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Antimicrobials in Future Caries Control?

A Review with Special Reference to Chlorhexidine Treatment

Svante Twetman

Department of Odontology, Pediatric Dentistry, Umeå University, Umeå, Sweden

Key Words
Antimicrobials · Chlorhexidine · Clinical trials · Caries prevention

Abstract
The aim of this paper was to examine recent evidence for the effect of the antibacterial approach to prevent and control caries with special reference to the use of chlorhexidine (CHX). Existing information from the mid 1990s provided limited evidence for the effectiveness of CHX gels, rinses and toothpaste in preventing caries in permanent teeth of children and adolescents. An updated literature search on CHX intervention in controlled clinical trials from 1995 to May 2003 unveiled 22 studies covering over 4,500 patients with clinical caries as end point. The vast majority (n = 21) were dealing with CHX-containing varnishes. Since the studies exhibited disparities in design, diagnosis and intervention, the findings were subgrouped with respect to caries type and localization. According to the ranking system of the Swedish Council on Technology Assessment in Health Care, the evidence for an anticaries effect of CHX varnishes was rated as inconclusive for caries-active schoolchildren and adolescents with regular fluoride exposure. Regarding fissure caries, a preventive effect of CHX varnishes was demonstrated in 4 studies out of 5 when compared to no treatment in children with low fluoride exposure. The evidence for arresting root caries in dry-mouth patients and frail elderly subjects was inconclusive. In conclusion, the evidence from the recent literature was inconclusive for the use of CHX varnishes for caries prevention in risk groups.

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It is generally understood that dental caries is an infectious disease of bacterial origin [van Houte, 1994] and, therefore, it must be considered relevant to utilize an antimicrobial approach to prevent and control the disease. The ultimate goal of antimicrobial therapy is to achieve a shift from an ecologically unfavourable to an ecologically stable biofilm [Marsh, 1994, 2003]. By suppressing the proportion of acidogenic and aciduric bacteria that have a growth advantage in low pH conditions, less acid is formed in the aqueous interphase between plaque and enamel, which enables and enhances remineralization by fluoride [ten Cate, 1999]. A wide range of antibacterial agents and products, including fluoride and sugar substitutes, are commonly used in preventive dentistry, and numerous in vitro and in vivo reports are available on their influence on bacterial growth and metabolism. This paper is focused on the 'traditional' antiseptic

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Dr. S. Twetman
Department of Odontology, Pediatric Dentistry
Medical and Odontological Faculty, Umeå University
SE–901 87 Umeå (Sweden)
Tel. +46 90 785 6230, Fax +46 90 770 330, E-Mail svante.twetman@odont.umu.se

agents and restricted to studies measuring clinical caries as end point. This standpoint may be justified by two main reasons. Firstly, recent findings indicate that surrogate end points, such as the effect of an antimicrobial agent on levels of mutans streptococci (MS) or plaque reduction may not always correlate with eventual caries reduction [Caufield and Dasanayake, 2001; Dasanayake et al., 2002; Anderson, 2003]. Secondly, the really important outcome from the patient's and dentist's perspective is proven reductions in caries. There seems to be consensus over the current indications for a chemotherapeutic approach for caries prevention, limiting its use to caries-active individuals and to subjects with an increased caries risk and ongoing caries activity [Kidd, 1991; Emilson, 1994; Rozier, 2001]. The aim of this paper was to review and discuss evidence for the efficacy of the antimicrobial approach to prevent dental caries and to identify questions of interest for future research.

Existing Information

It is generally accepted that chlorhexidine digluconate (CHX) remains the gold standard as antiplaque and antigingivitis agent [Matthijs and Adriaens, 2002]. Although CHX has substantial antimicrobial properties against caries-causing bacteria, its use as anticaries agent remains more controversial. The efficacy in caries prevention has been established in several clinical trials as thoroughly reviewed by Emilson [1994]. It was concluded that CHX gel administered in trays was the most effective regimen and that the outcome of the treatment should be monitored by follow-up bacterial samplings. A meta-analysis by van Rijkom et al. [1996] including 8 clinical trials performed between 1975 and 1994 with gels, rinses and toothpaste in schoolchildren and adolescents at risk (n = 612) revealed a prevented fraction of 46% (95% confidence interval 35–57%). This meta-analysis was however mostly based on studies conducted two decades ago in study populations with a higher caries prevalence than today, some were of short duration and some lacked a true control group. It was therefore justified to update the literature search for recent randomized (RCT) or controlled clinical trials (CCT) with CHX rinse, gel or varnish as main intervention with and without additional use of fluoride. The search terms were 'caries', 'chlorhexidine', 'chlorhexidine rinsing', 'gel', 'varnishes' and 'antibacterial treatment', and only papers published in English were considered. The outcome measure was limited to the incidence or progression/regression of manifest and incipient caries lesions on crowns and roots as diagnosed by visual inspection, probing and/or radiographs. Furthermore, interim reports or double publications were excluded. The PubMed (US National Library of Medicine) database disclosed 22 papers published from 1995 to May 2003 in which the efficacy of CHX-containing varnishes and rinses in over 4,500 subjects of various ages was investigated (tables 1 and 2). An immediate reflection was that no studies employing CHX gel with caries as end point seemed to have been performed in recent years. The selected papers were reviewed and subgrouped with respect to caries localization and type. The level of evidence was judged in 4 grades according to the protocol of the Swedish Council on Technology Assessment in Health Care [Britton, 2000; www.sbu.se]: 1 = strong evidence, requiring at least 2 studies with a high level of evidence (A) or a good systematic review; 2 = moderate evidence, requiring 1 study with level A and at least 2 studies with a moderate level of evidence (B); 3 = limited evidence, requiring at least 2 studies with level B; 4 = inconclusive evidence, less than 2 studies with level B.

All Tooth Surfaces

Three recent studies regarding CHX-containing varnish and caries increment in the young permanent dentition of risk and caries-active subjects were found [Forgie et al., 2000; Splieth et al., 2000; de Soet et al., 2002]. In an RCT with more than 1,200 Scottish schoolchildren selected at risk based on past caries experience and high salivary MS levels, Forgie et al. [2000] failed to demonstrate any reduction in caries increment over a 3-year period when a 10% CHX varnish or a placebo varnish was applied 6–12 times. The applications were initially frequent but reduced by time, which to some extent could explain the lack of efficacy. In the second study, Splieth et al. [2000] selected caries-active schoolchildren that had developed more than 1 new lesion per year for the past years for a treatment combination of CHX varnish and fluoride gel versus fluoride gel controls. Although the experimental group developed less caries over 12 months, the difference was not statistically significant. The study was however small, and larger experimental groups and prolonged study duration would have increased the power of this setting. The third study was performed in a high caries community (Surinam) with semi-annual CHX varnish applications [de Soet et al., 2002], and, again, no effect on caries increment in schoolchildren was demonstrated. On the contrary, it was speculated that a high carbohydrate intake in combination with the CHX treatments could even be detrimental for caries development.

Table 1. Summary of studies identified between 1995 and May 2003 with CHX varnish intervention and clinical caries outcome

Authors	Material	Age years	Risk	Design	Intervention	Control	Duration years	Drop-out, %	Diagnosis	Outcome	Statistics
Young permanent dentition											
Forgie et al. [2000]	1,240	11–13	$\geq 10^5$ CFU	RCT, DB	1	placebo	3	16	clin. + BW	6.8/6.4 DMFS	n.s.
De Soet et al. [2002]	238	13–14	high-caries population	RCT, DB	3	neutral gel	2.5	19	clin.	2.1/1.7 DMFS	n.s.
Splieth et al. [2000]	56	8–10	>1 DMFS/year	CCT, SB	2 + Fg	Fg	1	4	clin.	1.2/2.1 DMFS	n.s.
Proximal sites											
Haukali and Poulsen [2003]	85	8	≥1 proximal lesion	split, DB	2	placebo	2	14	BW	difference –0.21	n.s.
Petersson et al. [1998]	219	12	≥1 proximal lesion	CCT, SB	2 + Fv	Fv	3	0	BW	3.8/3.0 DFSa	n.s.
Petersson et al. [2000]	180	13–14	≥2 proximal lesions	RCT, SB	2	Fv	3	8	BW	3.1/2.7 DFSa	n.s.
Twetman and Petersson [1999]	174	8–10	$\geq 10^5$ CFU	CCT, SB	2	untreated	2	2	BW	22/20% DFSa	n.s.
Fissures											
Araujo et al. [2002]	16	6–8	no	split	2	untreated	2	0	clin. + BW	0/50%	$p < 0.01$
Baca et al. [2002]	229	6–7	no	RCT SB	2	untreated	2	21	clin.	0.9/1.8 DFSo	$p < 0.05$
Bratthall et al. [1995]	502	5–12	no	split, SB	2	untreated	2	16	clin.	7/16%	$p < 0.001$
Fennis-Ie et al. [1998]	332	5–12	no	RCT, DB	3	placebo	3	5	clin.	0.6/0.6 DFSo	n.s.
Joharji et al. [2001]	200	7–14	no	split, SB	2	cleaning	0.75	9	clin.	18/49%	$p < 0.001$
White spot lesions											
Jenatschke et al. [2001]	33	11–18	$\geq 10^5$ CFU	RCT	3	placebo	debond.	0	clin. + BW	31/32%	n.s.
Øgaard et al. [2001]	220	12–15	orthod.	RCT	2 + Fv	Fv	debond.	0	clin.	58/61%	n.s.
Madlena et al. [2000]	24	13–23	orthod.	split	2	placebo	debond.	0	clin.	0.7/2.1 DS	$p < 0.05$
Twetman et al. [1995]	18	11–18	orthod.	split	2	placebo	debond.	0	clin.	6/6%	n.s.
Root caries											
Banting et al. [2000]	240	45–75	dry mouth	RCT; DB	1	placebo	1	24	clin.	0.8/1.3	$p < 0.05$
Brailsford et al. [2002]	134	70–80	frail elderly	RCT, DB	2 + Fv	placebo + Fv	1	19	clin.	42/30% improved	n.s.
Powell et al. [1999]	297	≥60	low income	RCT, SB	R	program	3	32	clin.	23% reduction	n.s.

Intervention: 1 = Chlorzoin (10% CHX, Oralife, Canada); 2 = Cervitec (1% CHX, Vivadent, Schaan, Liechtenstein); 3 = EC-40 (40% CHX, Explore Biodent BV, Arnheim, the Netherlands); R = 0.12% CHX rinse; Fg = fluoride gel; Fv = fluoride varnish; outcome = caries increment in test/control (mean values of surface or percentage of surfaces); CFU = colony-forming units of mutans streptococci per millilitre saliva; RCT = randomized clinical trial; CCT = controlled clinical trial; split = split-mouth; DB = double-blind; SB = single-blind; clin. = clinical examination; BW = bitewing radiographs; n.s. = not significant.

Table 2. Summary of recent studies with maternal antibacterial intervention with clinical caries as outcome measure in the mother's children

Authors	Mothers	Risk	Design	Intervention	Time	Control	Child age years	Drop-out, %	Outcome	Statistics
Dasanayake et al. [2002]	75	selected	RCT	CHX varnish	6–36 months[a]	placebo	4	?	dft 2.5/2.1	n.s.
Günay et al. [1998]	86	selected	CCT	CHX rinse + varnish[b]	2nd trimester to 4 years	untreated	4	45	dfs 1.5/7.0	$p < 0.001$
Isokangas et al. [2000]	195	$>10^5$ CFU	RCT	CHX varnish	3–24 months[c]	F varnish	5	27	dmft 3.2/2.9	n.s.

[a] 9 applications (10% CHX varnish).
[b] CHX treatments as part of a comprehensive preventive programme.
[c] 3 applications (40% CHX varnish).

The reason could be that in frequent low-pH situations, the CHX-induced reduction of the sensitive bacteria may lead to an overgrowth of highly aciduric species such as MS and lactobacilli. It was therefore concluded that antibacterial treatments should always be accompanied by other preventive measures in caries-active children.

Approximal Caries

Four studies were identified in which only the approximal caries incidence in posterior teeth of caries-active schoolchildren was taken into account. The subjects were selected on the basis of having either proximal enamel lesions or elevated salivary bacterial counts. Two reports were 3-year CCTs with parallel arms in which CHX varnish or a mix of CHX and fluoride varnishes were tested against fluoride varnish applications in semi-annual or quarterly regimes [Petersson et al., 1998, 2000]. Caries incidence was determined from bitewing radiographs exposed with a film holder. Both studies were unable to unveil an additional caries-preventive effect of the CHX varnishes over the fluoride varnish alone. The other two papers were 2-year trials in schoolchildren, one with a split-mouth design [Haukali and Poulsen, 2003] and the other evaluated proximal caries incidence progression in relation to the degree of MS suppression [Twetman et al., 1999]. Both studies concluded that CHX varnish applications did not affect the overall proximal progression rate. In the latter study however, children who exhibited significantly suppressed MS counts after the treatments exhibited a lower incidence and progression rate compared with those with a less marked suppression. The results support previous findings that the outcome of the employed topical intervention must be monitored in order to decide whether or not to continue with further antibacterial treatments [Emilson, 1994].

Fissure Caries

Five studies were identified with fissure caries as end point [Bratthall et al., 1995; Fennis-Ie et al., 1998; Joharji and Adenubi, 2001; Araujo et al., 2002; Baca et al., 2002]. Three of the reports were split-mouth studies of first and second permanent molars in which a 1% CHX/thymol varnish was applied 3 times per year versus untreated controls. The findings were all in favour of the antibacterial varnish, but it must be underlined that the investigations were carried out in subjects where the regular use of fluoride toothpaste or exposure to fluoride supplements was low or uncertain. Moreover, with one exception, the diagnosis of fissure caries was based on clinical examination only and without the aid of bitewing radiographs. Two studies were RCTs in newly erupted first [Baca et al., 2002] and in first and second permanent molars [Fennis-Ie et al., 1998]. Radiographs were not used. In the latter study, a 40% CHX varnish was applied semi-annually for 3 years with a placebo varnish as control. The results disclosed no significant differences between the treatments when the entire study groups were taken into account. However, 15% of the children harboured high counts of salivary MS (10^6 CFU/ml mixed saliva) at baseline. In that subgroup, a post hoc statistical analysis indicated that the number of carious permanent molars was significantly reduced ($p < 0.05$) at the termination of the study. In the report by Baca et al. [2002], a CHX/thymol varnish was applied every third month for 2 years and the incidence of caries in the first molars was compared with that of untreated controls. A small but statistically significant reduction was disclosed, and the authors conclude that the antibacterial agent was a useful alternative to prevent fissure caries when appropriate dental facilities and resources were lacking. All papers explain the effectiveness of the varnish treatments in preventing fissure caries by the retentive nature of the occlusal surfaces, enabling a slow release of the antibacterial agent.

White Spot Lesions

Four studies dealing with early enamel lesion development were identified, all performed in patients undergoing treatment with fixed orthodontic appliances [Twetman et al., 1995; Madlena et al., 2000; Jenatschke et al., 2001; Øgaard et al., 2001]. Insertion of appliances may interfere with oral hygiene procedures, resulting in plaque accumulation and an increased risk for 'white spot lesions' adjacent to the luted bands or bonded bracket bases. Two studies were very small and utilized a split-mouth design with CHX varnish versus a placebo varnish applied during the time of active treatment. Conflicting results were reported. Madlena et al. [2000] found a significant reduction of white spot lesions following CHX varnish treatments among children with a higher caries increment while no effect could be found in a Swedish low-caries population [Twetman et al., 1995]. The two most recent investigations were RCTs comparing CHX varnish with placebo or fluoride varnish as controls [Jenatschke et al., 2001; Øgaard et al., 2001]. In the former study, the orthodontic patients were screened and recruited with high counts of salivary MS while the other included 220 non-selected cases with varying levels of MS. Both studies were unable to disclose any benefit from frequent CHX varnish applications on white spot lesion development during treatment with fixed orthodontic ap-

pliances, in spite of significant reductions in MS colonization.

Root Caries

Three papers dealt with CHX treatments and root caries development in elderly and low-income older adults [Powell et al., 1999], dry-mouth risk patients [Banting et al., 2000] and in frail institutionalized people [Brailsford et al., 2002]. Powell et al. [1999] demonstrated a non-significant reduction of root caries events following weekly 0.12% CHX rinses and fluoride varnish compared with a group receiving 'usual' care from private practitioners. The other studies were 1-year placebo-controlled randomized trials, and one of them demonstrated a significant reduction and control of root caries lesions, suggesting regular antibacterial applications to be beneficial for these patient groups [Banting et al., 2000]. Notably, neither Powell et al. [1999] nor Banting et al. [2000] found any significant impact on coronal caries increment, but to be fully conclusive on this matter, increased size of study groups and prolonged duration would have been desirable. The results of the root caries studies may however indicate that the antimicrobial therapy may act differently for lesions and cavities located in dentine and enamel, respectively.

Mother-Child Transmission

The primary preventive concept to interfere with the mother-child transmission route of MS has gained continuous interest during the recent decades. The 'classic' studies by Köhler et al. [1984] and Tenovuo et al. [1992] clearly showed that CHX gel treatments of highly infected mothers could reduce MS colonization and caries development in their children. Since then, a number of additional papers on this issue have been presented [Brambilla et al., 1998; Söderling et al., 2000; Gripp and Schlagenhauf, 2002; Thorild et al., 2003], but only three have reported caries as end point. These studies are compiled in table 2. In a German study, Günay et al. [1998] offered a comprehensive preventive programme for mothers and children that started during pregnancy and continued for 4 years. The programme, which included CHX-containing rinses and varnishes, resulted in significantly improved oral health for both the mothers and their children, but the role of the antibacterial agents could not be distinguished from the other measures within the programme. Isokangas et al. [2000] focused mainly on xylitol but included treatments with either CHX- or fluoride-containing varnishes of highly colonized mothers as controls. The mothers were treated on 3 occasions, when their children were 6, 12 and 18 months of age, but no differences in caries increment up to 5 years of age were noticed between the CHX and fluoride varnish groups. Recently, Dasanayake et al. [2002] have published a placebo-controlled RCT in which they evaluated the efficacy of CHX varnish treatments of mothers during the eruption of their children's first teeth and during the second year of life. Although a significant reduction of MS levels in both mothers and children could be seen, no effect on caries development was found among the children. Thus, topical applications of antibacterial agents may reduce the transmissions of oral MS from host to host, but this does not necessarily result in less caries. This approach merits to be further elucidated in terms of effectiveness and efficiency.

Other Antibacterial Agents of Clinical Interest

Triclosan is a broad-spectrum biocide that may affect many types of oral bacteria. The agent has been incorporated into dentifrices together with a copolymer, and reductions in supragingival plaque and gingivitis have been claimed [Gaffar et al., 1997]. A number of caries-focused RCTs with triclosan/copolymer-containing fluoride toothpastes have been carried out in schoolchildren and adults [Hawley et al., 1995; Feller et al, 1996; Mann et al., 1996]. The results clearly showed that the addition of the antibacterial agent neither compromised nor enhanced the anticaries effect of the toothpaste. However, in a recent study from Israel, the effect of unsupervised tooth brushing with two 0.243% sodium fluoride dentifrices with and without 0.3% triclosan and 2% copolymer on coronal caries was evaluated in adults [Mann et al., 2001]. The 2-year findings were significantly in favour of the dentifrice with triclosan, indicating an additional anticaries effect that should be further investigated.

The antibacterial properties of povidone-iodine as a mucosal antiseptic in medicine are well established, but the agent is rarely utilized in dentistry. Povidone-iodine is water soluble and non-irritating and exhibits no adverse effects such as discoloration and taste alterations, but iodine hypersensitivity, thyroid pathosis and pregnancy are contra-indications. The efficacy of a 10% povidone-iodine solution to prevent early childhood caries has recently been evaluated in a randomized double-blind placebo-controlled trial [Lopez et al., 2002]. The results showed that this topical antimicrobial therapy increased the time of 'disease-free survival' in toddlers with high risk of early caries development.

Future Perspectives for Research

Despite the recent decline, caries is still the most prevalent dental infectious disease with a giant unmet treatment need in many countries. A general concern is that the dental practitioner is still treating caries with a surgical approach rather than with prevention or pharmacotherapeutics. An urgent task for the scientific community is therefore to initiate clinical studies to confirm the efficacy and safety of non-surgical treatment of caries with focus both on the population and selected patient groups. It is not only a question of performing more investigations but also better ones. Well-designed multi-centre trials with antibacterial intervention according to a standard protocol would be desirable, and special efforts should be made to select representative study groups with enough power to ensure firm conclusions. Future research must also be extended to incorporate preschoolers, adults and elderly subjects. No studies can be designed without regular exposure of fluoride from toothpastes or any other commonly used alternative non-surgical treatment for ethical reasons. Since the existing antibacterial agents seem to be less effective for the caries-active patients with the highest need, more potent and long-lasting drugs with as few side-effects as possible need to be developed. In order to improve efficiency and compliance, it seems reasonable in the future to move from topical administrations by professionals to consumer products and home-care procedures, such as antibacterial constituents incorporated into dentifrices and chewing gums. The early intervention concept is interesting as it may be easier to affect the caries-associated bacteria before their permanent colonization compared to later in life when the resident oral flora is firmly established [Könönen, 2000]. The screening of mothers and potentially long treatment duration are however drawbacks in terms of cost and compliance. A full-scale investigation at the population level, including both parents, would be a project of high priority.

It may very well be that antibacterial agents are underutilized and factors such as dentist's knowledge and attitudes, poor patient compliance and low willingness to pay may likely play a role. In today's evidence-based care, also the patient's wishes and demands must be taken into account. Therefore, qualitative studies should be planned and undertaken parallel with, and linked to the intervention protocol in order to unveil the patient's thinking. Further, studies on how to communicate the preventive health message and increase motivation in caries risk patients and vulnerable groups should be encouraged.

Conclusions

The evidence for an anticaries effect of CHX-containing varnishes was rated as inconclusive for caries-active schoolchildren and adolescents with daily exposure to fluoride as well as for root caries arrest in elderly subjects. It must however be underlined that 'inconclusive evidence of effect' is not the same as 'evidence of no effect' in the sense that antibacterial methods are of no value and should be abandoned. It is however definitely a call for further research and development of well-designed studies.

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