

Xerostomia Management for Pediatric Oncology Patients with Lactoperoxidase Included Oral Health Care Products

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Abstract

Aim: Evaluating the efficacy of lactoperoxidase included oral care products for xerostomia in children with cancer undergoing chemotherapy and / or radiotherapy and to present an easy to follow oral care protocol.

Design: The study subjects consisted of twenty one pediatric cancer patients (mean age of 11,3±) with either leukemia or lymphoma used lactoperoxidase-system-containing mouth rinse (Biotene®) combined with (Biotene®) gel or (Biotene®) chewing gum for 3 weeks. Unstimulated saliva samples were collected at the base line and 4 weeks after the usage of the products. They were analyzed for selected biochemical factors and subjective symptoms as intra-oral dryness (xerostomia), eating ability and oral discomfort were graded by visual analogue scale.

Results: No major changes occurred in the level of saliva Thiocyanite and Peroxidase activity, but there was a increase in salivary pH and also salivary flow rate was notably higher in groups using Lactoperoxidase products. Changes related to buffering capacity of saliva were also recorded.

Conclusion: There is no clearly effective treatment for xerostomia but we have observed in our practice that the use of non-immunologic antimicrobial agents relieves subjective oral symptoms in most xerostomic pediatric patients.

Keywords: Xerostomia; Lactoperoxidase included products; Saliva; Palliative oral management

Introduction

The significance of human saliva not only for oral health but also for the general health is obvious [1,2]. The basic role of saliva is to protect the oral environment and the upper gastrointestinal tract against various insults [3,4]. The antibacterial, antiviral and antifungal factors of saliva are either non immunoglobulin, innate agents (such as lysozyme, lactoferrin, peroxidase systems, agglutinins) or immune, acquired agents (IgA, IgG, IgM) [5]. Cleansing and dental and mucosal coating and protection with consequent maintenance of tissue integrity in the mouth are important functions of saliva. Saliva also has multiple functions relating to speech, taste perception, mastication, bolus formation and swallowing [6]. Cancer patients undergoing treatment for their disease often experience severe difficulties in maintaining such functions. Furthermore, deterioration oral health and distressing oral symptoms including xerostomia have been shown to have a significant influence on their daily life.

Xerostomia is defined as a subjective complaint of dry mouth that may result from a decrease in the production of saliva [9]. As it is not a life-threatening issue in a serious disease such as cancer is, xerostomia is often sidelined and treated as an orphan topic in supportive care [7,8]. On the other hand, saliva is an essential factor in quality of life: without saliva, the patient will suffer from the persistent daily discomfort, e.g. during eating, speaking and sleeping, which will have a negative influence on his or her social life.

As a variety of adverse conditions associated with xerostomia can occur shortly after the onset of therapy and persist for the life of the individual, management and/or prevention may occur during and/or following the course of therapy. Treatment of the symptoms of xerostomia has been mainly palliative. Stimulation of remaining salivary function or various saliva substitutes have been recommended [10,11]. Oral hygiene products containing natural oral antimicrobial agents in combinations are among the recent approaches to relieve xerostomia symptoms and simultaneously enhance saliva-mediated

protection against infections [12]. One important defense mechanism is the peroxidase system, which is antimicrobial against several oral microorganisms including mutans streptococci, lactobacilli, fungi and some viruses [13]. Peroxidase enzymes combine with potassium thiocyanate, found in saliva, to produce the hypothiocyanate ion which inhibits the growth and acid production of plaque-forming bacteria [14]. The salivary peroxidase system can be enhanced in vivo by adding small amounts of hypothiocyanate-generating enzymes to toothpastes or mouth rinses [13,15]. Topical agents include oral rinses, toothpastes, gels and artificial saliva substitutes. Mechanical stimulants, such as chewing gum, work by stimulating salivary flow through function. All of these products have been shown to provide some comfort to patient suffering from xerostomia, but with variable degrees of success.

Biotene products contain the enzymes glucose oxidase, lactoferrin and lactoperoxidase. The Biotene gel not only acts as an oral lubricant, but also can potentially restore the salivary antimicrobial capacity of patients with hyposalivation, as the mouth's naturally occurring protective system comes from three pairs of salivary glands. When, for any reason, the amount of saliva is disrupted, this important antibacterial defence system is lost. The 'lactoperoxidase enzyme system' is designed to replace the action of saliva. [16] Biotene products have been developed to relieve symptoms of oral dryness and to restore

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the salivary antimicrobial capacity of patients with hyposalivation or xerostomia.

Therefore, in this study our aim was to evaluate the efficacy of lactoperoxidase included oral care products for xerostomia in children with cancer undergoing chemotherapy and/or radiotherapy and to present an easy- to follow oral care protocol.

Materials and Methods

Subjects and study design

The study subjects consisted of twenty- one pediatric cancer patients (mean age of 11.3±) with either leukaemia or lymphoma admitted to a University Hospital and their unstimulated salivary flow rate < 1.0ml/min [17]. All subjects had mixed dentition. Detailed description of the subjects on the basis of age, sex, clinical diagnosis is enrolled. All subjects' parents were informed about the purpose of this study.

Once the patient had entered the study they were required to complete a questionnaire administered by an interviewer. The questionnaire was used to assess the effect of xerostomia on the patients' everyday life by scoring 1 up to 5. The questionnaire used in this study was a mixture of questionnaires used in previous studies regarding the assessment and evaluation of xerostomia and products designed to relieve the symptoms of xerostomia in elderly patients [18].

Following questions were asked:

'Does the feeling of dry mouth cause you very strong discomfort, problems with speech, eating, or swallowing' and disturbances of taste were recorded. At the base-line appointment an oral examination was performed before sampling of saliva. Medical history and medications were obtained from each child.

After underlying data collection all patients were randomly assigned in 3 groups.

Group 1: Used a lactoperoxidase – system- containing mouth rinse (Biotene®) and they advised to rinse for 30 sec at least twice daily, in the morning and in the evening.

Group2: Used Biotene® gel, they applied the gel Biotene on oral mucosa with its applicator.

Group 3: Used only Biotene chewing gum Biotene after meals during 3 week period. The subjects maintained to use their daily antimicrobial products and continued their usual dietary habits.

Unstimulated saliva samples were collected 3 weeks after the usage of the products. They were analyzed for selected biochemical factors and subjective symptoms as intra-oral dryness (xerostomia), eating ability and oral discomfort with the same questionnaire which is graded by 1-5 grading scale. Specific aim was to evaluate longitudinally the efficacy and acceptability of these products by using the base-line status and 3 week after.

Products

Biotene mouth rinse contained purified water, Propylene Glycol, Xylitol, Polyglycitol, Poloxamer 407, Hydroxyethyl Cellulose, Sodium Benzoate, Benzoic Acid, Natural Peppermint, Sodium Phosphate, Zinc Gluconate, Calcium Lactate, Aloe Vera, Potassium Thiocyanate with bio-active enzymes Lactoferrin, Lysozyme, Lactoperoxidase, Glucose Oxidase.

Biotene gel contained, Lactoperoxidase per 50gm - 6,000 units, Lysozyme 6mg, Glucose Oxidase 6,000 units, Lactoferrin 6mg,

Hydrogenated Starch Hydrolysate, Xylitol, Hydroxyethyl Cellulose, Glyceryl Polymethacrylate, Beta-D-Glucose Aloe Vera, Potassium Thiocyanate, and Aloe Vera.

Biotene chewing gum contained Lactoperoxidase (0.11 units), Glucose Oxidase (0.15 units) and Xylitol.

Collection and treatment of saliva samples

Unstimulated saliva samples were collected at the base line and 3 weeks after the usage of the products. The subjects were asked not to eat for 1 h before sampling, which was always done between 0800 h and 1130 h.

Salivary secretion was assessed by collection of unstimulated saliva. Saliva was collected by having the patient drivel into a graduated glass for 5 min, but if the children were got tired or could not secrete as determined before, the rates were methodized. The secretion rate was determined as milliliters per minute. The normal flow rate of unstimulated saliva is 0.3ml/min. So flow of < 0.3ml/min is generally indicative of hyposalivation [22]. The salivary buffer capacity was assessed with the saliva testing kit and the pH with a pHM62 Standard pH Meter (Radiometer, Copenhagen, Denmark). Immediately after sampling 100 µl uncentrifuged saliva was used for Thiocyanite assay. Portions of centrifuged saliva needed for the analysis of total salivary peroxidase were stored frozen at -20°C before analysis.

Data analysis

Data from the test group was analysed using Excel™ and SPSS™ software at baseline and the follow-up examination two-tailed tests were used for within group comparisons with a level of significance of alpha=0.05.

Results

At the initial visit 17 of the 21 subjects reported that they were aware of their oral dryness (% 80.95). The discomfort experienced during the daytime was marked in this group (Table 1). For the 21 participants that completed the study all used multiple Biotene products: 7 (%33.33) used gel; 8 (%38.09) used mouth rinse; and 6 (%28.57) chewing gums. A 3 week daily use of a lactoperoxidase-system containing products mouth rinse, chewing gum and gel were relieved the symptoms notably. When asked to assess level of relief provided from xerostomia after using products; 5 subjects were satisfied with the taste of mouth rinse, 3 said it was too strong and told that they diluted the solution. All children liked chewing gum both its taste and the way it used. All of the children wanted to continue daily use of chewing gum.

The values for the studied non-immunologic antimicrobial factors in unstimulated whole saliva are shown in Table 2. Salivary flow rate was notably higher in each group after using Lactoperoxidase products. There was an increase in salivary pH and buffering capacity of saliva.

No major changes occurred in the level of salivary Thiocyanite and Peroxidase activity.

Discussion

For many pediatric cancer patients, oral sequelae and discomfort related to their treatment can have long term and potentially lethal consequences. Learning to manage these patients becomes important because up to 90 percent of pediatric oncology patients may suffer an oral complication of some kind [19]. One of the complications is the xerostomia. The resulting xerostomia is highly uncomfortable making the patient constantly in need of coughing to clear the thick, ropy saliva

and in need of moistening the mouth. Taste sensation diminishes, eating becomes difficult, and patients frequently lose their desire for food [19].

Natural saliva provides the best protection for the oral tissues. The teeth will be protected by it against acidic attacks both by the salivary buffer systems and by the pellicle of salivary proteins that is formed on dental enamel [20]. In addition, salivary antimicrobial systems, including antimicrobial proteins and peptides, e.g. lactoferrin, histatins and cystatins, play an important part in controlling the oral microbial ecosystems [21]. The presence of saliva usually is taken for granted, and it is not required for any life-sustaining functions. Nevertheless, its diminution or absence can cause significant morbidity and a reduction in a patient's perceptions of quality of life [9].

Palliative care for xerostomia can be given by wetting the oral tissues, using home-made or commercially available products, including special toothpastes, oral gels, mouthwashes and saliva substitutes. Our present results show that non-immunologic antimicrobial agents relieve subjective oral symptoms in most xerostomic pediatric patients. The subjective effects are consistent with those reported by Warde et al [23] who found major improvements after two-month review in people suffering post-irradiation xerostomia. Gel and chewing gum were both preferred over the mouth rinse. Similar results of a decreased frequency of subjective complaints has been reported with a combination of Biotene toothpaste and Oralbalance gel, the latter also containing the lactoperoxidase system components [24]. The acceptability of these products is probably related to that they do not contain any of the detergents, e.g. sodium lauryl sulfate (SLS), present in other dentifrices. SLS-containing dentifrices are less suitable for patients with dry mouth, because they can be too harsh for the frail mucosal surfaces. Our results together with the previous ones suggest that the daily use of these products give relief to many oral complaints in most patients with xerostomia. Davies et al. [25] concluded that both saliva substitutes and salivary stimulants were effective in the management of xerostomia. Davies [26] also demonstrated the comparable nature of the effectiveness of chewing gum and salivary substitutes in xerostomia of cancer patients. Shahdad et al. [28] defined that between-groups BioXtra® and Biotène Oralbalance® regarding in reduction of symptoms of xerostomia BioXtra® achieved superiority in some of the outcomes assessed compared with OB at their study which evaluated the efficacy of the of the systems in the treatment of post-radiotherapy xerostomia. In that crossover study, 20 patients with post-radiotherapy xerostomia

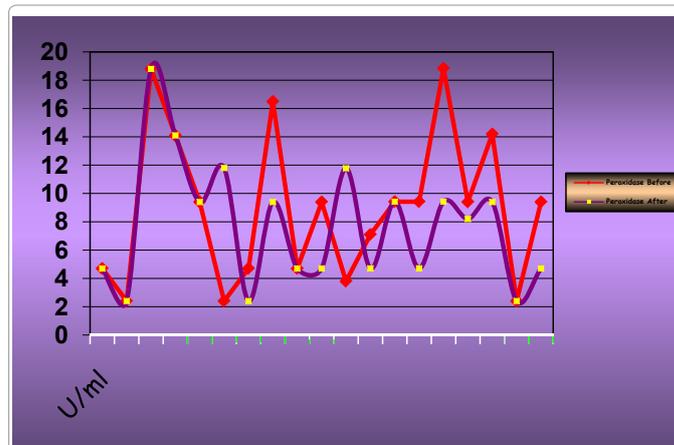


Figure 1: Changes in Salivary Peroxidase Levels.

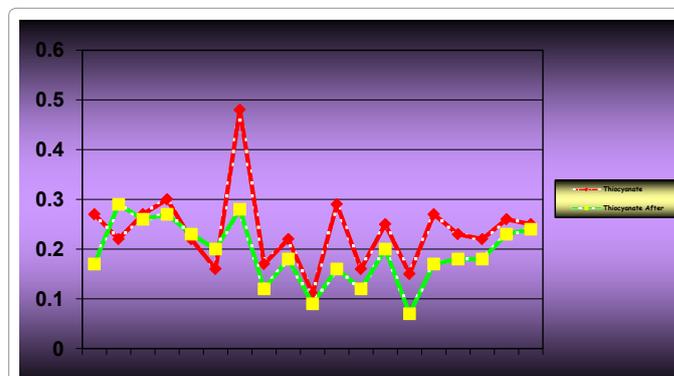


Figure 2: Changes in Salivary Thiocyanate Levels.

Question n=21	Before Mean	After Mean
Overall level of dryness?	2.64	1.47
Day time level of dryness?	2.23	1.35
Dry mouth of at night/awakening?	1.58	0.41
Need of liquid to aid speaking?	2.05	1.12
Need of liquid to aid swallowing?	1.05	0.24

Table1: Assessment of Xerostomia Questionnaire.

	Normal Values n=20 mean±s	Baseline mean±s n=21	3 weeks mean±s n=21	Significance
Salivary pH	7.0±0.2	6.46±0.2	6.53±0.2	NS
Flow rate (ml/min)	0.7±0.3	0.5 ±0.2	6.87±0.3	NS
Buffering capacity (ml/min)	6.3±0.2	4.45±0.2	4.47±0.2	NS

Table2: Assessment of changes in Salivary pH, FlowRate and Buffering Capacity.

were randomly allocated to receive either OB then BX, or vice versa, each product for 2 weeks, with a 1 week wash-out period in between. Subject-based dry mouth scores derived from 100-mm visual analogue scales were recorded at days 0 and 14 of each 2-week period, together with subjective perception of changes in dry mouth symptoms. Both treatments were effective, resulting in reduction of visual analogue scale scores from day 0-14. Between-groups comparisons identified that BX achieved significantly better improvements compared with OB for the perception of dry mouth and improvements in speech and was also rated as more pleasant to use than OB ($P < 0.05$). Dirix et al. [29] concluded in their study which they evaluated the clinical effectiveness of the BioXtra (BX) dry mouth care system is that BioXtra dry mouth care system is effective in reducing the symptoms of radiation-induced xerostomia and improving the quality of life of xerostomia patients, even if a proportion of the benefit is due to a placebo effect. Overall this study supports the finding recorded in the literature that Biotene system is effective in the treatment of xerostomia. The subjective xerostomia assessment showed a significant reduction in overall dryness and daytime dryness after using the Biotene products. No major changes occurred in the level of salivary Thiocyanite and Peroxidase activity (Figure 1 and Figure 2), but there was an increase in salivary pH and also salivary flow rate was notably higher in each group after using Lactoperoxidase products. Our results demonstrate as in Tenovuo et al. [27] study that obviously greater benefit of the incorporation of nonimmunoglobulin agents in oral hygiene products is gained by patients who have severe xerostomia (stimulated flow $\leq 0.2\text{ml/min}$) than in those who have subjective complaints of dry mouth

but the salivary flow rate is notably higher. The long-term efficacy of these products in preventing xerostomia remains to be shown.

Conclusions

Childhood cancers and their treatments can directly or indirectly affect the child's oral health and life quality negatively.

Because of that, proper oral care for immuno-suppressed patients should be considered critically. This study leads to outline an easy-to-follow oral hygiene protocol for use in home care and also for nursing staff in pediatric oncology unit for children with cancer as oral health care is not given priority during cancer therapies.

Findings from this study suggest that pediatric cancer patient should receive continuous oral care. Currently in Turkey, there are no oral evaluation tools or educational materials regarding oral care for children with hematological cancer. In this study we focused on enhancing saliva anticaries properties, by that way we planned to add lactoperoxidase included products especially chewing gums to daily oral care routine programme as the chemotherapeutic agents don't have good taste and some of the children vomit most of them.

Before standard oral care program for pediatric cancer patients, nurses can adequately be trained in providing oral hygiene care regimen.

Future plans include development of an oral hygiene educational booklet including oral home care for those special children.

It would be useful to use a larger sample size and examine other variables associated with different chemotherapy protocols.

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