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Effect of xylitol and xylitol–fluoride lozenges on approximal caries development in high-caries-risk children

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Aim. To evaluate the effect of xylitol- and xylitol/fluoride-containing lozenges on approximal caries development in young adolescents with high caries risk.

Study design. A 2-year double-blind trial with two parallel arms and a nonrandomized reference group.

Material and methods. One hundred and sixty healthy 10- to 12-year-old children with high caries risk were selected. After informed consent, they were randomly assigned into a xylitol and a xylitol/fluoride group. They were instructed to take two tablets three times a day (total xylitol and fluoride dose 2.5 g and 1.5 mg, respectively). The compliance was checked continuously and scored as good, fair, or poor. A reference no-tablet group was also selected ($n = 70$) for group comparison. The outcome measure was approximal caries incidence.

Results. The dropout rate was 28%, and 41% exhibited a good compliance with the study protocol. No statistically significant differences in caries incidence could be found between the study groups ($P > 0.05$). Among a subgroup of children who demonstrated good compliance, the mean ΔDMFSa value was significantly lower in the xylitol/fluoride group compared to the xylitol group, 1.0 ± 2.3 vs. 3.3 ± 4.6 ($P < 0.05$), while no difference could be displayed between any of the study groups and the reference group ($P > 0.05$).

Conclusion. The results from this 2-year trial did not support a self-administered regimen of xylitol- or xylitol/fluoride-containing lozenges for the prevention of approximal caries in young adolescents with high caries risk.

Introduction

The distribution of caries is highly uneven in childhood and the majority of children and adolescents have little or no experience while most caries occur in a minority of the population[1]. This well-known fact has been an argument for a high-risk approach to prevent the disease[2]. A prerequisite is, however, that effective measures are available and feasible for the high-risk individuals. Although the basic aetiology behind the caries process is the interaction between diet and bacteria[3,4], programs for caries prevention in high-risk children are mainly based on work on the resistance side through the use of additional fluorides[5].To some extent, this is accompanied by efforts to decrease the pathological side of the caries process by information on sugar restriction and self-performed oral hygiene. The compliance with and outcome of recommendations on diet for caries control has, however, not been scientifically demonstrated[6]. One reason for failures may be that the desired dietary changes not are culturally acceptable[7] and the outcome of high-risk strategies has not always been superior compared to basic prevention[8–10]. In a recent study aiming at improving oral health habits through frequent counselling sessions to 11- to 12-year-olds with active caries risk, little effects could be displayed except for an increase in the use of xylitol and fluoride lozenges[11].

Xylitol, a five-carbon sugar alcohol, has the ability to decrease the volume and acidogenicity of plaque[12,13]. Although favourable caries preventive results from xylitol have been presented[14–16], the effect has not always been confirmed[17]. We previously have shown a statistically significant shift towards xylitol-resistant mutans streptococci after a daily intake of 1.7 g/day[18], and it has been suggested that

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these strains have an impaired ability to colonize and adhere to tooth surfaces[19]. Even more beneficial results have been shown with doses around 6 g/day[12,13,20]. Such high doses are, however, often considered as inconvenient due to the high number of pieces. It was therefore considered of interest to investigate if the caries preventive effect of a rather low xylitol dose combined with fluoride was superior to xylitol alone in patients with an anticipated high caries risk. The aim of the study was to investigate the effects of lozenges containing either xylitol or xylitol/fluoride on approximal caries development in young adolescents with high caries risk and to make comparisons with a reference group who had been offered the conventional treatment for high-caries-risk subjects. The null hypothesis was that there would be no difference between the regimes.

Materials and methods

Subjects

Ten- to 12-year-old children with a predicted high caries risk or a proven caries activity were invited to the study and a signed consent was obtained from the parents of 160 children after verbal and written information. Seventy subjects assessed as high-caries-risk subjects with the same criteria as the study groups did not give informed consent for participation in the intervention but agreed to participate in the baseline and 2-year follow-up examinations. These subjects formed a nonrandomized reference group (Fig. 1). The mean age was 11.3 ± 1.5 years with an equal distribution between the sexes. The children were listed as regular recall-patients at a major public dental clinic in the city of Umeå in northern Sweden with approximately 1300 patients in these age groups. Caries risk was assessed by the regular dentists using a software program (T4, Practice Works, Atlanta, GA, USA) within the digital records. The computerized risk assessment was based on the caries prevalence (decayed, filled, and missing surfaces; total number of initial lesions) in combination with clinical data on oral hygiene, dietary, and fluoride habits. The estimated caries risk was expressed in three levels, from low to high (0–2), and only those assessed with score 2 were considered for inclusion.

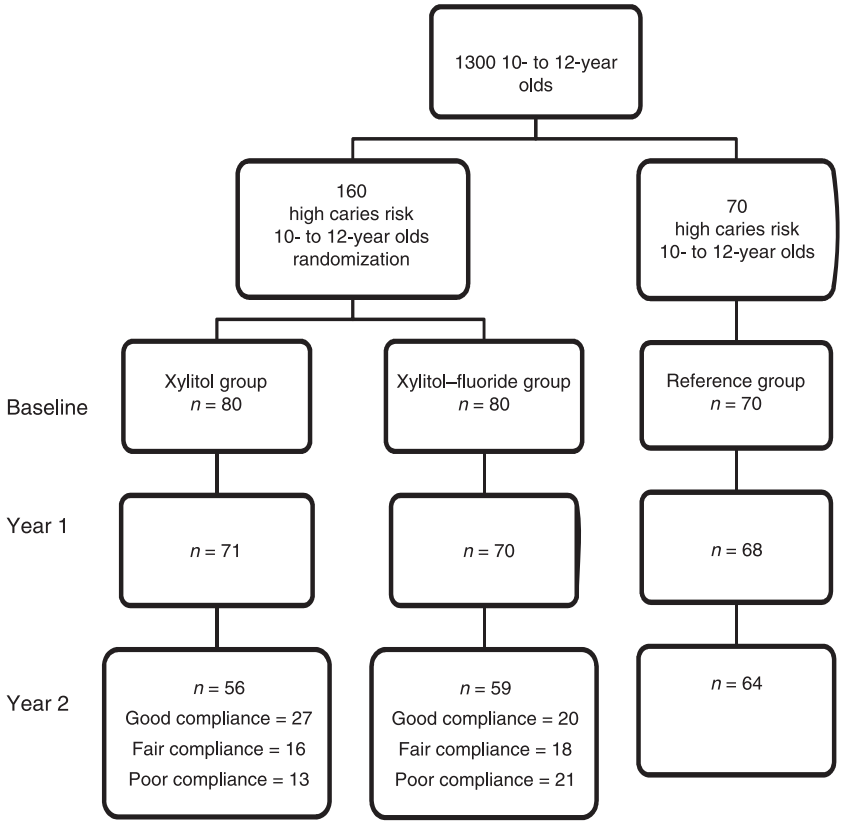

Fig. 1. Overview of study design and flow of subjects.

Score 2 included children with three or more dentine caries lesions, and or secondary caries, obvious active enamel lesions, caries on buccal or lingual surfaces, unacceptable oral hygiene, and frequent sugar consumption. Disabled children and individuals with complicated chronic diseases or mental handicap were not invited. The recruitment started in September 2001 and was finalized in September 2002 and all subjects were well informed that they had an anticipated high caries risk. The sample size was calculated on the basis of local epidemiological data showing a caries incidence of 1.5–2 new proximal lesions per year in young teenagers. With α- and β-values set at 0.05 and 0.2, respectively, 66 subjects per group were needed to disclose a 25% difference in approximal caries incidence between treatment groups. A dropout rate of 20% was estimated. During the first year of the study, 19 subjects in the study groups violated the study protocol and during the second year another 26 were lost. In the reference group, two subjects moved from the area during the first year and four during the second year.

Study design, randomization, and blinding

The study was carried out as a double-blind randomized trial with two parallel arms, and the protocol was approved by the local Ethical Committee of Umeå University. The planning was carried out according to the guidelines of the Swedish Medical Products Agency who also continuously monitored and supervised the project. The randomization was performed at the Department for Pharmaceutical Testing at the University Hospital Pharmacy, which kept the code list locked in a safe during the entire project. The subjects were randomly assigned to one of the two study groups: A: xylitol, and B: xylitol/fluoride, and each patient was given a code number. The code was broken when the study was finalized and all data were processed. The outcome measure was 2-year caries incidence assessed from bitewing radiographs and expressed as total approximal caries (ΔDMFSa) and lesions within the enamel (ΔDSe). At baseline, 180 surfaces (1.9%) could not be read due to technical reasons, mainly because of overlappings or the surface had not been exposed on the radiograph. At the end of the study the corresponding figure was 240 surfaces (2.9%).

Caries registration

The baseline caries prevalence for all participants was scored from a clinical examination including two bitewing radiographs that were exposed with the aid of a film holder (Kvickbite, Trollhätteplast, Sweden). After 24–28 months, the clinical examinations were renewed with bitewing radiographs. All radiographs were evaluated by two calibrated examiners (PLH and CSB) not involved in the treatment of the patients using a light desk and a magnifying Mattson viewer (Mattson, Denmark). All approximal surfaces from the distal surface of the canines to the mesial surface of the second molars were scored as follows: 0 = caries free; 1 = lesion within the enamel; and 2 = lesion passing into the dentin or restored or missing surface. The 2-year radiographs were scored without knowing the baseline registration and surfaces that could not be assessed due to overlaps or technical reasons were scored as healthy. The DMFSa index expressed the total prevalence of approximal enamel and dentin caries, fillings, and missing surfaces, while DSe was used as a measure of enamel caries only. Caries incidence was calculated as the difference between the follow up and baseline scores. A random sample of 50 sets of radiographs was re-examined after 1 month in order to check the intra- and interexaminer reliability.

Intervention

The study products were slow-melting lozenges distributed in identical pots and labelled with the patient's individual code number. The pots were packed and labelled at the Department for Pharmaceutical Testing at the University Hospital Pharmacy. Subjects in the xylitol/fluoride group were provided with lozenges with 0.25 mg sodium fluoride and 422 mg xylitol (Xerodent®, Actavis Group, Iceland) and those in the xylitol group received identical lozenges with 422 mg xylitol but without fluoride for 3 months use. The composition of the tablets is detailed in Table 1. The patients were instructed to use two tablets three times per day and

Table 1. Composition of the lozenges used in the study groups.

Xylitol	Xylitol–fluoride
Acid malic 28.6 mg,	Acid malic 28.6 mg
Xylitol 422 mg	Xylitol 422 mg
–	Sodium fluoride, corresponding to 0.25 mg F
Malic acid 29.0 mg	Malic acid 29.0 mg
Flavours	Flavours
Disodiumphosphate-dihydrate	Disodiumphosphate-dihydrate
Macrogol	Macrogol
Povidone	Povidone
Sodium stearyl fumarate	Sodium stearyl fumarate
Silicon dioxide	Silicon dioxide

return their pots every third month. A study coordinator checked the compliance and all nonconsumed tablets were collected before new pots were delivered. The returned pots were weighted and the number of remaining tablets was calculated as follows: total weight (tablets + pot) – empty pot weight/mean weight of one tablet. The mean weight of one tablet was calculated as the mean of ten tablets weighed ten times each. Subjects who not showed up for receiving new pots were given reminders through personal phone calls.

In the reference group, the conventional care for high caries risk was offered and included fluoride varnish application two times per year or three applications per year within a 10-day interval. Besides, advice on improved tooth-brushing and sugar restrictions was given on individual indications.

All participants in the study groups and the reference group were strongly encouraged to brush their teeth with fluoride toothpaste two times a day during the entire study period. The fluoride content in the pipe drinking water was ≤ 0.3 p.p.m. The patients' ordinary dental team was informed on the objectives of the study and kept the responsibility for the treatment. Decisions on the recall interval and restorative therapy were taken on an individual basis. No side-effects or adverse events were reported neither by the participating subjects or by their parents among those who fulfilled the study, whereas two children aborted treatment during the first month of the study due to insecurity whether problem with stomachache was caused by the lozenges.

Statistical method

All data were computerized and processed using spss software (version 15.0, Chicago, IL, USA). Analysis of variance (ANOVA) was used to analyse differences between the study groups. A *P*-value of < 0.05 was considered statistically significant.

Results

Seventy-two per cent of the randomized subjects completed the 2-year trial, giving a total attrition rate of 28%. The main reason for dropping out was relocation and violence of study protocol. The intra- and interexaminer reproducibility of the bitewing radiographs was kappa 0.89 and 0.85, respectively.

The caries prevalence at baseline and after 2 years as well as the calculated incidence in the two study groups and reference group is shown in Table 2. There was a slight but non-significant imbalance between the groups at baseline with a somewhat higher prevalence in the xylitol/fluoride group and this difference persisted after 2 years. The 2-year incidence of approximal enamel lesions and total approximal DMFS was similar in both study groups ($P > 0.05$) and when comparing the study groups with the reference group no statistically significant differences could be displayed ($P > 0.05$). As shown in Fig. 1, 41% of the children were classified with good compliance, 30% had fair,

Table 2. Mean values (± SD) of proximal caries prevalence (DMFSa and DSe) at baseline and after 2 years and the mean incidence (ΔDMFSa and (ΔDSe) in the two study groups.

	Xylitol *n* = 56	Xylitol-fluoride *n* = 59	Reference *n* = 64	*P*
Total proximal DMFSa				
Baseline	2.1 ± 1.6	2.9 ± 3.4	2.7 ± 2.3	NS
Year 2	4.8 ± 4.9	5.5 ± 5.9	4.4 ± 4.6	NS
ΔDMFSa	2.7 ± 4.3	2.7 ± 4.4	1.7 ± 3.5	NS
Proximal enamel lesions DSe				
Baseline	1.6 ± 1.3	2.0 ± 2.5	2.0 ± 1.8	NS
Year 2	3.6 ± 4.4	3.7 ± 4.2	3.0 ± 3.8	NS
ΔDSe	2.0 ± 4.0	1.7 ± 3.8	1.0 ± 3.0	NS

NS, not statistically significant; SD, standard deviation.

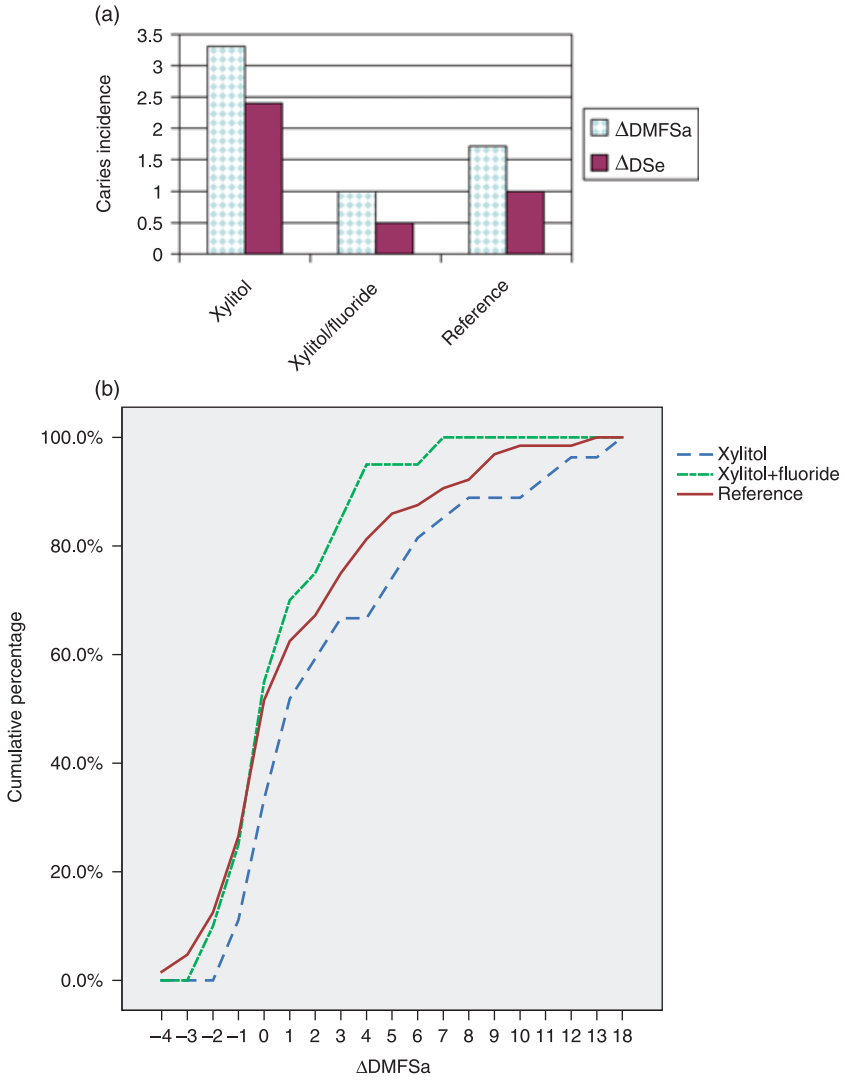

Fig. 2. (a) Mean 2-year caries incidence among the subjects with good compliance with the study protocol in the xylitol ($n = 27$), xylitol/fluoride ($n = 20$) study groups, and the reference group ($n = 64$). The difference in (ΔDMFSa) between the xylitol and the xylitol–fluoride group was statistically significant (ANOVA ($P < 0.05$)). (b) Cumulative distribution frequency of total proximal caries incidence (ΔDMFSa) among subjects with good compliance with the study protocol in the xylitol (- - -), the xylitol–fluoride (-----), and the reference (—) groups. Negative values indicate reversals.

Table 3. Scoring of compliance with the intervention.

Score	Definition
Good	Consumed almost all lozenges and returned pots during the whole study period.
Fair	Consumed almost all lozenges and returned pots during the first year and consumed lozenges and returned pots occasionally during the second year.
Poor	Consumed lozenges and returned pots occasionally during the whole study period.

and 29% had poor compliance (Table 3). There was a nonsignificant tendency to higher incidence among those with poor compliance (3.2 ± 4.1, $n = 34$) compared to those with good (2.3 ± 4.0; $n = 47$) and fair compliance (2.6 ± 5.1; $n = 34$). When comparing the caries incidence between those with good compliance in the two study groups, the mean ΔDMFSa value was significantly lower in the xylitol/fluoride group, 1.0 ± 2.3 vs 3.3 ± 4.6 ($P < 0.05$), while the differences compared to the reference group were statistically nonsignificant ($P > 0.05$) (Fig. 2a). The cumulative distribution of the individual ΔDMFSa values in the two study group and the reference group is shown in Fig. 2(b).

Discussion

Xylitol and fluoride are both well-established anticaries agents[7,21]. While xylitol is thought to act on the pathological side of the caries balance

by diminishing acid production and plaque formation, the evidence for the fluoride-promoted remineralization on the defence side is firm. In this study it was investigated if the caries preventive effect of self-administered supplements of xylitol and fluoride was superior to xylitol alone when added to regular tooth-brushing with fluoridated toothpaste in selected children with high caries risk. The children had a mixed socioeconomic background and were patients at public dental clinic, providing comprehensive dental care for children free of charge. Epidemiological data indicated that the clinic was representative for a low-caries community in Sweden. A third fluoride tablet group would clearly have been desirable instead of a nonrandomized reference group, but the relatively low number of patients assessed at high caries risk who were willing to participate during the recruitment period limited the study design to two parallel arms.

It was thought that it would be attractive to use 'tablets for prevention' in this age group, especially since we previously experienced excellent compliance with lozenges in patients undergoing orthodontic treatment with fixed appliances[18], and a recent Finnish study involving high-risk individuals in similar age groups shoved an increase in the use of fluoride and xylitol lozenges after counseling[11]. Obviously, the present regime was not successful among the caries-risk teenagers as only 41% of the patients exhibited good compliance with the study protocol in spite that they were under the supervision of a study coordinator, who reminded and encouraged them during the course of the study. The reason for the low compliance was not fully clear but a recent qualitative study in adolescents with high caries risk has shown that major obstacles for regular oral hygiene habits were forgetfulness and lack of time rather than lack of knowledge[22]. Lack of compliance with prophylactic treatment has previously been pin-pointed[1,23] and this study confirms the difficulties in targeting preventive measures to young adolescents with caries risk.

Based on the mechanisms of action, it could be expected that the combined effect of xylitol and fluoride would be stronger than the effect of xylitol alone but this was not the case in this study. Thus, the null hypothesis could not be rejected and one may speculate whether the scanty results were linked to problems with compliance or with an ineffectiveness of the anticaries agents *per se* or a combination thereof. An indirect answer pointing to the last alternative could be found after the analyses of the subgrouped material. The level of compliance had a certain impact on approximal caries development and a statistically significantly lower caries incidence was found in those who followed the protocol in the xylitol/fluoride group compared to the xylitol group. No difference between the two study groups and the reference group who had been offered mainly fluoride applications could, however, be displayed. The numbers of subjects in those subgroups were, however, small with large individual ranges so differences may appear by chance. In the absence of a randomized control group, the children with the poorest compliance could be looked upon as an almost nontreated reference group. Although they, on average, exhibited somewhat more new lesions than those with better compliance, the difference was not statistically significant. An explanation for the outcome could be found in the daily dose of xylitol. In this study, the children were given 2.5 g xylitol per day and we have previously shown a statistically significant shift towards xylitol-resistant mutans streptococci after a daily intake of 1.7 g xylitol consumption with the present lozenges[18]. These resistant strains have been suggested to have an impaired ability to colonize and adhere to tooth surfaces[19]. More recent studies have, however, suggested that more beneficial results are achieved with daily doses around 6 g[12,13,20]. If such a dose should have been used in the present trial, an even more inconvenient regimen with 14 daily tablets would have been needed. Moreover, the fluoride exposure had exceeded the 1.5 mg that is recommended in caries-active adolescents. It should be noted that besides the two anticaries agents, that lozenges also contained malic acid that is thought to stimulate the saliva secretion but its possible impact could not be evaluated with this study design. It should be stressed that the xylitol concentration obtained in saliva with the lozenges did not differ from chewing gums containing 0.66 g xylitol per piece[24].

The high-risk strategy has recently been questioned by Batchelor and Sheiham[25], but the skewed distribution of caries in childhood is problematic and cannot be disregarded. The search for cost-effective and culturally acceptable caries management strategies targeted at high-caries risk individuals is therefore important. The study population developed an average of 2.7 DMFS during this 2-year trial, of which the majority (1.8) were lesions within the enamel. One should keep in mind that these children very likely will continue to be at risk since past caries experience is considered as the single most reliable method for identifying individuals who will exhibit further progression[26,27]. For example, in 11- to 12-year olds, it has been shown that subjects with one approximal lesion or more have 2.5 times higher risk for new proximal caries lesions compared to those with a lower score[28]. An interesting approach to the problem is school-based fluoride varnish treatments carried out every 6 months[29]. This outreach concept was proven successful, especially in young teenagers from a high-caries community, and one of the reasons might have been that the children did not have to take own responsibility for the intervention. In conclusion the results from this 2-year trial did not support a self-administered regimen of xylitol- or xylitol/fluoride-containing lozenges for the prevention of approximal caries in young adolescents with high-caries risk.

What this paper adds

- The caries preventive effect of a self-administered regimen consisting of xylitol- or xylitol/fluoride-containing lozenges for the prevention of approximal caries in young high-caries risk adolescents is not different to the effect of an intervention consisting mainly of fluoride varnish applications and advice on improved toothbrushing and sugar restriction.

Why this paper is important to paediatric dentists

- The paper underlines the difficulties with high-risk strategies and the need for development of cost-effective and culturally acceptable caries management strategies targeted at high-caries-risk individuals.

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