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Bardellini E, Amadori F, Majorana A. Oral hygiene grade and quality of life in children with chemotherapy-related oral mucositis: a randomized study on the impact of a fluoride toothpaste with salivary enzymes, essential oils, proteins and colostrum extract versus a fluoride toothpaste without menthol.

Oral hygiene grade and quality of life in children with chemotherapy-related oral mucositis: a randomized study on the impact of a fluoride toothpaste with salivary enzymes, essential oils, proteins and colostrum extract versus a fluoride toothpaste without menthol

Abstract: *Aim:* The aim of this study was to assess the impact of the use of a fluoride toothpaste (Bioxtra®, Biopharm, Milan, Italy) with salivary enzymes, essential oils, proteins and colostrum extract versus a fluoride toothpaste without menthol on the oral hygiene grade and on the quality of life (QoL) of children with oral mucositis (OM) grade 1 or 2 receiving chemotherapy for Acute Lymphoblastic Leukaemia (ALL). *Methods:* Patients between 6 and 14 years with OM were randomly assigned to two groups, group A (Bioxtra® toothpaste) and group B (fluoride toothpaste without menthol). The patients were instructed to brush their teeth at least twice a day using a soft toothbrush with a small head. Oral hygiene grade was assessed using the simplified oral hygiene index (OHI-s); quality of life was assessed using the short form of the Oral Health Impact Profile (OHIP-14) questionnaires. The patients were evaluated on day 1(diagnosis of OM-T0) and on day 8 (T1). Statistical analysis was performed. *Results:* A total of 64 patients were enrolled. A significant difference ($P < 0.001$) between the mean of the OHI-s in group A (0.9 ± 1.2) and in group B (1.5 ± 1.3) was found; the overall OHIP-14 scores were not associated with the use of one or the other toothpaste ($P = 0.33$). *Conclusions:* Although the use of Bioxtra® toothpaste does not affect the QoL of children undergoing chemotherapy, it may be recommended as clinically effective in improving the oral hygiene grade.

Key words: colostrum; mucositis; toothpastes

Introduction

Children undergoing chemotherapy often present various psychological, physical and emotional changes that could impair their quality of life (QoL). Among the oral complications, chemotherapy-induced oral mucositis (OM) is the most debilitating and problematic side effect (1, 2). OM associated with immunosuppression can lead to serious and potentially life-threatening consequences interfering with the treatment and with patients' QoL (1, 2).

Management of oral mucositis has been largely palliative to date, although targeted therapeutic interventions are now being developed. Based on a comprehensive systematic review of the literature, the Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) has developed clinical practice guidelines for the management of mucositis, divided into: nutritional support, pain control, oral decontamination, palliation of dry mouth, management of oral bleeding and therapeutic interventions for oral mucositis (3). As regards oral decontamination, the MASCC/ISOO guidelines recommend using a standardized oral care protocol which includes brushing with a soft toothbrush, flossing and the use of non-medicated rinses (e.g. saline or sodium bicarbonate rinses). Patients and caregivers should be educated as regards the importance of effective oral hygiene (4–6).

The mechanisms through which various basic oral care strategies may directly influence the pathogenesis of OM are unclear, although most have little potential for affecting the complex interplay of molecular factors that lead to mucosal tissue injury (4–6). First, it has been hypothesized that microbial colonization of oral mucositis lesions exacerbates the severity of oral mucositis and therefore, decontamination may help to reduce mucositis, promoting an oral environment that reduces the potential for, or retards the development of, oral infection. Indeed, multiple studies have demonstrated that maintenance of good oral hygiene can reduce the severity of oral mucositis (4–6).

In children with OM, the use of the most common toothpastes is frequently suspended as it becomes intolerable for patients with inflamed oral mucosa, often suffering also from dysgeusia and xerostomia. The discomfort is mainly due to the irritant components of most commercial toothpastes, such as abrasives, surfactants, flavourings, antibacterial agents, etc. Avoiding the use of toothpaste, of course, the efficacy of the daily oral hygiene is reduced, increasing the risk of infections. (2–6). Mild toothpastes without menthol – which is a cyclic monoterpene alcohol with well-known cooling and irritating characteristics – have been introduced onto the market because they can be used during homeopathic treatment but no specific toothpaste for oral mucositis is currently available.

Recently, a specific toothpaste with fluoride, salivary enzymes, essential oils, proteins and colostrum extract has been proposed for oral mucositis, especially in the case of xerostomia.

The aim of this study was to evaluate the impact of Bioxtra® (Biopharm, Milan) toothpaste versus a fluoride toothpaste without menthol on the oral hygiene grade and on the QoL in children with OM receiving chemotherapy for Acute Lymphoblastic Leukemia.

Study population and methodology

Sample selection

Children hospitalized in the Paediatric Oncology Unit of Spedali Civili of Brescia (Italy) between November 2013 and March 2015 receiving chemotherapy for Acute Lymphoblastic Leukemia (undergoing ALL 2009 Standard protocol) and with OM grade 1 or 2 were considered eligible for this study. Treatment for ALL 2009 consists of an induction phase (combinations of four-five drugs including vincristine, prednisone, cyclophosphamide, doxorubicin and L-asparaginase), a intensification/consolidation phase with multiagent therapy (including cytarabine, methotrexate, cyclophosphamide, etoposide, mitoxantrone, asparaginase, doxorubicin, 6-MP, 6-thiouguanine and vincristine) and a maintenance therapy (including 6-mercaptopurine and methotrexate).

Enrolment criteria were: patients aged between 6 and 14 years with ALL undergoing any one of the phases of the chemotherapy protocol and with OM grade 1 or 2. Exclusion criteria were: other hematologic malignancies than ALL, no mucosal lesions or OM grade >2, hypersensitivity or allergy to any of the components included in the study.

Study design

This study was designed as a randomized, controlled and double-blinded clinical study. Randomization was performed using an automatically generated list in a 1:1 block size for two patients. Patients received a number after inclusion and they were randomly assigned to one of the two toothpastes by a member of the team who performed a permuted-block randomization of the participants. Patients codes where inserted in closed envelopes.

The patients were randomized by the computer code in two groups: group A (Bioxtra® toothpaste) and group B (fluoride toothpaste without menthol). The two toothpastes were comparable, both being devoid of components irritant to the oral mucosa. In detail, Bioxtra® toothpaste was composed of lysozyme, lactoferrin, lactoperoxidase, colostrum purified standardized extract, sorbitol, xylitol, isoceteth-20, sodium monofluorophosphate, hydroxyethylcellulose, sodium benzoate and titanium dioxide; the fluoride toothpaste without menthol was composed of aqua, sorbitol, hydrated silica, hydroxyethylcellulose, olaflur, titanium dioxide, aroma, limonene and saccharin.

The two products were identical as regards packaging. The patients and their caregivers were instructed to brush at least twice a day using a soft toothbrush with a small head and a roll-on technique. The roll-on technique was chosen as it is easier to learn and less time-consuming, as compared to other complex tooth brushing techniques. A pamphlet containing pictures depicting the correct method of tooth brushing and instructions for the parents was printed; the instructions included the use of a pea-sized amount of the toothpaste and the method of cleaning and storage of the toothbrush. On the overleaf of the pamphlet, a planner was given in which the children were asked to put a tick whenever they brushed their teeth. Each child was given a new toothbrush and toothpaste at the beginning of the study. Both patients and researchers were blinded throughout the study.

Oral mucositis scoring was performed at the onset of OM in order to exclusively select patients with OM grade 1 or 2. The

clinical evaluation of the severity of OM was conducted in both groups in accordance with the World health Organization (WHO). Lesions were classified as Grade 0 = none; Grade 1 = soreness and erythema; Grade 2 = erythema and ulcers without difficulties in swallowing solid food; Grade 3 = ulcers requiring only a liquid diet and Grade 4 = introduction of parental nutrition.

QoL measurements

A single member of the Paediatric Dentistry Department, blind to toothpaste assignation, administered by interview the QoL questionnaire to the patients in both groups on the first day of diagnosis of OM (T0) and after 8 days (T1); the researcher was blinded for the randomization allocation.

The short form of the Oral Health Impact Profile (OHIP-14) questionnaire was used to evaluate QoL in relation to oral health. The instrument has been already validated for Italian (7). OHIP-14 summarizes the following seven domains of impact on daily activities as a result of oral problems: functional limitation (domain 1), physical pain (domain 2), psychological discomfort (domain 3), physical activity (domain 4), psychological disability (domain 5), social disability (domain 6) and handicap or disability (domain 7).

The OHIP-14 instrument consists of 14 questions related to oral health, whose response options are five: 0 = never, 1 = hardly ever, 2 = occasionally, 3 = fairly often, 4 = very often. The final score is the sum of the individual scores, with higher values indicating worse OH-QoL; the maximum possible score is 56.

Oral hygiene

As the children were hospitalized, the clinical assessment of the oral hygiene grade was done by two calibrated researchers (EB, FA) according to the criteria of a simplified oral hygiene index (OHI-s) by Greene and Vermillion with a mouth mirror and explorer (8), on the first day of diagnosis of OM (T0) and after 8 days (T1).

Statistical analysis

OHI-s index was evaluated using split-plot analysis of variance (ANOVA); the differences in the OHIP-14 were analysed using the Wilcoxon rank sum test. A 5% significance level was used for the analysis. Taking the hypothesis that there is a success percentage of 80% on day eight for the group treated by Bioxtra and 45% for the control group, the minimum number of patients for the study, assuming alpha 0.05 and beta 0.10 (study power=90%), was calculated to be 56 (at least 28 per group).

Ethical considerations

The research was performed in compliance with the Declaration of Helsinki and Good Clinical Practice. All patients and their caregivers were informed about the research and signed an IRB approved informed consent. Ethical approval for the research was granted by the Ethic Committee (NP 1811 AOBS) of Spedali Civili di Brescia, Italy.

Results

Characteristics of patients

Among 108 patients affected by ALL, a total of 64 patients (41 females and 23 males) met the inclusion criteria and were accepted to participate in the study (Fig. 1). They were randomly assigned to two groups: group A ($n = 32$) and group B ($n = 32$). Mean age of the total sample was 8 ± 1.8 years. There was no difference ($P > 0.05$) between the clinical and demographic characteristics of the two groups, which resulted homogeneous. The groups were homogeneous also for OM grade ($P = 0.73$) (Table 1).

Clinical evaluation of OHI-s

While at T0 no differences in the mean of OHI-s were observed between group A and group B, at T1 a significant difference ($P < 0.001$) between the mean of the OHI-s in group A (0.9 ± 1.2) and in group B (1.5 ± 1.3) was found (Table 2).

Quality of life

The statistical analysis showed that the use of Bioxtra ®was not associated with total scores for the OHIP-14 ($P = 0.33$). Therefore, the use of one or the other toothpaste did not influence patients' QoL. The highest scores, indicating poor QoL, were found on day +8, indicating a progressive deterioration in QoL (Table 2).

Discussion

The major finding in this study is that the use of a specific toothpaste such as Bioxtra ® in children with OM grade 1 or 2, despite not having a substantial a substantial impact on their QoL, significantly affects the grade of oral hygiene. We evaluated QoL using the OHIP-14 scale, which is not designed to evaluate QoL in general, but specifically related to oral health, so that the effect of confounding factors is reduced. No patient refused to answer the survey. All participants were selected in order to have OM grade 1 or 2. In fact, according to the Literature (9, 10) patients with OM grade 1 or 2 should brush their teeth with a soft toothbrush and fluoride toothpaste while patients with OM grade >2 may clean the oral cavity with a gauze or oral sponge if they cannot use the toothbrush. Unexpectedly, most patients ($n = 19$) of group B reported not having brushed their teeth for at least for two consecutive days, due to pain and burning while all the patients belonging to group A managed to brush every day.

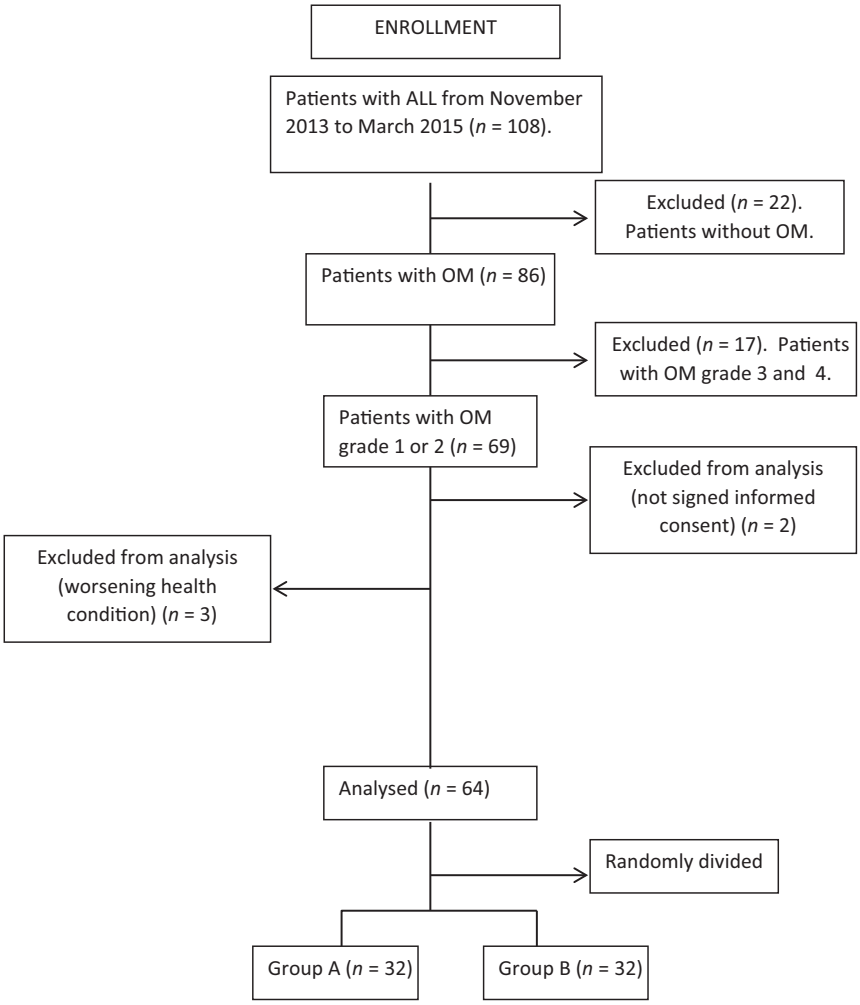

Fig. 1. Enrolment flow-chart.

Table 1. **Demographic and clinical characteristics of the patients**

	Group A(n = 32)	Group B (n = 32)	Total (n = 64)
Male:Female	13:19	10:22	23:41
Mean age (range)	8 ± 1.9 (6–14)	8 ± 1.4 (6–14)	8 ± 1.8 (6–14)
OM score (median)	1.5	1.5	1.5

Mean±SD

We did not exclude these children from the control group (even if they had not fully adhered to the oral hygiene instruction) because of the high number of patients in respect to the study group, which must be interpreted as a significant difference in the tolerability between the two toothpastes ($P < 0.05$). The clinical evaluation of the oral hygiene grade revealed that children using a toothpaste with salivary enzymes, essential oils, proteins and colostrum extract had a significantly lower OHI-s. This could be attributed to the greater tolerance of this toothpaste allowing greater accuracy and more time spent on oral hygiene, accompanied by the antibacterial properties of the toothpaste obtained from the extract of colostrum. The high nutritive value and diverse functional properties of milk proteins are well known. Such proteins are found in abundance in colostrum which is the initial milk secreted by mammalian species during late pregnancy and the first few days after birth of the offspring (11). The colostrum-based bioactive proteins include alpha-lactalbumin, beta-lactoglobulin, immunoglobulins, lactoferrin, lactoperoxidase and growth factors. These native proteins exhibit a wide range of biological activities that are known to affect the digestive function, metabolic responses to absorbed nutrients, growth and development of organs and disease resistance (12). Of great importance for the oral cavity, enzymes are key components of the acquired pellicle with high relevance to its protective properties (12, 13). This applies especially to the antibacterial lysozyme and to peroxidases preventing oxidative stress in the oral cavity by hydrolysis of peroxides and radicals (13, 14). Lactoperoxidase from cow's milk and lysozyme from hen's egg white are cheap and rather similar to their counterparts in human saliva (15). Thus, they are typical ingredients

Table 2. **OHI-s and OHIP-14 values at T0 and T1 in group A and in group B**

	Group A(n = 32)		Group B (n = 32)		
	T0	T1	T0	T1	*P*
OHI-s (mean±SD)	2.8 ± 0.8	0.5 ± 0.6	2.9 ± 1.0	1.6 ± 1.2	<0.001*
OHIP-14 -median (range)	5 (2–14)	8 (4–20)	4 (2–12)	8.5 (4–18)	0.33†

*ANOVA test, *P*-value<0.05
†Wilcoxon rank sum test, *P*-value<0.05

of enzymatic oral health care compounds (12, 15). Tooth brushing allows direct interaction of the enzymatic compounds of the toothpaste with the pellicle layer for facilitated immobilization of enzymes. In contrast to enzymatic mouth rinses, enzymatic toothpaste has been found suitable for targeted immobilization of enzymes in the acquired pellicle. The brushing ensured direct contact of the enzymatic slurry with the pellicle and supplied the respective enzymes immediately when the pellicle was re-established after removal of the outer layers of the pellicle (12, 15).

The pathogenesis of chemotherapy-induced OM appears to be related to oxidative stress induced by the treatment. The reactive oxygen species (ROS) cause direct and indirect damage through transcription factors, which induce the production of pro-inflammatory cytokines (16, 17). Therefore, the major tolerability of Bioxtra® in the case of OM can be attributed also to a mild anti-inflammatory effect due to the antioxidant components.

Bio-inspired and biomimetic strategies are of considerable interest for oral health care to avoid disturbance of the ecological equilibrium in the oral cavity, especially in conditions such as OM in which the respect of the oral mucosa is desirable. Although not affecting the QoL of children undergoing chemotherapy, the use of Bioxtra® toothpaste may be recommended in these patients as clinically effective in improving the oral hygiene grade.

Clinical relevance

Scientific rationale for study

Oral decontamination represents a prime factor in the management of chemotherapy-induced oral mucositis in children. The use of the most common toothpastes, in these children, is frequently avoided, as it is intolerable for the inflamed oral mucosa. This study evaluated the effectiveness of toothpaste with salivary enzymes, essential oils, proteins and colostrum extract both in terms of the effects on the oral hygiene grade and on the quality of life of these patients.

Principal findings

Children with oral mucositis showed a significantly increased oral hygiene grade when using Bioxtra® toothpaste. On the contrary, their quality of life resulted not significantly influenced.

Practical implications

The use of Bioxtra® toothpaste may be recommended in onco-hematologic paediatric patients suffering from oral mucositis.

Conflict of interest

The Authors declare that they have no competing interests.

Sources of funding statements

Authors did not receive any funding. The two toothpastes were freely provided by the Company.

References

1 Bensadoun RJ, Franquin JC, Ciais G *et al.* Low-Energy He/Ne Laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer. *Support Care Cancer* 1999; **7**: 244–252.
2 Cheng KKF, Chang AM, Yuen MP. Prevention of oral mucositis in pediatric patients treated with chemotherapy: a randomized crossover trial comparing two protocols of oral care. *Eur J Cancer* 2004; **40**: 1208–1216.
3 Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dent Clin North Am* 2008; **52**: 61–77.
4 McGuire DB, Fulton JS, Park J *et al.* Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; **21**: 3165–3177.
5 Cheng KK, Molassiotis A, Chang AM, Wai WC, Cheung SS. Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. *Eur J Cancer* 2001; **37**: 2056–2063.
6 Levy-Polack MP, Sebelli P, Polack NL. Incidence of oral complications and application of a preventive protocol in children with acute leukemia. *Spec Care Dentist* 1998; **18**: 189–193.
7 Corridore D, Campus G, Guerra F, Ripari F, Sale S, Ottolenghi L. Validation of the Italian version of the Oral Health Impact Profile-14 (IOHIP-14). *Ann Stomatol (Roma)* 2014; **4**: 239–243.
8 Green JC, Vermillion JR. The simplified oral hygiene index. *J Am Dent Assoc* 1964; **68**: 7–13.
9 Glenny AM, Gibson F, Auld E *et al.* The development of evidence-based guidelines on mouth care for children, teenagers and young adults treated for cancer. *Eur J Cancer* 2010; **46**: 1399–1412.

10 Miller MM, Donald DV, Hagemann TM. Prevention and treatment of oral mucositis in children with cancer. *J Pediatr Pharmacol Ther* 2012; **17**: 340–350.
11 Korhonen HJ. Production and properties of health-promoting proteins and peptides from bovine colostrum and milk. *Cell Mol Biol (Noisy-le-grand)* 2013; **59**: 12–24.
12 Hannig C, Hannig M, Attin T. Enzymes in the acquired enamel pellicle. *Eur J Oral Sci* 2005; **113**: 2–13.
13 Hannig C, Spitzmüller B, Lux HC, Altenburger M, Al-Ahmad A, Hannig M. Efficacy of enzymatic toothpastes for immobilisation of protective enzymes in the *in situ* pellicle. *Arch Oral Biol* 2010; **55**: 463–469.
14 Pruitt KM, Caldwell RC, Jamieson AD, Taylor RE. The interaction of salivary proteins with tooth surface. *J Dent Res* 1969; **48**: 818–823.
15 Tenovuo J. Clinical applications of antimicrobial host protein lactoperoxidase, lysozyme and lactoferrin in xerostomia: efficacy and safety. *Oral Dis* 2002; **8**: 23–29.
16 Wong WR, Kossodo S, Kochevar IE. Influence of cytokines on matrix metalloproteinases produced by fibroblasts cultured in monolayer and collagen gels. *J Formos Med Assoc* 2001; **100**: 377–382.
17 Herouy Y. Matrix metalloproteinases in skin pathology. *Int J Mol Med* 2001; **7**: 3–12.