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Randomized controlled clinical trials on agents used for chemical plaque control

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Abstract: Taking into account the limitations of the daily self-performed oral hygiene the use of chemical agents that can be incorporated in dentifrice or mouth rinse formulations has been advocated. The present review deals with randomized controlled clinical trials of ≥6 months in duration, on the use of those agents and their effects on plaque and gingival inflammation.

Key words: chemical agents; chemical plaque control; dentifrices; mouth rinses

The role of bacterial plaque as primary aetiological factor of periodontal inflammation is well established. The classic experiments by Löe *et al.* (1) and Theilade *et al.* (2) showed a clear relationship between plaque accumulation and maturation of plaque and onset of gingivitis. Recommencement of thorough plaque control led to the resolution of the clinical signs of gingival inflammation. Plaque-induced gingivitis is a very common disease but is of little consequence for the patient, because it almost never causes pain or dysfunction. Prevention of gingivitis is based almost exclusively on the assumption that gingivitis is the precursor of the periodontitis (3, 4). Several studies demonstrated the importance of plaque as aetiological factor of periodontitis (4–6). This led to the concept that strict plaque control is a prerequisite for a stable and healthy periodontal condition (7). Information towards identification of patients that potentially will develop periodontitis is lacking and therefore, preventive measures will inevitably lead to over-treatment.

Many methods have been employed for plaque removal including the use of toothbrushes of different shapes and designs, dental floss, woodsticks. Mechanical tooth cleaning by means of a toothbrush is considered as the most common way of controlling the plaque development. In industrialized countries the average person brushes for <1 min, which may be not adequate for

achieving an optimal level of plaque removal. Additionally, the toothbrush is not effective in removing plaque from the interdental areas. Furthermore, the effectiveness of plaque removal is dependent on factors such as dexterity and compliance of the individuals (8, 9). The necessity of further improving the plaque removal provided the basis of chemical plaque control.

Chemical plaque control

Chemotherapeutic agents for local use in the oral cavity have taken a variety of forms over the years. Many of them were treated with scepticism because of their limited or transitory effects in the oral cavity. In 1985 the Council on Dental Therapeutics of the American Dental Association (ADA) established guidelines for the acceptance of anti-plaque/gingivitis agents (10).

According to these guidelines (10, 11) a chemical agent could prevent or reverse gingivitis if it: (a) eliminates all plaque; or (b) reduces plaque below an individual's threshold for disease; or (iii) alters the bacteria of plaque in such a way that health would not convert to disease.

Other pathways might also be considered. These include modification of the pathogenicity of plaque; i.e. detoxification by removing or altering potentially toxic products such as endotoxin or butyrate (12). In addition, it has been suggested that chemotherapeutic agents could also affect gingivitis directly if they possessed anti-inflammatory activity (13).

According to the guidelines of ADA's Council on Dental Therapeutics, the clinical effectiveness and safety of a given agent should be evaluated by using prospective clinical trials in which plaque and gingival indices allow for evaluation of their efficacy and at the same time the condition of the oral tissues and the composition of the oral flora allow for evaluation of safety of the product. Given those guidelines, the present introduction will primarily focus upon the available literature on agents used for chemical plaque control that are incorporated in dentifrice or mouthrinse formulations. Prospective randomized controlled clinical trials (RCT) of at least 6 months of duration have been included, as providing a high level of evidence for chemotherapeutic agents to support self-performed oral hygiene.

Cationic organic molecules

Bisbiguanides

The major representative of this category is chlorhexidine (CHX), which is a cationic antiseptic with broad action against a wide array of bacteria including Gram-positive and negative bacteria, yeasts, dermatophytes and some lipophylic viruses (14). CHX acts on the bacterial cell membrane by changing its structures. As a result the osmotic equilibrium is lost, the membrane extrudes, vesicles are formed the cytoplasm precipitates (15, 16). It shows different effects at different concentrations: bacteriostatic at lower concentrations and bactericidal at higher concentrations. The safety of CHX has been extensively tested in animal models. It is poorly absorbed by the gastrointestinal tract and it therefore displays very low toxicity. The superiority of this agent as opposed to other chemical agents used for plaque control derives from the increased persistence of this agent (substantivity) that prolongs its anti-bacterial action (17). It is beyond the scope of this review to refer to the vast amount of literature written on CHX. Excellent reviews give the reader more insight about the short-term superiority of this agent (17–19). The present review will focus upon the RCT on CHX used in dentifrice or mouthrinse formulations.

Dentifrices

In the past, the use of CHX in dentifrices gained little advance because of the inactivation by anionic ingredients contained in toothpaste and the competition for oral retention sites (20). However, recent evidence suggested that these problems could be overcome and CHX-containing dentifrices have been formulated without interactions between CHX and anionic or cationic ingredients. In Table 1 the RCT (21, 22) on the use of CHX dentifrices are presented. By adding zinc to a CHX-containing dentifrice, the development of extrinsic dental stain seemed to be decreased. One study (22) documented the efficacy of a dentifrice containing 0.4% CHX/0.34% Zn^{++} and a placebo mouthrinse as opposed to the daily use of sodium monofluorophosphate (MPF) dentifrice and placebo mouthrinse and reported statistically significant reduction in plaque and gingivitis for the CHX-Zn^{++} combination (Table 1).

Mouthrinses

Different CHX concentrations have been used the last decades. Concentrations of 0.12% or 0.2% CHX mouthwash significantly reduce plaque and gingivitis (23–25).

Table 1 describes the RCT (22, 26–32) giving evidence on the superiority of this agent. Compared with placebo CHX used either in 0.12% or 0.2% concentration demonstrated 35–71% reductions of plaque and 11–39.6% reductions of gingivitis. Two studies (29, 32) compared the CHX to negative control and

Table 1. **(A) Characteristics of studies chlorhexidine dentifrices. (B) Characteristics of studies chlorhexidine mouthrinses next to normal unsupervised oral hygiene**

Author (Ref.)	*n*	Design	Duration	Blindness	Groups compared	Plaque		Gingivitis	
						Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction versus placebo or control (%)
(A)									
Yates *et al.* (21)	296	Parallel with prophylaxis at start	6 months	Double blind	1% CHX dentifrice Control dentifrice	Q–H* 2.3–1.2 2.4–1.5	24*†	GI* 1.2–0.8 1.2–1.0	20*†
Sanz *et al.* (22)	191	Parallel with prophylaxis at start Next to unsupervised daily OH	6 months	Double blind	(0.4% CHX + 0.34% Zn^{++}) dentifrice + placebo mouthrinse control (MFP) dentifrice + placebo mouthrinse	PI* 0.90–0.5 0.86–0.6	27†	GI* 1.57–1.1 1.57–1.05	12
(B)									
Grossmann *et al.* (26)	430	Parallel with prophylaxis at start	6 months	Double blind	0.12% CHX mouthrinse Placebo mouthrinse	Q–H 1.43–0.61 1.43–1.56	61†	GI 0.57–0.22 0.57–0.30	37†
Grossmann *et al.* (27)	481	Parallel with prophylaxis at start	6 months	Double blind	0.12% CHX mouthrinse Placebo mouthrinse	Q–H 1.41–0.76 1.40–1.49	49†	GI 0.53–0.25 0.50–0.37	31.1†
Banting *et al.* (28)	272	Parallel with prophylaxis at start and every 6 months	24 months	Blind?	0.12% CHX mouthrinse Placebo mouthrinse	Q–H* ?–1.3 ?–2.1	35†	GI* ?–0.28 ?–0.47	39.6†
Overholser *et al.* (29)	124	Parallel with prophylaxis at start	6 months	Double blind	CHX mouthrinse Negative control	Q–H 2.34–0.82 2.35–1.64	50.3†	ModGI‡ 2.28–0.81 2.22–1.17	30.5†
Sanz *et al.* (22)	191	Parallel with prophylaxis at start	6 months	Double blind	MFP dentifrice + 0.12% CHX mouthrinse MFP dentifrice + placebo mouthrinse	PI* 0.89–0.4 0.86–0.6	35†	GI* 1.57–1.05 0.53–1.30	17
Lang *et al.* (30)	132	Parallel with prophylaxis at start	6 months	Double blind	0.2% CHX mouthrinse Placebo mouthrinse	PI* 1.0– 0.30 1.1–0.80	71†	BOP* 50–10% 53–38%	11†
Hase *et al.* (31)	130	Parallel with prophylaxis at start	6 months	Double blind	0.2% CHX mouthrinse Placebo mouthrise	Q–H* 1.55–0.90 1.6–1.6	38†	BOP* 41–29% 43–37%	22†
Charles *et al.* (32)	107	Parallel with prophylaxis at start	6 months	Examiner blind	0.2% CHX Negative control	Q–H 2.64–1.71 2.31–2.18	21.5†	GI 1.35–0.99 1.27–1.21	18†

Q–H: Quigley & Hein Index (119) [modification by Turesky *et al.* (123)], PI: Plaque Index [Silness & Löe (121)], GI: Gingival Index [Löe & Silness (117)].

Percent reduction calculations are made versus control (or placebo) and are computed by using the formula: % red = (control or placebo – CHX group)/(control or placebo) × 100%.

*Data approximation based on figures.

†Statistically significant when compared with control group.

‡Data approximation based on figures.

reported significant plaque (21.5–50.3%) and gingivitis (18–30.5%) drops in favour of CHX. The studies comparing CHX (26, 29–31) with other active agents such essential oils, sanguinarine and delmopinol seem to agree on the superiority of CHX. Only one study (32) found no difference between CHX and Listerine® (Pfizer Inc., Morris Plains, NJ, USA). This could be explained by the fact that subjects were requested not to brush the day of the measurements, a fact that may have influenced the plaque scores.

In conclusion, there is some evidence to support the beneficial use of a CHX-containing dentifrice in comparison with control or placebo products. There is ample evidence to illustrate the superiority of the CHX mouthrinses in comparison with placebo or control products. It seems that the adjunctive use of CHX mouthrinse offers more advantages than the use of a dentifrice containing this agent.

Quaternary ammonium compounds

Agents belonging to this category are anionic in nature. Because they are strongly positively charged they bind easily to oral tissues. Their substantivity is less than that of CHX (33). The best known agent of this category is cetylpyridinium chloride (CPC). It has demonstrated antimicrobial activity against a broad spectrum of oral bacteria (34, 35). It can interact with the bacterial cell membrane, resulting in leakage of cellular components, disruption of cellular metabolism, inhibition of cell growth and cell death (36, 37). Incorporation of CPC in dentifrice formulations is difficult because of its poor compatibility of this agent with other dentifrice components and its prolonged use results in stain development. CPC mouthrinses have been marketed in the United States since 1940. CPC shares some of the side-effects as CHX. These include some staining and enhanced calculus formation, especially when used at higher concentrations. Burning sensation and transient desquamation of the oral mucosa have also been reported. Short-term clinical studies showed equivocal results (38). One 6-month controlled clinical trial (39) reported plaque reduction of 28.2% and gingivitis reduction of 24% in comparison with control.

The present review did not identify any RCT's supporting the use of this agent as anti-plaque or anti-gingivitis agent.

Plant alkaloids – sanguinarine

The blood root plant *Sanguinaria canadensis* provides an alkaloid extract which bears the name sanguinarine. The product is incorporated in dentifrice and mouthrinse formulations. The current formulation contains the extract at 0.03% (equivalent to 0.01% sanguinarine) and 0.2% zinc chloride to enhance the anti-plaque effect. The product has been evaluated either in dentifrice or dentifrice/mouthrinse regimens.

Table 2 presents the RCT providing evidence of the action of this agent. One RCT (27) found a significant effect on plaque reduction (12.1%) compared with a placebo mouthrinse, but no effect on gingivitis. Two RCT (40, 41) dealt with dentifrice formulations and showed a variety of results when sanguainarine was compared with control dentifrice (Table 2). When mouthrinse and dentifrice were combined (42–44), however, significant reductions in plaque and gingivitis were reported in three 6-month RCT with plaque reductions of 17–42% and reduction in gingivitis of 18–57% (Table 2). The study by Harper *et al.* (45) confirmed the safety of the use of this combination; the combination did not promote opportunistic overgrowth of pathogens in the oral flora. Additionally, the alterations in organisms associated with gingivitis may account for reductions in gingivitis seen in the active group. There were no untoward side-effects (except for an occasional burning sensation) reported in these studies and no microbiological evidence of opportunistic overgrowth of oral pathogens has been reported.

Briefly, sanguinarine, when used next to normal mechanical plaque control, appears to be an effective inhibitory plaque agent when compared with control or placebo products. One comparative study demonstrated, however, that the plaque reductions achieved are far below the reductions observed with CHX. Unlike CHX it is not able to prevent the development of gingivitis. It seems that mouthrinses containing sanguinarine are more effective in reducing plaque than dentifrice formulations containing this agent.

Metal salts

Fluorides

Stannous fluoride

The combination of the stannous ion (Sn^{++}) with fluoride (stannous fluoride or SnF^2) has been used in dentifrice formulations already since the early 1950s. Numerous studies have confirmed the anti-caries efficacy of this agent, however, its anti-inflammatory properties are not extensively defined.

In the early 1970s several studies of short duration have confirmed the anti-plaque properties of SnF_2. Following the twice daily use of a dentifrice formulation plaque reductions have been observed in comparison with control (46–48), but not all studies seemed to agree with those findings (49–51). It was

Table 2. **Characteristics of studies on sanguinarine products**

Author	*n*	Design	Duration	Blindness	Groups compared	Plaque		Gingivitis	
						Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction versus placebo or control (%)
Lobene *et al.* (40)	100	Parallel with prophylaxis at start	6 months	Double blind	Sanguinaria dentifrice	PI 0.71–0.86	12	GI 0.63–0.94	20*
					Vehicle control dentifrice	0.71–0.98		0.69–1.18	
Grossman *et al.* (27)	481	Parallel with prophylaxis at start	6 months	Double blind	Sanguinaria mouthrinse	Q–H 1.49–1.31	12.1*	GI 0.55–0.35	2.8
					Placebo mouthrinse	1.40–1.49		0.50–0.37	
Hannah *et al.* (42)†	24	Parallel pre-exper. Period with prophylaxis	6 months	Double blind	Sanguinaria dent + rinse	PI 0.64–0.39	39.3*	GI 0.72–0.32	33.8*
					Placebo dent + rinse	0.77–0.68		0.83–0.76	
Harper *et al.* (43)	53	Parallel with polishing at start	7 months	Double blind	Sanguinaria dent + rinse	Q–H 2.14–2.0	20.7*	MGI 1.87–1.49	24.6*
					Placebo dent + rinse	2.20–2.53		1.91–1.98	
Kopczyk *et al.* (44)	113	Parallel no prophylaxis at start	6 months	Double blind	Sanguinaria dent + rinse	Q–H 2.82–2.34	17.3*	MGI 1.63–1.40	18.1*
					Placebo dent + rinse	2.93–2.83		1.82–1.71	
Mauriello & Bader (41)	115	Parallel with prophylaxis at start	6 months	Double blind	Sanguinaria dentifrice	PI 1.22–1.09	−4	GI 0.76–0.91	5
					Non-F control dentifrice	1.21–1.05		0.78–0.96	

PI: Plaque Index [Silness & Löe (121)], Q–H: Quigley & Hein [119) Index 1962 [modification by Turesky *et al.* (123)], GI: Gingival Index [Löe & Silness (117)], MGI: Modification of Gingival Index [Lobene *et al.* (116)].
Percent reduction calculations are made versus control or placebo and are computed by using the formula: % red = (control or placebo – sanguinarine group)/(control or placebo) × 100%.
*Statistically significant when compared with control (placebo) group.
†Study conducted in orthodontic patients.

soon realized that the discrepancy of the results of the several studies had to do with the stability of the SnF_2 in the formulations used. Careful formulation of the stannous fluoride is critical, because rapid oxidation and hydrolysis of stannous ions can inactivate stannous fluoride (52). It is suggested that products containing stannous fluoride may have limited shelf-life and stannous fluoride alone in a dentifrice without stabilization may be insufficient in order to obtain optimal clinical efficacy. The microbiological safety of the dentifrices containing stabilized SnF_2 has been documented in a 6-month clinical trial (53). They found no significant changes in microbial flora and no immergence of bacterial resistance. Table 3 presents the RCT on the effects of several SnF_2 formulations on plaque and gingivitis.

SnF_2 in dentifrice formulations. The table shows that although not all studies reported favourable results on plaque, they seemed to agree that dentifrices containing SnF_2 provide statistically significant improvements in gingivitis (range 18–22.3%) as opposed to NaF control dentifrice. Three studies reported also significant improvements in plaque (range 6.9–22.7%) in comparison with control.

SnF_2 in gel formulations. Two studies (50, 54) reported conflicting results. One RCT (54) conducted in orthodontic patients examined the additional effect of SnF_2 gel as adjunct to the daily oral hygiene with a conventional (NaF) dentifrice. For both groups an increase in plaque and gingivitis was noticed, but the experimental group demonstrated less changes in com-

Table 3. **Characteristics of studies on SnF_2 products**

Author	*n*	Design	Duration	Blindness	Groups compared	Plaque		Gingivitis	
						Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction versus placebo or control (%)
						PI	8.7	GI	5.2
Leverett *et al.* (55)	268	Parallel with supervised rinsing	28 months	Double blind	0.1% SnF_2 mouthrinse	1.05–0.94		1.0–0.90	
					0.05% control (NaF) mouthrinse	1.05–1.03		0.98–0.95	
						PI		BI	
Wolff *et al.* (50)	281	Parallel	18 months	Double blind	0.75% (NaMFP) dentifr + 0.4% SnF_2 gel		?	0.97–0.90	–1
					0.75% (NaMFP) dentifr + 0.22% NaF gel		?	0.92–0.85	1
					0.75% (NaMFP) dentifr + placebo gel			0.91–0.89	
						PI	36*	GI	40*
Boyd & Chun (54)†	55	Parallel with prophylaxis at start	18 months	Operator-blind	NaF dentifr + high avialability Sn^{++}(HASn) gel	0.66–0.68		0.64–0.81	
					Control (NaF) dentifrice	0.74–1.06		0.76–1.35	
						Q–H	3	GI	21*
Perlich *et al.* (107)	328	Parallel with prophylaxis at start	6 months	Double blind	0.454% SnF_2 dentifrice	1.93–2.16		0.68–0.41	
					0.243% NaF dentifrice	1.90–2.23		0.71–0.51	
						PI	3	GI	19*
Beiswanger *et al.* (48)	549	Parallel with prophylaxis at start	6 months	Double blind	0.454% SnF_2/4.16% sodium gluconate dentifrice	1.03–0.71		0.67–0.36	
					Control (NaF) dentifrice	0.95–0.73		0.71–0.45	
						PI	–2	GI	18*
Beiswanger *et al.* (108)	635	Parallel with prophylaxis at start	6 months	Double blind	Stabilized 0.454% SnF_2 dentifrice	0.73–0.55		0.86–0.64	
					Control (NaF) dentifrice	0.67–0.54		0.84–0.78	
						Q–H	3	GI	21*
McClanahan *et al.* (109)	483	Parallel with prophylaxis at start	6 months	Double blind	Stabilized 0.454% SnF_2 dentifrice	1.94–2.16		0.68–0.41	
					Control (NaF) dentifrice	1.90–2.23		0.71–0.52	
						Q–H	20.3	mod GI	21*
Mankodi *et al.* (46)	104	Parallel with prophylaxis at start	6 months	Double blind	Stabilized 0.454% SnF_2 dentifrice	2.68–2.08		1.17–0.94	
					Control (NaF) dentifrice	2.60–2.61		1.18–1.19	
						Q–H	22.7*	mod GI	22.3*
Williams *et al.* (47)	112	Parallel with prophylaxis at start	6 months	Double blind	Stabilized 0.454% SnF_2dentifrice	2.48–1.70		1.27–1.01	
					Control (NaF) dentifrice	2.49–2.20		1.28–1.30	
						Q–H	6.9*	MGI	21.9*
Mankodi *et al.* (110)	130	Parallel with prophylaxis at start	6 months	Double blind	0.454% SnF_2 + sodium hexametaphosphate dentifrice	2.73–2.14		2.03–1.57	
					Control (MFP) dentifrice	2.91–2.30		2.04–2.01	

PI: Plaque Index [Silness & Löe (121)], Q–H: Quigley & Hein Index 1962 (119) [modification by Turesky *et al.* (123)], MGI: modification of the Gingival Index [Lobene *et al.* (116)], mod GI: Talbott *et al.* (122) modification of the Gingival Index (1977), BOP: bleeding on probing.
Percent reduction calculations are made versus control and are computed by using the formula: % red = (control – SnF_2 group)/(control) × 100%.
*Statistically significant when compared with control group.
†Study in orthodontic patients.

parison with the control. A second 18-month RCT (50) found no additional benefit of the additional SnF_2 gel use as opposed to a placebo or NaF gel.

SnF_2 in mouthrinse formulations. The use of stannous fluoride in mouthrinse formulations was rather difficult because of its little stability in aqueous solutions. The addition of stannous pyrophosphate or stannous chloride helps maintaining stability (49). In one 28-month RCT (55) the panellists had to rinse with either SnF_2 or NaF. They authors found no statistically significant differences between groups.

In conclusion, most of the studies on SnF_2 dentifrices seem to agree that that this agent provides some benefits with regard to plaque reductions. Some studies demonstrated also reductions in gingivitis. Inconclusive evidence exists with regard to gel formulations. Also, little evidence exists with respect to mouthrinse formulations.

Amine Fluoride

Amine fluoride was developed at the University of Zürich in the beginning of the 1950s. It has substantial anti-cariogenic activities as it acts as carrier for the fluoride ion because of its surface activity (56, 57). The amine group itself has intrinsic anti-glycolytic activities (58, 59). However, the use of this agent alone seems not to be effective in reducing plaque or gingivitis. No RCT were identified reporting on plaque and gingivitis effects of this agent.

Amine fluoride/stannous fluoride

The combination (AmF/SnF_2) provides anti-bacterial action through synergistic action of three groups: the fluoride ions, the stannous ions and the amine group. Table 4 summarizes the RCT reporting on this combination.

AmF/SnF_2 in dentifrice formulations. Two studies (60, 61) reported no significant benefits of the test dentifrice when compared with a conventional control dentifrice.

AmF/SnF_2 in mouthrinse formulations. One 7-month study (62) compared the AmF/SnF_2 mouthrinse with a placebo and demonstrated significant plaque and gingivitis reductions.

AmF/SnF_2 dentifrice + mouthrinse formulations. One study (63) used a combined regimen (dentifrice + mouthrinse). No statistically significant differences were reported between groups for gingivitis.

Table 4. **Characteristics of studies on AmF/SnF_2 products**

						Plaque		Gingivitis	
Author	*n*	Design	Duration	Blindness	Groups compared	Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction versus placebo or control (%)
Sgan-Cohen *et al.* (60)	246	Parallel	6 months	Double blind	AmF/SnF_2 dentifrice	PHP Index 0.57–0.55	3.5	GI 0.95–0.72	7.7
					Control (NaF) dentifrice	0.57–0.57		1.01–0.78	
Shapira *et al.* (61)	103	Parallel	6 months	Double blind	AmF/SnF_2 dentifrice	PI 1.19–0.76	8.4	GI 1.43–1.33	4.3
					Control (NaF) dentifrice	1.28–0.83		1.43–1.39	
Zimmermann *et al.* (62)	102	Parallel	7 months	Double blind	AmF/SnF_2 mouthrinse	API 61.3–50.6%	5.2*	Mod SBI 52–29.3%	29.9*
					Placebo mouthrinse	55.1–53.4%		43.7–41.8%	
Mengel *et al.* (63)	130	Parallel	9 months	Double blind	AmF/SnF_2 mouthrinse and dentifrice	API 69.9–49.5%	11.8	Mod SBI 21.6–13.1%	24
					AmF/SnF_2 dentifrice and control (NaF) mouthrinse	68.9–53.9%	3.9	19.9–14.9%	13.8
					Control (NaF) mouthrinse and control dentifrice	55.1–56.1%		24.7–17.2%	

PHP: Patient Hygiene Performance Index [Podshadley & Haley (118)], GI: Gingival Index [Löe & Silness (117)], ModSBI: Modified Sulcus Bleeding Index [Lange (115)], API: Approximal Plaque Index [Lange *et al.* (114)].
Percent reduction calculations are made versus control (or placebo) and are computed by using the formula:% red = (control or placebo – AmF/SnF_2 group)/(control or placebo) × 100%.
*Statistically significant when compared with control group.

In summary, the use of amine fluoride alone appears to have no favourable effects on plaque and gingivitis. The combination of SnF_2 with amine fluoride, however, seems to exert some beneficial anti-plaque or anti-gingivitis effects when it is incorporated in mouthrinse formulations or in combination with a dentifrice also containing the same combination, but the evidence is relatively limited.

Oxygenating agents

Peroxides and perborates

The agents are well known because of their use in cases of acute necrotizing ulcerative gingivitis and pericoronitis. Short-term studies demonstrated the efficacy of H_2O_2 alone in reducing plaque and gingivitis (64, 65). The combination of 5% povidone–iodine and 1.5% hydrogen peroxide in a rinse formulation has also shown usefulness against plaque and gingivitis (66, 67). Several studies indicate that the use of oxidizing mouthwashes containing peroxyborate or hydrogen peroxide may help control the dental stain associated with CHX use (68–71).

Three RCT reported on various formulations containing peroxides. A 4-year study (72) conducted in periodontitis patients, examined the additional effect of a dentifrice containing salt and peroxide next to habitual oral hygiene as opposed to the oral hygiene without this product. After 24 months both regimens were proven to be equally effective in reducing plaque (0.25–0.3 drop in plaque index) and gingivitis (0.40–0.50 drop in gingival index) measures of periodontal disease to a state favouring periodontal health. In a comparative 6-month study the combination 0.5% thiocyanate (SCN^-)/0.1% H_20_2 was tested against a triclosan/copolymer-containing dentifrice. Both products demonstrated comparative plaque (approximately 5%) and gingivitis (approximately 30%) reductions (73). Hasturk *et al.* (74) examined the effect of a fluoridated H_2O_2 mouthrinse on plaque and gingivitis parameters and compared it with that of placebo. After 6 months, reductions of plaque and gingivitis for the test product reached 10% and 40%, respectively, as compared with baseline values. For the placebo an increase in clinical parameters was noted. However, when the test product was compared with placebo, only the reduction in gingivitis (11%) proved to be significant.

In summary, limited evidence exists with regard to the value of these agents in suppressing supragingival plaque formation although some retardation of plaque growth has been noted with the use of oxygenating mouthwashes. In view of the importance of obligate anaerobic bacteria in the development of gingivitis and periodontitis these compounds deserve further investigation.

Table 5. **Characteristics of studies on triclosan/zinc citrate dentifrice products**

						Plaque		Gingivitis	
Author	*n*	Design	Duration	Blindness	Groups compared	Index base–end	reduction versus placebo or control (%)	Index base–end	reduction versus placebo or control (%)
Stephen *et al.* (76)	146	Parallel with prophylaxis at start	6 months	?	Triclosan/zinc citrate Control (MFP)	PI 0.70–0.21 0.72–0.28	24.9	A–B 32–12% 32–24.5%	50**
Svatun *et al.* (80)	140	Parallel with prophylaxis at start	7 months	Double blind	Triclosan/zinc citrate Control (NaF)	PI 0.29–0.14 0.29–0.21	33*	S–O 28.5–12% 27–24%	47*
Svatun *et al.* (81)	93	Parallel with prophylaxis at start	7 months	Double blind	Triclosan/zinc citrate Control (MFP)	PI 0.33–0.18 0.32–0.25	28*	S - O 30–10% 28–20%	50*
Palomo *et al.* (82)	143	Parallel with prophylaxis at start	6 months	Double blind	Control (NaF) Triclosan/zinc citrate	Q–H 2.98–2.05 3.00–1.93	–6	mod GI 2.14–1.26 2.12–1.21	–4

PI: Plaque Index [Silness & Löe (121)], Q–H: Quigley & Hein Index 1962 (119) [modification by Turesky (123)], A–B: Ainamo & Bay (113), S–O: Saxton–van der Ouderaa (120), mod GI: Talbott *et al.* (122) modification of the Gingival Index (1977).
Percent reduction calculations are made versus control (NaF or MFP) and are computed by using the formula: % red = (control – triclosan group)/(NaF or MFP) × 100%.
*Statistically sign when compared with control (NaF or MFP) group.

Table 6. **Characteristics of studies on triclosan/copolymer dentifrice products**

Author	*n*	Design	Duration	Blindness	Groups compared	Plaque		Gingivitis	
						Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction versus placebo or control (%)
Cubells *et al.* (83)	108	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 2.87–2.17 2.86–2.89	25*	GI 1.41–1.16 1.41–1.45	19.72*
Deasy *et al.* (84)	121	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 1.79–1.11 1.75–1.65	32.7*	mod GI 1.16–0.87 1.17–1.17	28.9*
Bolden *et al.* (85)	306	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 2.46–1.63 2.45–1.97	17.2*	GI 1.41–0.81 1.43–1.14	29*
Denepitiya *et al.* (86)	145	Parallel with prophylaxis at start	6-months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 2.25–1.82 2.24–2.22	18*	GI 1.60–0.65 1.59–0.95	31.5*
Lindhe *et al.* (88)	110	Parallel	6 months		Triclosan/copolymer Control (NaF)	Q–H 2.1–1.1 2.2–1.6	31*	GI 1.5–1.1 1.6–1.5	26.6*
Svatun *et al.* (80)	140	Parallel with prophylaxis at start	7 months	Double blind	Triclosan/copolymer Control (NaF)	PI 0.28–0.17 0.29–0.21	19*	S–O 27–18% 27–24%	25*
Palomo *et al.* (82)	143	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 3.00–1.72 3.00–1.93	11*	mod GI 2.10–0.96 2.12–1.21	21*
Kanchanakamol *et al.* (87)	124	Parallel with prophylaxis at start	6 months	Single blind	Triclosan/copolymer Control (their own)	Q–H 3.47–2.84 3.55–3.23	12*	mod GI 1.34–0.97 1.34–0.98	1
McClanahan *et al.* (89)	483	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 1.88–2.23 1.90–2.23	0	GI 0.70–0.51 0.71–0.52	2*
Charles *et al.* (91)	303	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer + control mouthrinse Control (MFP) dentifrice + control mouthrinse	Q–H 2.96–1.68 2.94–2.16	22.1*	MGI 2.10–1.53 2.11–1.93	20.8*
Triratana *et al.* (90)	119	Parallel	6 months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 2.95–1.57 2.96–2.41	35*	GI 1.70–1.07 1.72–1.44	26*
Winston *et al.* (92)	77	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer Control (NaF)	Q–H 1.89–1.09 1.92–1.20	9	GI 0.97–0.94 1.04–0.93	0.3
Grossman *et al.* (93)	158	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/pyrophosphate Control (NaF)	Q–H 1.62–1.33 1.65–1.58	13.9*	mod GI 0.61–0.63 0.55–0.58	4
Allen *et al.* (94)	110	Parallel with prophylaxis at start	6 months	Double blind	Triclosan/copolymer Placebo	Q–H 2.16–1.63 2.14–2.27	29.9*	mod GI 1.38–0.97 1.35–1.23	23.2*

Q–H: Quigley & Hein Index 1962 (119) [modification by Turesky *et al.* (123)], GI: Gingival Index [Löe & Silness (117)], mod GI: Talbott *et al.* (122) modification of the Gingival Index (1977), MGI: modification of Gingival Index [Lobene *et al.* 116)].
Percent reduction calculations are made versus control (NaF) or placebo and are computed by using the formula: % red = (control or placebo – triclosan group)/(NaF or placebo) × 100%.
*Statistical significance when compared with control (NaF or MFP) group.

Non-charged phenolics

Triclosan

Triclosan is a bisphenol as well as a non-ionic germicide with low toxicity and a broad spectrum of antibacterial activity (75). It has been widely used in soaps, antiperspirants, and cosmetic toiletries. It has both anti-bacterial and anti-inflammatory properties. The antibacterial action seems to be associated with the cytoplasmic membrane disruption of the bacterial cell (prevention of the amino acid uptake), whereas its anti-inflammatory action lies on the inhibition of the oxygenase/lipoxygenase pathway in the arachidonic acid metabolism. It has been used as in dentifrice or mouthrinse formulations. The safety of several triclosan-containing formulations has been established by several long-term studies (76–78) with no shifts in the microflora of the supragingival plaque and no immergence of opportunistic pathogens.

Triclosan in dentifrice formulations

Triclosan + zinc citrate. The anti-plaque and anti-gingivitis action of this combination was confirmed by both short- and long-term (for review see ref. 79). Table 5 provides the RCT (76, 80–82) where the effect of this combination on plaque and gingivitis was compared with that of a control (NaF or MFP) dentifrice. The papers by Stephen *et al.* (76) and Svatun *et al.* (80, 81) reported significant drops in plaque (range 24.9–33%) and gingivitis (range 47–50%) as opposed to control dentifrice. The Palomo *et al.* (82) study is not consistent with those findings. They found no statistically significant differences between the two study groups with respect to plaque and gingivitis parameters.

Triclosan + copolymer [methoxyethylene and maleic acid (Gantrez)]. Of 12 RCTs (80, 82–94) selected for this review (Table 6), 10 reported a 0–35% reduction of plaque and 0.3–31.5% gingivitis in comparison with NaF control. With the exception of two studies (88, 89, 92) that reported modest (non-significant) plaque and/or gingivitis reduction, all other RCT showed statistically significant reductions when compared with NaF control. Although in one study (88) the control dentifrice was not defined (subjects shad to use their own dentifrice), this study still reported significant reductions in plaque (12%) in relation to control. One study (94) reported statistically significant reductions in plaque and gingivitis in comparison with placebo. Finally, one study (90) compared the combined regimen of a triclosan/copolymer dentifrice and a control mouthrinse to the daily use of a MFP dentifrice and mouthrinse. They found a statistically significant drop in plaque and gingivitis in favour of the triclosan-containing dentifrice + mouthrinse group.

Triclosan + copolymer versus triclosan + zinc citrate. Two RCT compared the effectiveness of the above-mentioned combinations (80, 82) (Tables 5 and 6) with a control dentifrice. The

Table 7. **Characteristics of studies on triclosan mouthrinse products**

						Plaque		Gingivitis	
Author	*n*	Design	Duration	Blindness	Groups compared	Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction *versus* placebo or control (%)
Worthington *et al.* (95)	117	Parallel	6 months	Double blind	Triclosan/copolymer Placebo	PI* 2.55–1.9 2.55–2.55	24† 	S - O* 1.20–0.9 1.20–1.20	23†
Ayad *et al.* (96)	71	Parallel	6 months	Double blind	Triclosan/copolymer Placebo	PI 2.76–1.85 2.74–2.46	24.8† 	mod GI 1.66–1.16 1.66–1.49	22.1†
Triratana *et al.* (97)	118	Parallel	6 months	Double blind	Triclosan/copolymer Placebo	Q–H 3.03–2.02 2.98–2.85	35.5† 	GI 2.20–1.77 2.18–2.13	18.8†
Schaeken *et al.* (98)	290	Parallel	7 months	Double blind	Triclosan/copolymer Control	PI* 1.5–0.7 1.5–1.0	30% 	S–O* 37–28% 37–14%	46.1†

PI: Plaque Index (Silness & Löe (121)), Q–H: Quigley & Hein Index 1962 (119) [modification by Turesky *et al.* (123)], S–O: Saxton–van der Ouderaa (120), mod GI: Talbott *et al.* (122) modification of the Gingival Index (1977), GI: Gingival Index [Löe & Silness (117)].
Percent reduction calculations are made versus placebo (or control) and are computed by using the formula: % red = (placebo or control – triclosan group)/(placebo or control) × 100%.
*Data approximation based on figures.
†Statistically significant when compared with placebo or control group.

studies provided contradictory results with regard to which combination provided more benefits.

Triclosan + copolymer (Gantrez) in mouthrinse formulations

Several short-term studies demonstrated beneficial results (for review see ref. 83). These results were later confirmed by RCTs (95–98) that also reported plaque reductions of 23–28% compared with placebo control rinse (Table 7). A 7-month study verified the superiority of this combination in comparison with control mouthrinse. They reported 46.1% reduction in gingivitis in comparison with the control mouthrinse (Table 7).

In conclusion, the above-mentioned results have extensively displayed the anti-gingivitis and anti-plaque value of the various triclosan formulations when compared with control or placebo products. There is disagreement in the literature with respect to the effectiveness of triclosan + copolymer as opposed to the of triclosan + zinc citrate. It appears that the

Table 8. **Characteristics of studies on Listerine® mouthrinse next to unsupervised oral hygiene**

						Plaque		Gingivitis	
Author	*n*	Design	Duration	Blindness	Groups compared	Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction versus placebo or control (%)
Lamster *et al.* (101)	129	Parallel with no prophylaxis at start Supervised rinsing	6 months	Double blind	Listerine mouthrinse Placebo (water) mouthrinse	Q–H ?–1.92 ?–2.48	22.2*	GI ?–1.20 ?–1.7	28.2*
Gordon *et al.* (111)	85	Parallel with prophylaxis at start	9 months	Double blind	Listerine Placebo (water)	Q–H 1.99–1.93 2.13–2.49	14.9*	GI 1.59–1.13 1.60–1.52	20*
Grossman *et al.* (27)	481	Parallel with prophylaxis at start	6 months	Double blind	Listerine mouthrinse Placebo mouthrinse	Q–H 1.48–? 1.40–?	24.2*	GI 0.52–0.59 0.50–0.65	9.4%
DePaola *et al.* (112)	107	Parallel with prophylaxis at start	6 months	Double blind	Listerine Negative control (hydro-alcohol 5%)	Q–H ?–1.15 ?–1.75	34*	MGI ?–0.92 ?–1.39	34*
Overholser *et al.* (29)	124	Parallel with prophylaxis at start	6 months	Double blind	Listerine Negative control (hydro-alcohol)	Q–H 2.49–1.05 2.35–1.64	36.1*	MGI 2.23–0.75 2.22–1.17	35.9*
Charles *et al.* (91)	303	Parallel with prophylaxis at start	6 months	Double blind	MFP dentifrice + Listerine MFP dentifrice + control (hydro-alcohol) mouthrinse	Q–H 2.94–0.95 2.94–2.16	56.1*	MGI 2.11–1.49 2.11–1.93	22.9*
Sharma *et al.* (102)	241	Parallel with prophylaxis at start and OHI	6 months	Examiner-blind	Brushing + flossing + Listerine Brushing + flossing + control mouthrinse Brushing + flossing (negative control)	Q–H 2.75–1.13 2.78–2.37 2.77–2.61	56.3* 9.3	MGI 2.11–1.44 2.10–1.81 2.11–2.04	29.9* 11.2
Charles *et al.* (32)	107	Parallel with prophylaxis at start	6 months	Examiner blind	Listerine Negative control (hydro-alcohol 5%)	Q–H 2.5–1.77 2.31–2.18	18.8*	GI 1.31–1.04 1.27–1.21	14*

Q–H: Quigley & Hein Index 1962 (119) [modification by Turesky *et al.* (123)], GI: Gingival Index [Löe & Silness (117)], MGI: modification of the Gingival Index [Lobene *et al.* (116)].
Percent reduction calculations are made versus control (or placebo) and are computed by using the formula: % red = (control or placebo – listerine group)/(control or placebo) × 100%.
*Statistically significant when compared with control group.

use of triclosan as mouthrinse next to daily oral hygiene does not offer more advantages with regard to plaque and/or gingivitis reductions than the use of this agent in dentifrices.

Essential oils

The traditional view of the mechanism of action of phenolics is by cell wall disruption and inhibition of bacterial enzymes (75). Listerine®, is a combination of the two phenol-related essential oils, thymol and eucalyptol, mixed with menthol and methylsalicylate in a hydroalcoholic vehicle. The agent is used in a mouthrinse form. The effects of this agent on plaque growth and gingivitis are well documented both short and long-term. Safety has also been demonstrated for this agent also from microbiological point of view with no emergence of opportunistic, potential or presumptive pathogens (99, 100). The recommended use is twice daily following the toothbrushing.

Table 8 presents the 6-month RCT on the essential oils. All but one study (101) used a parallel design with professional prophylaxis at start in order to eliminate plaque and calculus. In most of these studies the product had been used next to unsupervised oral hygiene and was compared either with a placebo or a negative control. Plaque and gingivitis reductions versus placebo ranged between 14.9% and 24.2% and 9.4% and 28.2% respectively. Reductions versus negative control were 18.8–36.1% and 14–35.9% respectively. One study (90) standardized the dentifrice of the individuals during the daily-unsupervised oral hygiene. They also reported 56.1% reduction in plaque and 22.9% reduction in gingivitis when subjects rinsed with Listerine®. Finally, another study (102) examined the additional effect of rinsing with Listerine® next to more rigid oral hygiene (i.e. brushing and flossing) and reported even greater plaque and gingivitis reductions (56.3% and 29.9% respectively) as compared with control group that used no mouthrinse at all.

Briefly, the existing evidence supports that Listerine® used next to unsupervised brushing provides a benefit with regard to plaque and gingivitis reduction as compared with placebo or control. When compared with CHX mouthrinses, with the exception of one study, all other studies seem to agree that the plaque/gingivitis reducing efficacy of Listerine® is inferior to that of CHX.

Surface modifying agents

Delmopinol

Delmopinol is amino-alcohol with documented anti-bacterial action. The suggested mechanism of action is its interference

Table 9. **Characteristics of studies on delmopinol mouthrinses used as adjuncts to customary oral hygiene**

						Plaque		Gingivitis	
Author	*n*	Design	Duration	Blindness	Groups compared	Index base–end	Reduction versus placebo or control (%)	Index base–end	Reduction versus placebo or control (%)
Lang *et al.* (30)	132	Parallel with prophylaxis at start	6 months	Double blind	Delmopinol mouthrinse Placebo mouthrinse	PI* 1.1–0.5 1.1–0.8	35†	BOP* 50–22% 53–38%	3
Claydon *et al.* (106)	422	Parallel with prophylaxis at start	6 months	Double blind	0.1% Delmopinol mouthrinse 0.2% Delmopinol mouthrinse Placebo mouthrinse	Q–H 1.67–1.27 1.66–1.17 1.71–1.40	9.3† 16.4†	MGI 1.85–1.13 1.89–1.11 1.83–1.12	–1 1
Hase *et al.* (31)	130	Parallel with prophylaxis at start	6 months	Double blind	Delmopinol mouthrinse Placebo mouthrinse	Q–H* 1.60–1.4 1.6–1.6	13†	BOP* 45–32% 43–37%	18†

PI: Plaque Index [Silness & Löe (121)], Q–H: Quigley & Hein Index 1962 (119) [modification by Turesky *et al.* (123)], MGI: modification of the Gingival Index [Lobene *et al.* (116)], BOP: Bleeding on Probing.
In all studies mouthrinses were used next to unsupervised oral hygiene procedures performed by the participants who used their own toothbrush and dentifrice.
Percent reduction calculations are made versus placebo and are computed by using the formula: % red = (placebo – delmpinol group)/(placebo) × 100%.
*Data approximation based on figures.
†Statistically significant when compared with placebo group.

with plaque matrix formation and reduction of bacterial adherence (103, 104). This would cause the plaque to be more loosely adherent to the tooth so that it would be more easily removed by mechanical cleaning procedures, and would therefore be suitable for a pre-brush mouthrinse. The long-term study by Elworthy *et al.* (105) documented the changes in microbial flora as a result of the use of this agent. No major shifts were observed. Also, information on adverse effects delmopinol were provided by Claydon *et al.* (106). A few adverse signs and symptoms were reported and these included transitory numbness of the tongue, tooth and tongue staining, taste disturbance and rarely mucosal soreness and erosion. No systemic effects attributable to the agent were observed and no shifts in haematological and biochemical parameters occurred.

Three double-blind randomized 6-month clinical trials (30, 31, 106) were identified describing the changes of plaque and gingivitis indices associated with the use of delmopinol as well as the safety of the use of this agent (Table 9). All studies have used a similar design and compared delmopinol with a placebo mouthrinse and 0.2% CHX. Plaque reductions for delmopinol ranged between 9.3% and 35% compared with placebo and gingivitis reductions 1% and 18%.

In conclusion, it can be said that studies seem to agree upon the fact that delmopinol reduces plaque more than placebo. Two of the three studies demonstrated also reduction of gingivitis as opposed to placebo. It seems however, that the plaque and/or gingivitis effectiveness of this agent is far below that of CHX.

Conclusion

A variety of chemical agents has been presented in this chapter. For some of those evidence exists with regard to their plaque inhibiting and anti-gingivitis properties. Most of the comparisons were made against placebo or control (positive or negative). The results of the studies presented should be, however, viewed in the light of the baseline and end-values displayed. Often too low baseline values result only in minor changes in plaque or gingivitis; too small to be of clinical significance. Also, a critical view of the results indicates that plaque and gingival inflammation are always present (although to a lesser extent) at the end of the experimental period. The question is what level of plaque reduction constitutes 'efficacy'. More accurate parameter to describe the condition of the gingival tissues would be that of gingival inflammation. However, insufficient information exists with regard to which level of gingival inflammation can ensure the prevention of the transition of gingivitis to periodontitis. CHX is the most studied and by far the most effective anti-microbial agent in oral care. Taking into consideration the plaque and gingivitis reductions reported for CHX one can speak about efficacy only when the plaque and gingivitis reductions reported for any chemical factor approach are superior to those of CHX. Most of chemical agents presented in this chapter demonstrate anti-plaque and/or anti-gingivitis action in comparison with control or placebo, but the results indicate that plaque and gingivitis reductions are far below those achieved by CHX. However, side-effects such as unpleasant taste, alterations of taste sensation, non-aesthetic discoloration of the teeth and, in some cases, desquamative oral lesions may prohibit the prolonged use of CHX. Research still seeks for the ideal chemical agent that would combine the anti-plaque and/or anti-gingivitis efficacy of CHX and the possibility of long-term use without side-effects.

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