subject throughout the study could be determined. The dentifrice was supplied in an amount to result in complete usage of the material at the end of each study period if instructions were followed by the subjects. The average amount of treatment dentifrice actually used by all subjects was 36.5% (mean 299.75 gm, range 53.8 to 845.5 gm). Only three subjects used more than 50% of the dentifrice provided, with only one of these three subjects demonstrating 100% compliance by using all the dentifrice as instructed.

The effect of compliance on GI scores was then evaluated. Compliant subjects were defined as those individu-

Table V. Averaged numeric values: PI

Time	Group 1 (n = 10)*	Group 2 (n = 9)†
Baseline	0.997 ± 0.269	1.173 ± 0.322
1 month	0.640 ± 0.237	0.744 ± 0.254
2 months	0.601 ± 0.246	0.736 ± 0.313
3 months	0.541 ± 0.304	0.726 ± 0.341
4 months	0.634 ± 0.356	0.754 ± 0.357
5 months	0.673 ± 0.359	0.707 ± 0.411
6 months	0.668 ± 0.476	0.737 ± 0.0513

Values are mean ± SD.

*Test dentifrice used months 1 to 3, placebo dentifrice used months 4 to 6.

†Placebo dentifrice used months 1 to 3, test dentifrice used months 4 to 6.

als who used 33% or more of the dentifrice during the study period. In this manner, nine subjects were identified as compliers with the remaining 10 subjects as noncompliers. The average percent improvement in GI scores for compliers was found to be greater compared with that of noncompliers (% change compliers, 14.5%; noncompliers, 0.2%). A *t* test for average percent change was used and a positive effect was found for compliant subjects compared with noncompliant subjects ($t = -1.614$, degrees of freedom = 17, $p = 0.12$). The lack of significance at the 5% level may be attributable to the small sample size for this subject subset.

DISCUSSION

The results of this study suggest the possibility of some beneficial effect of using the salivary peroxidase system delivered as a dentifrice in improving gingival health in a population of patients with irradiated head and neck cancer. These effects appear to be related to the level of subject compliance with instructions as measured by the amount of dentifrice used over the study period. In spite of instructions to completely use all of the dentifrice provided, the average amount of dentifrice used by the subjects was 36.5%. When data were analyzed on the basis of compliance, a marked qualitative improvement in gingival health was found. Although not significant at the 5% level, possibly a result of the reduced sample size, the results suggest that an increase in subject compliance would have resulted in an even greater response in overall gingival health. Use of salivary peroxidase enzyme elements had no effect on plaque accumulations in this population. However, this finding may also be related to subject compliance levels.

Not all subjects who were identified as candidates and indicated a willingness to participate completed the study. Sixty subjects were originally identified as candidates willing to participate in the study. Subject dropout resulted in only 19 subjects completing the trial. Failure to comply with study instructions resulted in a subject subset further reduced in size. A number of physical and emotional factors might have an impact on the

ability of this patient population to participate in controlled trials after oncologic treatment. These could include therapy outcome, general health and feelings of physical well-being after therapy, time demands for medical follow-up and health maintenance, and the psychosocial effect on patients and their ultimate outlook on life. Such factors could have an effect on compliance with study instructions or result in subject dropout. Although not specifically included in this study design, it is suspected that these factors were responsible for the complications in data collection encountered in this study. It is recommended that future efforts be directed at more creative study designs to overcome these compliance problems.

CLINICAL IMPLICATIONS

Salivary peroxidase may offer potential application for improved gingival health in irradiated patients. Because gingival disease is commonly recognized as a precursor to some forms of periodontal disease, it could then be suggested that a dentifrice that contains these elements might ultimately prove effective in periodontal disease prevention. After irradiation these individuals demonstrate a decreased oral defense capacity to continuous insult by the resident microflora while possessing a concomitant decrease in the ability to effect physiologic repair in response to these pathogens. This condition potentiates periodontal pathologic disorders that can lead to the need for postradiation tooth extractions. Poor oral health results in patient discomfort and loss of masticatory performance. Further, these conditions are commonly recognized as predisposing factor for the development of osteoradionecrosis.

The addition of measures such as salivary peroxidase to the traditionally accepted maintenance regimens for irradiated patients could provide enhanced protection to maximize oral health. This simple to use, inexpensive adjunct might prove invaluable in a patient population that remains at indefinite risk for significant odontogenic disease activity.

Clearly, such adjunctive therapies alone cannot be the sole answer for a difficult, long-term management problem. Close supervision and active patient participation remain the key to oral health. However, future studies designed to assess therapeutic agents such as salivary peroxidase are warranted.

SUMMARY

A double-blind crossover trial was conducted to assess the efficacy of a dentifrice containing elements of the salivary peroxidase system in controlling plaque and gingival pathologic features in a population of patients with irradiated head and neck cancer. Plaque accumulations and gingival health were assessed with standard plaque and gingival index values. A weak positive effect

on gingival index scores was noted with use of the test dentifrice. When correlated with subject compliance, the test dentifrice resulted in an average improvement in gingival index score of 14.5% for compliers versus 0.2% for noncompliers. Full subject compliance may have yielded even more significant improvements. These results suggest that use of such a dentifrice could provide preventive benefits for this patient population.

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Noteworthy Abstracts of the Current Literature

Treatment of fenestration and dehiscence bone defects around oral implants using the guided tissue re-generation technique: a prospective multicenter study.

Dahlin C, Lekholm U, Becker W, Becker B, Higuchi K, Callens A, van Steenberghe D. *Int J Oral Maxillofac Implants* 1995;10:312-8.

Purpose. Bone deficiencies compromise the osseointegration process. Augmentation membrane techniques have been proposed to address conditions that are not easily resolved with other methods. This article detailed a prospective multicenter study of the efficacy of barrier membrane bone augmentation techniques for correction of marginal dehiscences or buccolingual fenestrations.

Material and Methods. Clinicians from four treatment centers participated and the study design used 40 dehiscences and 15 fenestrations in 45 patients. A total of 55 implants were placed (35 maxilla, 20 mandible). One patient was lost to follow-up because of death. All implants demonstrated primary stability. Bone defects around implants were measured before placement of an expanded polytetrafluoroethylene membrane. No bone grafts or secondary space maintaining devices were used. Dental prostheses were prohibited for 2 weeks, after which removable prostheses with soft base materials were inserted. Membranes were to be left in place for 3 to 4 months in the mandible and 5 to 6 months in the maxilla unless membrane exposure was encountered. Premature membrane removal was planned only if soft tissue dehiscence exposed the membrane.

Results. Six membranes were exposed during the healing period and were removed prematurely. The remaining 48 membranes were retained for the planned healing time. Four implants were not osseointegrated at surgical uncover, which caused their removal from the study. For the membranes that remained covered throughout the healing period, a statistically significant decrease in defect size was seen ($p < 0.001$). The group of implants that did not have membrane coverage throughout the healing period also demonstrated significant defect reduction ($p < 0.01$). Mean defect fill was 82%.

Conclusions. New bone formation is possible under barrier membranes adjacent to endosseous implants. A mean bone fill of 82% compares favorable with other studies. Space-making devices or bone graft materials may be assumed to improve predictability. 32 References—SE Eckert