IJD ISSN:1806-146X

Clinical and laboratorial evidences of dental caries control with Chlorhexidine and Xylitol use

Evidências clínicas e laboratoriais do controle da doença cárie com o uso de clorexidina e xilitol

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RESUMO

O controle da doença cárie tem sido um dos principais objetivos da odontologia principalmente em populações específicas, onde a prevalência desta doença ainda permanece elevada. O controle químico da cárie tem sido vastamente estudado como uma estratégia extra para pacientes com alto risco ou alta prevalência da doença. De todos os agentes químicos disponíveis na odontologia, a clorexidina, um antibacteriano, e o xilitol, um substituto do açúcar, têm demonstrado expressiva evidência para o controle da cárie. Desta forma o objetivo do presente artigo é fazer uma revisão da literatura sobre as evidências clínicas e laboratoriais do controle da cárie com a clorexidina e o xilitol. As substâncias Clorexidina e Xilitol utilizadas em separado ou associadas parecem apresentar uma exelente performance para o controle do Streptococus mutans, do biofilme e da doença cárie.
Palavras chave: Biofilme; Cárie; Clorexidina; Streptococcus mutans; Xilitol.

ABSTRACT

The control of dental caries has been one of the mainly objectives of dentistry, mostly in specific populations, where the prevalence of this disease is still high. Chemical control has been widely studied as an extra strategy for patients with high risk or high prevalence of dental caries. From all chemical agents available in dentistry, chlorhexidine, an antibacterial, and xylitol, a sugar substitute, have been demonstrated expressive evidence for caries control. The purpose of this paper is to review the literature about clinical and laboratorial evidences of dental caries control with chlorhexidine and xylitol. Chlorhexidine and xylitol separately or associated seem to have an excellent performance for Streptococcus mutans, biofilm and dental caries control.

Keywords: Biofilm; Dental caries; Chlorhexidine; Streptococcus mutans; Xylitol.

INTRODUCTION

Dentistry offers different strategies to prevent or control dental caries and the most effective are the mechanical and chemical controls of cariogenic microorganisms.

Mechanical control implies the disorganization or mechanical removal of the dental biofilm microbiota and it has been included in oral health programs due to its effective preventive results. Chemical control includes the capacity that a chemical agent has to interfere in the metabolic activity of the biofilm bacteria or their levels of adherence. This latter approach has determined many laboratory and clinical studies as well as inclusion in some oral health programs (1).

A wide variety of chemical agents are available in dentistry such as alexidine, cetylpyridinium chloride, hexetidine, sanguinarine extract, sodium dodecyl sulphate, and triclosan. Among these agents, two are particularly important: chlorhexidine, an antimicrobial agent, considered the most powerful chemical agent in the control of *Streptococcus mutans* (SM); and xylitol, which is a sugar substitute with a specific mechanism for SM control (1).

These agents have received great attention for their capacity of reducing SM levels, biofilm, and the incidence of dental caries (2-10). Additionally, some attention has been given to the association of these agents, which contributes to the good

performance of the caries control mechanism (11-13).

The purpose of this paper is to review the literature for clinical and laboratorial evidences about dental caries control with chlorhexidine and / or xylitol.

CHLORHEXIDINE

Chlorhexidine is a broad-spectrum antimicrobial agent, active against Gram-positive and Gram-negative bacteria, yeast, facultative anaerobic and aerobic organisms. However, it is more effective against Gram-positive bacteria, and particularly effective against *Streptococcus mutans* (14). In greater concentrations, its bactericidal properties have an immediate action, as it penetrates the cellular wall, causing cytoplasm precipitation. In smaller concentrations, it has hydrophilic-hydrophobic properties and bacteriostatic effect, which intervenes in the membrane transport allowing the lightweight molecule to infiltrate in the microorganism (1, 3).

This substance also has high substantivity rates, allowing its molecule to adhere to the oral surfaces, to salivary proteins and to extracellular polysaccharides (15). These now start functioning as reservoirs, releasing chlorhexidine for a long period of time thus preventing the bacteria from resuming their normal activity for some time.

Chlorhexidine has been widely used in dentistry at different levels of concentration and with different vehicles: as chlorhexidine varnish in concentrations of 1%, 10%, 20%, 25%, 33% and 40% (3); as gel in concentration of 1% (16); in mouthwashes, for daily use, in concentrations of 0,12% and 0,2% (12) ; and finally as chewing gum (17, 18). According to Emilson (1994) (19), SM reduction was better observed in longer period of time after the varnish application followed by the gel and mouthwashes.

Many clinical researches have shown that chlorhexidine reduces SM levels in saliva and biofilm, both at large and small concentrations, as well as in different vehicles. Such levels can become almost undetectable (20-23). A significant reduction in bacteria levels in the oral environment for longer periods can dramatically reduce the incidence of dental caries. This reduction can be observed in the proximal, occlusal (fossulae and fissures) and buccal surfaces with statistically significant data when compared to other chemical agents or control groups (6, 21, 22, 24).

SM inhibition will depend on how the chlorhexidine is used, the vehicle used and type of analyzed material (10, 20, 21). When the administration of this agent is interrupted, bacterial levels are restored, demanding further therapy to keep them low (19). Recolonization will depend on the same factors (16, 25). The recolonization process seems to follow a pattern within the oral cavity, where the molars are the first to be recolonized, followed by the premolars and then the incisors. It usually starts from the proximal face followed by the lingual and then the occlusal (25).

The effective chemoprophylactic properties of chlorhexidine against caries, and particularly against SM, and its substantivity, have not been found in any other chemical substance. According to Emilson (1994) (19), these properties make this substance be used quite frequently as a positive control to evaluate the anticariogenic potential of other chemical agents.

The wide variety of vehicles and concentrations found in chlorhexidine gives the professional a great flexibility in choosing the more appropriate and convenient one for clinical or research use. However, since a protocol for each type of vehicle with different formulations has not been found in the studies, comparison of the results has been a very hard task.

In the literature, many studies developed with chlorhexidine showed that this substance is extremely effective in reducing SM levels, biofilm rate and enhancing dental caries prevention and control. However, some authors have not reached the same results when it comes to dental caries control (26-28). Arguably, failure to reduce the incidence of caries can be put down to the different methodologies used. In the study developed by Dasanayake (2002) (27), for example, when the application of varnish was suspended, after chlorhexidine varnish was applied and the SM levels were reduced, and the increment of lesions continued being evaluated, the author concluded that chlorhexidine did not contribute to the reduction of carious lesions. These results are justifiable because the effect of chlorhexidine is not definitive; and when its use is interrupted, bacterial colonization is restored and also is the risk of a carious process. The anticariogenic potential of chlorhexidine is still more evident when the

benefits of this substance are observed in highly susceptible situations (caries–prone patients), as is the case with patients already with a high incidence of caries (29), erupting in first permanent molars (6, 20) and patients undergoing radiotherapeutic treatment (30). Additionally, delayed SM colonization was observed in the oral cavity of children after the chlorhexidine use by the mothers with high levels of the bacteria (31) and an ensuing fall in the incidence of dental caries in these children in long term (18) confirm the action of this substance on the control of dental caries.

One of the most serious clinical problems of this antimicrobial agent is that in spite of its high substantivity, bacterial colonization will recur when the treatment with chlorhexidine comes to an end. The model adopted for this process is largely acceptable particularly because the teeth with larger areas are those recolonized in the first place therefore, the ones that receive the largest concentration of microorganisms initially.

Other problems associated with chlorhexidine that make its use for longer periods unfeasible are first and foremost its unpleasant taste, although many authors have reported that the levels of acceptance of this treatment are quite high, both among adults (32) and children (21, 24). Secondly, there are side effects caused by the prolonged use of chlorhexidine, such as staining of the teeth, tongue irritation and taste alteration. Therefore, it would be interesting if some strategy capable of prolonging the effects of chlorhexidine was introduced, enhancing its good properties and minimizing its undesirable effects. This would avoid the need for the constant use of this substance at such short intervals.

XYLITOL

Xylitol is a pentiol considered to be a caloric sugar substitute. It is usually found in fruits and plants, or where it can be produced by means of xylose hydrogenation, and is usually extracted from betula. Commercially, it can be found as a sugar substitute in expectoration tablets, saliva substitutes and toothpastes (1). Some researchers have added it to foods (33), candies (34), but it is more usually added to chewing gum formulae (18, 35-37).

This sugar substitute is considered a non-cariogenic as well as an anti-cariogenic substance (38). Its non-cariogenic potential has been put down to the fact that this substance cannot be metabolized in acids by SM. Intracellular accumulation of xylitol 5-phosphate molecules acts as a toxic agent against bacteria inhibiting their proliferation (39, 40). According to Sahni et al (2002) (38) and Söderling et al (2008) (41), the inhibition of these bacteria was observed *in vitro* with low xylitol concentrations (0.01% to 1.56%) whereas greater concentrations were necessary for the reduction of *Streptococcus salivarius and Streptococcus sanguis* (12.5%) colonies. Additionally, it has been found that xylitol possesses a dose-dependent effect, which means that the greater the concentration of this substance, the more reduced the levels of SM both in the saliva and in the biofilm (42).

The reduction of SM levels in the saliva and in the biofilm caused by the xylitol lasts only for a very short period of time after which SM levels are restored to their initial salivary levels, which can take from 3 to 6 months (43, 44).

The prolonged use of xylitol does not result in lower salivary levels of SM (45); however, it seems that a strain undergoes a selective process. Xylitol-resistant strains increase in number while there is a fall in the number of xylitol-sensitive ones (39, 46), a change in proportion that according to Trahan & Mouton (1987) (39) varies from 1:9 to 9:1 within the oral cavity.

The non-cariogenic potential of xylitol seems to be associated with the presence of these xylitol-resistant strains (46, 47). According to Trahan et al (1992) (46), these strains adherence capacity to hard surfaces is probably rather insignificant if compared to xylitol-sensitive strains, a conclusion that has been confirmed by laboratory and clinical studies. In both studies, low SM levels are found in the biofilm of xylitol users, while their salivary levels remained high; this confirms the easiness with which these bacteria can dislodge from their main habitat, the dental surface (35). Besides their poor adherence, these strains fail to produce acid from glucose in the presence of xylitol (48).

The easy dislodgement of new strains explains the reduction in the biofilm compared to those patients that have not used xylitol (35, 37).

A lower incidence of dental caries after the prolonged use of xylitol can be observed in some classical studies. Significant results were found in the studies developed in

Belize, Ylivieska, Hungria and Montreal when xylitol was compared to controls in which the teeth were not treated chemically (35, 36), to fluoride or to other sugars such as sucrose (36) and sorbitol (35, 36). This superior performance remains when the use of xylitol alone is compared to xylitol associated with sorbitol (35, 36).

It is interesting to point out that the same dose-dependent effect of xylitol on SM levels can be observed in caries reduction. Clinical studies investigating chewing gums containing xylitol at different concentrations and application frequency have concluded that performance improves as xylitol concentrations increase and its use becomes more frequent (35, 36, 49).

One of the most popular discussions among researchers into xylitol today is its use in chewing gums. In the opinion of many researchers, the most beneficial effect of xylitol-based gums results from the stimulation of saliva (50). Studies of xylitol and sucrose-based gums disclosed that sucrose was more responsible for the greatest incidence of dental caries than any other sweetener used in chewing gums (35, 36). If salivary stimulation were in fact what caused the beneficial effect, it alone would be enough to prevent caries even among the subjects of the group that used sucrose gum, which did not occur. It has already been found that xylitol added to sweets is as efficient against dental caries as when it is added to chewing gum (51). However, it cannot be denied that there is an association between the anticariogenic properties of xylitol and the increased saliva flow prompted by the gum. In view of this, it would be interesting if studies of other salivary nonstimulating vehicles were developed so that the effects of xylitol could be better evaluated dissociated from salivary stimulation.

Trahan & Mouton (1987) (39) believe that the selection of SM strains probably results from the incapacity of the xylitol-resistant strain to accumulate enough xylitol 5-fosfate within it and remain viable in the oral microbiota, while the xylitol-sensitive strain can easily accumulate this toxic molecule. This selective mechanism contributes for the species in the oral micro-environment to thrive. Although the presence of this strain justifies the low biofilm rates in long term (35); this biofilm mass reduction was also demonstrated in clinical studies, where this picture rather than being justified by the presence of resistant strains is justified by the initial period of reduction of these bacteria in the oral cavity (52).

Although the *in vitro* analyses associated with those developed in the clinical area may make it easier for the xylitol-inherent mechanisms to be understood, the whole process associated with the non-cariogenic and anticariogenic characteristics has not been made clear enough. On the other hand, this can be confirmed by studies that found a significant reduction in mother-child SM transmission with the mother with a high incidence of these microorganisms, but who had used of this sugar substitute. As a result, when they were five years old, these children had a 70% reduction in the dmf index, and at six years old SM levels were substantially lower than those of other groups (45, 53, 54). A similar result was observed by Thorild et al (2006) (17).

As for collateral effects, xylitol is digested and absorbed in very small amounts; larger concentrations of the substance may cause stomachache and diarrhea (38). On the other hand, studies that set out to investigate this aspect came to the conclusion that patients reacted well to the substance, and even when they received the substance in larger concentrations there was no report of side effects, not even in children or pre-school children (43). However, the replacement of the sucrose with xylitol in the diet would be precipitated.

CHLORHEXIDINE AND XYLITOL ASSOCIATION

Very few studies reported the effects of chlorhexidine-xylitol on SM levels, biofilm and dental caries.

As for bacterial levels, Simons et al (1999) (11) conducted a 14-day study on the effects of chlorhexidine-xylitol-based chewing gums and found that the association of these two substances had significantly reduced SM salivary levels, much more than when only xylitol was used.

Another research showed that chlorhexidine followed by the continuous use of xylitol reduced SM levels. SM returned to its initial levels more slowly in the test group treated with xylitol than in the placebo group (12).

Modesto, Drake (2002) (13) observed that 0.12% chlorhexidine treatment followed by 0.5% xylitol solution treatment

dramatically inhibited the formation of SM biofilm *in vitro*, which corroborates to the results reached by Simons et al (1999) (11) who found that chlorhexidine-xylitol-based chewing gum contributed to the biofilm reduction when compared to xylitol-based gum. The association of these substances presented the best results.

Chlorhexidine and xylitol association, according to Thorild et al (2003) (17) can also reduce the mother-child transmission of salivary mutans streptococci.

FINAL CONSIDERATIONS

Chlorhexidine and xylitol separately or associated seem to have an excellent performance for *Streptococcus mutans*, biofilm and dental caries control. The association of these agents, with a prior tested protocol for chlorhexidine, seems to enhance the beneficial effects of both substances, and minimize their side effects. In this way, bacterial levels would be suppressed and the low level of these bacteria will be selected for less pathogenic strains which seem to be the perfect situation for dental caries control.

It is important to point out that chemoprophylactic agents should not be used indiscriminately as a panacea, since dental caries is a multifactorial process and all factors responsible for it deserve consideration and close control for the prevention and monitoring of the disease.

ABBREVIATURES

SM – *Streptococcus mutans*

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