Antibacterial agents for prevention and therapy of early childhood caries

Antibakterielle Wirkstoffe zur Prävention und Therapie der frühkindlichen Karies

Early acquisition of caries-associated bacteria is a major risk factor for early childhood caries (ECC) and significantly increased proportions of mutans streptococci in saliva and biofilm are demonstrated in cases with severe ECC. Thus, an antibacterial approach to combat the disease may be considered and there are several antiseptics available for topical application such as chlorhexidine (CHX) and povidone iodine (PI). The aim of the present paper was to review the current evidence for topical applications of antibacterial agents in infants and preschool children and examine projects designed to interfere with the vertical transmission of caries-associated bacteria between the mother and her child. Due to methodological limitations, use of surrogate endpoints and mixed results, the evidence to support and recommend topical applications of CHX and PI in order to prevent and/or arrest early childhood caries were insufficient.

The evidence for various antibacterial measures as part of preventive programs to combat the vertical transmission of mutans streptococci from mothers to their offspring’s was graded as limited. Yet, parents of infants and toddlers should be informed and encouraged to reduce behaviour that promote the early transmission of mutans streptococci. From the literature, it seemed clear that any antibacterial intervention should be an integrated part of a comprehensive preventive program.

Keywords: chlorhexidine; infant caries; povidone iodine; xylitol


Schlüsselwörter: Chlorhexidin; frühkindliche Karies; Povidon-Jod; Xylit

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Introduction

Caries is the result of acids produced by bacteria that dissolves the dental hard tissues and these bacteria are generally members of the commensal microflora. In that context, early childhood caries (ECC) is an aggressive form of tooth decay that affects the primary teeth of infants and toddlers that is characterized by an early acquisition and overgrowth of certain acid-tolerating and acidogenic species. For example, studies have suggested that up to 30% of the cultivable microflora in children with ECC can consist of mutants streptococci and children with ECC can harbour 100 times more mutants streptococci than caries-free controls [2]. Therefore, an antibacterial approach to prevent and control caries in early ages would be rational; hence the majority of the research efforts concerning ECC up to now have been focused on fluoride-based methods. The aim of the present paper was to review the evidence of efficacy for the investigated antibacterial approaches in preventing ECC and to discuss the possible reasons for the mediocre outcome.

Antibacterial approaches

There are several principle home-based and professional ways to combat oral microorganisms; i) exclusion or reduction of fermentable carbohydrates from diet, ii) mechanical removal of plaque, iii) topical application of antibacterial agents, and iv) measures that interfere with bacterial acquisition and initial oral colonisation. Although tooth cleaning is probably the most common way of eliminating bacteria, this aspect will not be further addressed here. Likewise, diet control...
and possible antibacterial effects of fluoride is beyond the scope of this paper but it should be underlined that the fluoride effect on bacterial metabolism in vivo is highly unlikely with the therapeutic levels advocated in paediatric dental care. The paper is therefore focused on the effect of topical applications of antiseptic agents and measures taken to interfere with the initial colonisation of caries-associated bacteria in the oral biofilm.

Topical application of antibacterial agents

The most commonly antiseptics used professionally to prevent and manage ECC and caries in general are chlorhexidine (CHX) and povidone iodine (PI). CHX is available as rinsing solutions, gels or dental varnishes in various concentrations (0.1–40 %) while PI is a 10 % solution for topical application. In contrast to antibiotics, these antiseptics act rapidly at multiple target sites of susceptible bacteria and may be less prone to induce drug resistance. Both agents are commonly used in adjunct to fluoride exposure with repeated treatments. While there is good evidence that these agents are highly effective for skin disinfection and moderately effective in reducing and suppressing the levels of mutans streptococci in plaque and saliva in infants, the outcome, when measured as caries increment, is diverse [for a review, see 30]. Especially, the use of PI has originated contrasting findings. While Lopez et al. [19, 26] reported favourable results in Puerto Rican infants, others have been unable to confirm an additional effect of PI in adjunct to fluoride and extensive restorative procedures [32, 34]. In general, the study groups were small and the methodology in the trial was compromised by a high probability of bias and confounders. Due to the conflicting findings, no prevented fraction could be estimated. Thus, no firm conclusions on the efficacy of CHX and PI in preventing ECC could be drawn and its use can therefore not be recommended. A restricted use is further justified by the fact that both agents were associated with some minor harmful side-effects and compliance problems.

A novel approach to reduce the incidence of dental caries among very young children was recently suggested by Milgrom and co-workers [22]. In a double-blind randomised trial carried out on the Marshall Islands, the use of a topical oral syrup containing xylitol (daily dose 8 gram) was compared with placebo syrup in 94 infants over twelve months. The syrup was administrated two to three times daily by the parents. The results displayed a prevented fraction ranging from 50 % to 70 % depending on follow-up and the calculated number needed to treat (NNT) was four. This means that four children had to go through the program in order to gain one caries-free subject. The study population experienced no serious adverse events except for an increased proportion of children with loose stools or diarrhoea immediately after enrolment. Xylitol is known to alter oral ecology through inhibition of growth, metabolism and polysaccharide production of mutans streptococci and eventually reduce the total amount of plaque [24]. Although these findings provide support that xylitol along with fluoride may be a useful tool for the prevention of ECC, the body of evidence is still insufficient for the topical pharmacologic approach.

Measures to combat vertical transmission of cariogenic bacteria

The concept of taking action towards parents for the benefit of their children is termed primary-primary prevention. This concept has been evaluated in paediatric preventive dentistry with the background thinking to combat or delay the initial acquisition of mutans streptococci. The intervention is most often directed to pregnant women and/or mothers of newborn babies with high counts of salivary mutans streptococci as assessed by a pre-study screening. The findings from the major clinical trials are summarised in Table 1.

The studies of Söderling et al. [23], Isokangas et al. [16] and Thorild et al. [27] were perhaps more interesting. The investigations tested the hypothesis that the vertical transmission of mutans streptococci from highly colonised mothers to their offspring’s could be delayed or hampered by maternal use of xylitol-containing chewing gums (around 6 grams xylitol per day) during the period of primary tooth eruption. The former study [16, 23] was conducted in Finland with CHX- or F-varnish applications as controls and the mothers were actively using the chewing gums over a 21-month period starting at three months of age. The findings when the children were five years showed a significantly lower caries incidence in children to mothers of the xylitol gum group. The latter study from southern Sweden was a double-blind RCT with CHX- and F-containing chewing gums as positive controls in order to eliminate the possible impact of chewing [27]. The total chewing period was 18 months, starting when the babies were six months and a low amount of xylitol (3 gram daily) was utilized. Again, the results at four years...
were significantly in favour for the xylitol gum group when compared with the fluoride control gum group. A small beneficial effect was also seen in the CHX group. Interestingly, the prevented fraction was 72 % in both abovementioned projects, a figure which also happened to be the median value of all seven studies that reported a caries endpoint. The tentative explanation for the beneficial outcome was that the transmission of mutans streptococci was hindered by the xylitol induced shift from xylitol-sensitive to less adherent xylitol-resistant strains of the caries-associated bacterium. A 10-year follow-up of the pioneering Finnish project has recently been performed and the need for restorative care in the primary dentition was lowest in the xylitol group over the years (Laitala, personal communication, 2009). In fact, a cost-benefit analyse indicated that the net gain was in average 3.2 “caries-free years” in the xylitol gum group compared to the treatment group with fluoride varnish. The findings from the Nordic countries were however recently challenged by Fontana et al. [10] that failed to affect the mother-child transmission of mutans streptococci after a daily dose of 4 gram xylitol over a 9-month period. The findings suggest that the mother-child approach may not be effective or even applicable everywhere and illustrate the importance of repeating studies with enough power in various cultural and socioeconomic settings in order to build up best available evidence for any intervention in the oral ecosystem. At present, the body of evidence for primary-primary prevention of ECC is limited but parents would likely benefit from information on the common routes of transmission and advises on a safe handling of pacifiers and baby-bottles.

Discussion

What is the reason for the limited outcome of the antibacterial measures taken for ECC prevention and control? A simple answer would be that neither fluoride nor existing antiseptics can fully counteract or compensate the carbohydrate (sucrose) challenge and shortcomings in behaviour and parental care that are key factors in infant caries aetiology. Caries is simply not a “classical” infectious disease that can be cured with a one-week antibiotic cure. It is well known that even extensive efforts to control ECC can fail [28] and in addition, genetic differences with respect to caries susceptibility may be overlooked [4, 6]. A more complex answer can be found in recent insights concerning the functions of the oral biofilm. Antibacterial agents, such as CHX and PI, are extremely efficient for skin disinfection and there is no doubt that also caries-associated bacteria are sensitive for its exposure, especially in planktonic monocultures using traditional culturing techniques. However, the complex and diverse biofilm in the oral cavity, consisting of over 700 different species, is characterised by an increased tolerance to antibacterial agents [12] and the effect in vivo may, at its best, be short-termed and transient. A natural consequence is that chlorhexidine is unsuitable for caries prevention in general dentistry [1, 31]. The reasons for this impaired efficacy in biofilm are not fully known but factors such as inhibition of diffusion, adaption, bacterial cross-talk, reactions to stress and up-regulation of protein production are likely to play an important role [25]. Another key question is whether or not it is advisable, or even realistic, to try to eradicate certain pathogenic strains from the biofilm. The ecological plaque hypothesis suggests that no single species, not even S. mutans, mediate the initiation or progression of dental caries [21]. It is well established that various bacteria may act “friendly” or “hostile” and oral health is associated with a diverse and balanced microbial community (microbial homeostasis) that is protective against invasions of pathogens. Molecular biology techniques have clearly displayed a diminished diversity in children with severe ECC [18] with an over-abundance of acid-tolerating strains and an under-abundance of strains associated with health such as S. sanguinis and S. mitis/oralis [5]. The ecological long-term strategy would therefore be to restore the microbial balance rather than removing or killing selective pathogens, especially since the “kill” approach may create sites that are open for a rapid repopulation by the pathogens [14]. The risk for development of resistant strains in the future is also a possible concern. Thus, novel antibacterial approaches to modify the oral biofilm diversity beneficially are currently emerging as an alternative to selective killing. Examples are replacement therapy, probiotics, and plant-derived agents and antibacterial peptides regulating bacterial metabolism. Even if some of these methods will prove to be promising, the safety and efficacy must be established in well-conducted randomised controlled trials of appropriate size. The next challenge is then to develop delivery methods that are practical for infant children.

Conclusions

There is insufficient evidence to support and recommend topical applications of antibacterial agents, such as chlorhexidine and povidone iodine, in order to prevent and/or arrest early childhood caries. Although the current evidence for various antibacterial measures to combat the vertical mother-child transmission of caries-associated bacteria still is limited, parents of infants and toddlers should be encouraged to reduce behaviours that promote the early transmission of mutans streptococci. From the available literature and considering the aggressive nature of ECC, it is obvious that any antibacterial intervention should be an integrated part of a comprehensive preventive program.

Conflicts of interest: The author declares no conflict of interest.

Literaturverzeichnis

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