Community Dent Oral Epidemiol 2013; 41; 79–96
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COMMUNITY DENTISTRY AND ORAL EPIDEMIOLOGY

Unsolicited Systematic Review

Non-surgical management methods of noncavitated carious lesions

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Tellez M, Gomez J, Kaur S, Pretty IA, Ellwood R, Ismail AI. Non-surgical management methods of noncavitated carious lesions. Community Dent Oral Epidemiol 2013; 41: 79–96. © 2012 John Wiley & Sons A/S. Published by Blackwell Publishing Ltd

Abstract – *Objective:* To critically appraise all evidence related to the efficacy of nonsurgical caries preventive methods to arrest or reverse the progression of noncavitated carious lesions (NCCls). *Methods:* A detailed search of Medline (via OVID), Cochrane Collaboration, Scielo, and EMBASE identified 625 publications. After title and abstract review, 103 publications were selected for further review, and 29 were finally included. The final publications evaluated the following therapies: fluorides (F) in varying vehicles (toothpaste, gel, varnish, mouthrinse, and combination), chlorhexidine (CHX) alone or in combination with F, resin infiltration (I), sealants (S), xylitol (X) in varying vehicles (lozenges, gum, or in combination with F and/or xylitol), casein phosphopeptide amorphous calcium phosphate (CPP-ACP) or in combination with calcium fluoride phosphate. All included studies were randomized clinical trials, were conducted with human subjects and natural NCCls, and reported findings that can yield outcomes measures such as caries incidence/increments, percentage of progression and/or arrest, odds ratio progression test to control, fluorescence loss/mean values, changes in lesion area/volume and lesion depth. Data were extracted from the selected studies and checked for errors. The quality of the studies was evaluated by three different methods (ADA, Cochrane, author's consensus). *Results:* Sample size for these trials ranged between 15 and 3903 subjects, with a duration between 2 weeks and 4.02 years. More than half of the trials assessed had moderate to high risk of bias or may be categorized as 'poor'. The great majority (65.5%) did not use intention to treat analysis, 21% did not use any blinding techniques, and 41% reported concealment allocation procedures. Slightly more than half of the trials (55%) factored in background exposure to other fluoride sources, and only 41% properly adjusted for potential confounders. *Conclusions:* Fluoride interventions (varnishes, gels, and toothpaste) seem to have the most consistent benefit in decreasing the progression and incidence of NCCls. Studies using xylitol, CHX, and CPP-ACP vehicles alone or in combination with fluoride therapy are very limited in number and in the majority of the cases did not show a statistically significant reduction. Sealants and resin infiltration studies point to a potential consistent benefit in slowing the progression or reversing NCCls.

Key words: chlorhexidine; CPP-ACP; fluorides; randomized clinical trial; sealants; xylitol

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Submitted 22 March 2012;
accepted 2 November 2012

The diagnosis of early carious lesions is essential for nonsurgical management of dental caries (1). The measurement of incipient or noncavitated carious lesions (NCCls) increases the sensitivity and efficiency of clinical trials (2). However, caries trials have often excluded initial lesions because of difficulties they pose for reliable detection (3). More recent studies have demonstrated that early carious lesions can be measured reliably (4) and detecting subtle changes in progressing incipient lesions

doi: 10.1111/cdoe.12028

in enamel would enhance both the possibility of remineralization before changes become irreversible (5, 6) and the modification of the biofilm to reduce the cariogenic challenge (7). Dental research has led to the development of multiple secondary prevention strategies that centre on the prompt treatment for disease at an early stage and include measures, which arrest and/or reverse the caries process after initiation of clinical signs (8). In spite of this, these measures have not been utilized efficiently by the profession as remuneration systems do not encourage their use (7). Unfortunately, operative care has remained the central management strategy for caries control in general practice, which has impacted negatively caries epidemiology, clinical outcomes, and patient's quality of life among others. A number of novel preventive treatment options are being developed to help dentists better control the caries process. However, scientific information supporting their efficacy in managing NCCIs is scarce. There is a need to assess what is known about the efficacy of professional remineralization strategies and caries prevention interventions in varying populations, as a step prior to surgical intervention for NCCIs. A previous systematic review of selected caries prevention and management methods (3) reported that the most problematic aspect among the studies included was the lack of standardized criteria for initially identifying NCCIs and for assessing their progression. This review included eight studies that had assessed NCCIs. However, half of those studies identified the lesions using radiographic criteria, so it was unknown whether they were in fact noncavitated. With the development of modern caries detection and assessment systems that emphasize the importance of early detection (9), it is expected, that a more robust literature will be available for critical appraisal and for outlining evidence-based clinical recommendations.

The aim of this systematic review is to critically appraise all evidence related to the efficacy of non-surgical caries preventive methods to arrest or reverse the progression of NCCIs.

Materials and methods

The publications included in this review evaluated the following therapies: fluorides (F) in varying vehicles (toothpaste, gel, varnish, mouthrinse, and combination), chlorhexidine (CHX) alone or in combination with F, resin infiltration (I), sealants (S), xylitol (X) in varying vehicles (lozenges, gum, or in combination with F and/or xylitol), casein phosphopeptide amorphous calcium phosphate (CPP-ACP) or in combination with calcium fluoride phosphate. A systematic search for papers (not restricted to English) published between 1966 and December 2011 was carried out using Medline Ovid, Embase, Cochrane Oral Health Group's Specialized Register, Cochrane Central Register of Controlled Trials, and Scielo. Reports in the gray literature, defined as theses, dissertations, product reports, and unpublished studies, were not included. Bibliographic references of identified systematic reviews, and review articles, were also checked. Hand searching of Table of Contents of Caries Research published since 1980 was also conducted.

- The search of Medline in Ovid plus hand searching identified 450 citations, with 175 additional citations identified from other databases (Fig. 1). Inclusion and exclusion criteria were applied by examining titles and abstracts, and if information relevant to the eligibility criteria was not available in the abstract or the abstract was not available, the full paper was selected for further review. The following inclusion criteria were followed to select relevant studies: a randomized clinical trial was conducted.
- Study was conducted with human subjects and natural carious lesions.
- Analysis of data was conducted at the noncavitated level only.
- Study was published in peer-reviewed journals.

In addition, papers were excluded if they met one or more of the following criteria: (i) incomplete description of sample selection, outcomes, or small sample size (defined by number of lesions considered as unit of analysis) and (ii) not meeting the highest evidence criteria under the therapy category of the Oxford Centre for Evidence-Based Medicine (10) (systematic reviews of randomized clinical trials, and individual randomized clinical trials). The systematic search strategy included combined MeSH and free text terms such as 'enamel caries', 'non-cavitated caries', 'incipient lesions', 'efficacy', 'randomized clinical trial', 'fluorides', 'sealants', 'xylitol', 'cpp-acp', and 'CHX'. The primary clinical outcomes considered for this review were caries incidence/increments, percentage of progression and/or arrest, odds ratio progression test to control, fluorescence loss/mean fluorescence values, changes in lesion area/volume and lesion depth. After training and calibration,

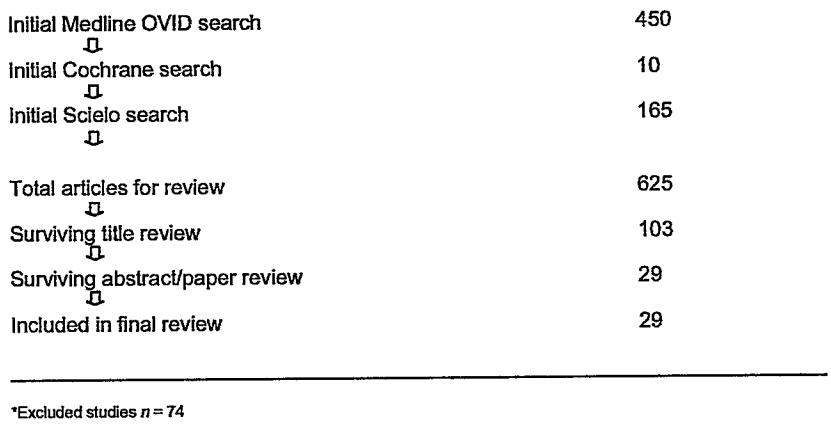

Fig. 1. Flow diagram of identification and inclusion.

data were extracted independently by two reviewers (MT, SK) and reviewed by a third (JG). The tables were checked for consistency, and corrections were made through consensus. The quality of the studies was assessed initially using the criteria reported in the ADA Clinical Recommendations Handbook (11) for randomized clinical trials, which included initial assembly of comparable groups, adequate randomization, maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination), differential loss to follow-up, reliability of measurements, clarity of interventions, blinding, control of confounders, and intention to treat analysis (ITT). The studies were categorized as good, fair, or poor based on ADA's criteria. In addition, two more quality assessments were conducted following Cochrane's recommendations for clinical trials, which rate allocation concealment and blinding as key criteria (12) (low risk of bias: possible bias unlikely to seriously alter the results, medium risk: possible bias that raises some doubts about the results, high risk: possible bias that seriously weakens confidence on the results). Finally, the overall strength of the evidence ratings (poor, fair, good) was assigned by consensus of three authors (MT, JG, SK). No formal weighting scheme was employed in making these judgments, but authors considered all the parameters accounted for in the ADA's quality assessment in addition to sample size and duration of the trial.

Results

Of the 103 papers, 74 were excluded. The reasons for the exclusion were as follows: caries outcome reported at the dentine level only (24.33%), studies that were not randomized controlled trials (RCT) (9.46%), data analysis that collapsed cavitated and noncavitated lesions (8.11%), unknown if incipient lesions were noncavitated (5.41%), and the remaining 52.69% because of small sample size, not commercially available, used artificial lesions or provided insufficient data.

Twenty-nine studies evaluating different nonsurgical methods for noncavitated carious lesions were assessed. The quality assessment varied depending on the criteria used. Following ADA's criteria, 6.9% of the studies were rated as 'fair', while 93.1% were rated as 'poor'. The consensus process conducted by the investigators yielded the following: 6.9% of studies were rated as 'good', 27.6% were rated as 'fair' and 65.5% as 'poor'. Following Cochrane's guidelines, 41.3% of the studies had low risk of bias, 37.9% were ranked as medium, and 20.8% had high risk of bias. The great majority of studies (65.5%) did not use ITT, 13.8% did not have a need to use ITT as there were no drop outs, and only 3.4% did conduct this analysis. In addition, 21% did not use any blinding techniques, 41% reported concealment allocation procedures while this same parameter was not reported in 59% of the publications. Twenty-eight percent of the studies did not meet the criteria for comparability of baseline characteristics between test and control groups. Slightly more than half of the trials (55%) factored in background exposure to other fluoride sources, and only 41% properly adjusted for potential confounders. Sample size for these trials ranged between 15 and 3903 subjects, with a duration between 2 weeks and 4.02 years. Most of the studies tested the different interventions

Table 1. Summary information and quality scores for studies on fluoride (n = 13)

Authors/years	N	Duration	Age at start	Intervention: Test	Intervention: Control	Dx method	Loss to follow up
Zantner et al., 2006	44 (39¶)	6 months	12–38 years	Group 1: NaF TP(1500 ppm) Group 2: Amine fluoride TP (1250 ppm)	G2: None	QLF	8.50%
Du et al., 2011	110 (96¶)	6 months	12–22 years	Varnish 22 600 ppmF	Saline solution	Diagnodent	12.70%
Biesbrock et al., 1998	3093 (1411¶)	3 years	6–13 years	Group 1: 0.243% NaF/silica dentifrice, Group 2: 0.4% stannous fluoride/ calcium pyrophosphate	Non-fluoridated placebo/calcium pyrophosphate	Visual-tactile a nd radiographic	54.30%
Ferreira et al., 2005	307 (258¶)	3 months	7–12 years	Group 1: 1.23% APF gel for 1 minute once a week. No F dentifrice	Group 2: Topical application of placebo, Group 3: No intervention	Visual-tactile	14.00%
Truin et al., 2007	596 (517¶)	4 years	9.5–11.5 years	Neutral 1% NaF gel (4500 ppm)	Placebo gel	Visual-tactile and radiographic	13.20%
Truin et al., 2005	773 (676¶)	4.02 years	4.5–6.5 years	Oral hygiene + FTP + neutral 1% NaF gel (4500 ppm fluoride)	Oral hygiene + FTP + Placebogel	Visual-tactile and radio graphic	12.55%
Karl sson et al., 2007	181 (135¶)	12 months	13–17 years	Amine fluoride dentifrice (1250 ppm) + Amine fluoride gel (4000 ppmF)	Amine fluoride dentifrice (1250 ppm) + Placebo gel	QLF and visual-tactile	25.42%
Ferreira et al., 2009	15	1 months	7–12 years	G1: 5% NaF varnish, G2: 6%NaF + 6% CaF2 varnish	None	Visual-tactile	0%

Definition outcome	Comparison	Outcome		Overall significance	Authors quality score	ADA quality score	Cochrane (risk of bias)
		Test	Control				
WSL (change in Fluorescence 3 QLF metrics)	BL	Group 1: ΔF:−14.41 ± 5.03, Group 2: ΔF:−14.41 ± 2.95		NS	Poor	Poor	Moderate
	Follow ups	Group 1: ΔF: −14.19 ± 4.9 to −15.93 ± 4.97, Group 2: ΔF: −14.17 ± 3.08 to 15.01 ± 4.52		NS			
WSL (mean DD readings decrease)	BL	17.66 ± 5.36	16.19 ± 5.70	NS	Fair	Poor	Low
	3 months	11.88 ± 4.27	13.75 ± 4.76	S			
	6 months	10.10±4.86	13.10±5.19	S			
Caries lesion reversals							
	Year 1	Group 1: 0.65 ± 0.99, Group 2: 0.63 ± 0.98	0.55 ± 0.90	NS	Poor	Poor	Moderate
	Year 2	Group 1: 0.61 ± 0.93, Group 2: 0.58 ± 0.96	0.46 ± 0.82	NS			
	Year 3	Group 1: 0.48 ± 0.84, Group 2: 0.43 ± 0.84	0.33 ± 0.64	S (for NAF versus Placebo)			
% WS	3 months	Group 1: 57.9%	Group 2: 56.8%, Group3: NR	S	Fair	Poor	Low
Mean D2S (enamel caries) increment	BL	3.9 ± 2.9	3.6 ± 3.0	NS	Good	Fair	Low
	4 years	2.27 ± 0.22	2.98 ± 0.28	NS			
D2S (enamel caries) increment		Permanent 0.55 ± 0.07	Permanent 0.69 ± 0.08				
	4 years	Primary 0.39 ± 0.10	Primary 0.56 ± 0.10	NS	Fair	Poor	Low
WSL (change in fluorescence Δf- A mm^2)							
	BL	1.62 mm^2 (lesion area); ΔF: 8.62%	1.75 mm^2 (lesion area); ΔF: 8.40%	NS	Poor	Poor	Moderate
	12 months	1.73 mm^2 (lesion area)	NR	NS			
Mean dimension values of WSL							
	BL	4.05 ± 1.27	3.62 ± 2.13	NS	Poor	Poor	High
	Week 4	2.86 ± 1.33	2.33 ± 1.53	NS			

Table 1. Continued

Authors/years	N	Duration	Age at start	Intervention		Dx method	Loss to follow up
				Test	Control		
Agrawal et al., 2011	257 (239¶)	12 months	9–16 years	1.23% APF gel (baseline and 6 months) + Oral health education at BL	No intervention	Visual-tactile	7.00%
Tranaeus et al., 2001	34 (31¶)	6 months	13–15 years	Fluorprotector Varnish (0.1% F) NaF mouth rinse (50 ppm), fluoride -free TP	Professional-tooth cleaning (every 6 W for 6 M) Control mouthrinse (No NaF), fluoride-free TP	QLF Computerized image analysis of calibrated photographic images (polarized light)	8.83%
Willmot, 2004	26 (21¶)	26 weeks	NR				19.24%
Feng et al., 2006	305 (296¶)	6 months	11.82 years	Toothpaste (NaF 1450 ppm F MFP 1450 ppm)	No Fluoride tooth paste (herbal)	QLF	3%
Schirrmeister et al., 2007	30	2 weeks	23–39	Toothpaste 5000 ppmF	Toothpaste 1450 ppmF	DD	0

NS, non significant; NR, not reported; APF, acidulated-phosphate-fluoride; MFP, monoflurophosphate; QLF, quantitative light induced fluorescence; WSL, white spot lesions.
¶Effective sample size for analysis.

in permanent dentition (26/29), followed by primary (2/29) and mixed dentition (1/29).

Fluorides (n = 13 studies)

Thirteen trials evaluated the efficacy of varying fluoride (F) vehicles: (i) toothpaste as 1500 ppm NaF, 1250 ppm Amine F, 0.243% NaF/Silica, 1450 ppm sodium-monoflurophosphate (MFP) 1450 ppm, 5000 ppmF, 0.4% stannous F/calcium pyrophosphate (13–17); (ii) varnish as 5% NaF, 6% NaF + 6% CaF, and 0.1% F (18–20); (iii) gel as 1.23% acidulated-phosphate-fluoride (APF), 1% NaF neutral (4500 ppm), and 4000 ppm Amine F (15, 21–24); and (iv) mouthrinse as 50 ppm NaF

Definition outcome	Comparison	Outcome		Overall significance	Authors quality score	ADA quality score	Cochrane (risk of bias)
		Test	Control				
Change Incipient lesions (Nyvad)							
	BL	5.04 ± 1.95	4.93 ± 1.90	NS	Poor	Poor	Moderate
	6 months	3.23 ± 1.22	4.36 ± 1.76	S			
	12 months	1.18 ± 1.18	3.03 ± 1.32	S			
		A (mm^2)	A (mm^2)				
[Mean (SE) Change in average fluorescence]		−0.152 ± 0.056	−0.006 ± 0.047				
		ΔQ	ΔQ				
		−0.107 ± 0.032	−0.008 ± 0.027				
	BL-6 months			S	Fair	Poor	Low
Lesion size and proportion (DWL %); percentage reduction (ADPR) at debond							
	12 weeks	ADPR: 40.0% ± 14.5	ADPR: 51.5% ± 13.3	NS	Poor	Poor	Low
	26 weeks	ADPR: 54.3% ± 12.3	ADPR:66.1% ± 15.5	NS			
		Δf = NaF 0.30 ± 0.20					
		MFP 0.32 ± 0.22					
		A (mm^2)					
WSL (mean (SE) Differences between 3 QLF metrics)	3 months Test versus Placebo Δ values	NaF −0.19 ± 0.11		NaF = NS			
		MFP 0.23 ± 0.11		MFP = S			
		ΔQ		(A−ΔQ)			
		NaF 2.39 ± 1.56			Fair	Poor	Low
		MFP 3.88 ± 1.69					
		Δf = NaF 0.71 ± 0.23					
		MFP 0.69 ± 0.23					
		A (mm^2) = Na F					
	6 months Test versus Placebo Δ values	−0.42 ± 0.12		NaF = S			
		MFP −0.39 ± 0.12		MFP = S			
		ΔQ = Na F 5.43 ± 1.77		(Δf-A-ΔQ)			
		MFP 6.32 ± 1.90					
Non cavitated (mean (SD) DD readings decrease)	2 weeks	11.9 ± 1.6	15.6 ± 3.0	S			
					Fair	Poor	Low

(Willmot). Sample sizes for the trials ranged from 15 to 3093 subjects and were conducted between 2 weeks and 4.02 years (loss to follow-up ranged from 0% to 54.3%). Twelve studies evaluated permanent dentition, and one evaluated primary teeth, and were conducted in Europe, South America, North America, and Asia. Five studies used some type of placebo, four studies used positive and/or negative controls, and other four studies did not report having any sort of control group. The diagnostic methods to detect noncavitated lesions varied among studies: (i) visual-tactile (VT) (n = 3), (ii) VT + radiography (n = 3), (iii) Laser fluorescence alone or in combination with visual (n = 6), and (iv) computerized image analysis (n = 1).

Six of thirteen studies were rated as 'poor', other six studies were rated as 'fair', and only 1 study was rated as 'good' (author's consensus process). Eight of thirteen studies reported overall significant differences between test and control groups. Du et al. (18) reported a decrease in the mean DIAGNOdent (DD) reading in white spot lesions (WSLs) after testing 5% NaF varnish at 3 and 6 months and concluded that topical fluoride varnish application was effective in reversing WSLs after debonding. Even with lower concentrations of F (0.1%), repeated applications of varnish had a favorable effect on the remineralization of WSLs measured by quantitative light-induced fluorescence (QLF) (19). Three trials that evaluated the efficacy of different F gels also reported significant differences between test and control. Agrawal and Ferreira (21, 22) reported that supervised toothbrushing with and topical applications of 1.23% APF gel achieved a change in the percentage of WSLs. In addition, studies using varying methods of laser fluorescence reported that QLF methodology could detect within a 3–6 month periods of supervised toothbrushing, a difference in remineralization between fluoride containing and nonfluoride containing dentifrices (16) and that a dentifrice containing 5000 ppm F was significantly better than the dentifrice containing 1450 ppm F regarding reversal of noncavitated fissure carious lesions detected with DD (17) (Table 1).

Chlorhexidine (n = 1 study)

Lundström and Krasse (25) conducted a study during 1.8 years in 40 subjects 11–15 years old from Sweden, who were randomly allocated to a test group that received CHX digluconate 1% gel in addition to F Varnish (Duraphat, Colgate Oral Pharmaceuticals Subsidiary of Colgate-Palmolive Company, New York, NY, USA) and F toothpaste and a control group [F Varnish (Duraphat) and F toothpaste]. There were no significant differences at baseline or during the course of the orthodontic treatment. This study was rated as poor and with moderate risk of bias (Table 2).

Xylitol (n = 1 study)

Stecksén-Blicks et al. (26) conducted a study during 2 years in 160 subjects 10–20 years old from Sweden, who were allocated to two test groups. Group 1 received lozenges with 422 mg of Xylitol, Group 2 received lozenges with 422 mg of Xylitol and 0.25 mg of NaF. A comparison group did not receive any tablet. There were no significant differences at baseline or after the 2-year period between the study groups. This study was rated as poor and with moderate risk of bias (Table 2).

Casein phosphopeptide amorphous calcium phosphate [CPP-ACP (n = 6 studies)]

Five trials (27–31) evaluated CPP-ACP, while 1 study (32) evaluated casein phosphopeptide amorphous calcium fluoride phosphate (CPP-ACFP). Sample sizes for the trials ranged from 26 subjects to 2720 and were conducted between 3 weeks and 24 months (loss to follow-up ranged from 0 to 19.4%). All studies evaluated permanent dentition, and four of them were conducted in Europe, while two studies were conducted in Australia. Different types of CPP-ACP and CPP-ACFP vehicles were tested (crème, mousse, gum) in addition to F dentifrice, generally NaF 900–1450 ppm. Only one study used a placebo cream, while the others provided F toothpaste/sugar-free gum to the control groups. Four studies used some type of laser fluorescence (QLF-DD) in addition to visual criteria for the detection of noncavitated lesions, one study used visual and standardized bitewing radiography, and another study used visual only (ICDAS) only. There were significant differences between the study groups in two studies. In particular, Morgan et al. (28) concluded that those subjects who had CPP-ACP gum three times per day (10 minutes each time) were 18% less likely to have a surface experiencing caries progression when compared with the subjects chewing the control gum (OR = 0.82, P = 0.03), while Bailey et al. (29) concluded that 31% more of WSLs had regressed with the remineralizing cream than with the placebo at 12 weeks (OR = 2.3, P = 0.04). Two studies were rated as 'fair' (28, 29), while the remaining four studies were rated as 'poor'. No concealment of allocation, limited control for confounding, and lack of ITT were the major issues in these studies (Table 3).

Sealants/Resin Infiltration (n = 6 studies)

Four trials (33–36) evaluated sealants, while two studies (37, 38) evaluated resin infiltration. Sample sizes for the trials ranged from 22 subjects to 91 and were conducted between 12 months and 3 years (loss to follow-up ranged from 0% to 38%). All studies evaluated permanent dentition except one and were mainly conducted in South America (Brazil, Chile, and Colombia) and Europe (Denmark and Germany). Five studies used a split mouth design and tested sealants only, in combination with F varnish or home-based flossing

Table 2. Summary information and quality scores for studies on chlorhexidine, xylitol, and combination of interventions (n = 4)

Author/ year	N	Duration	Age at start	Intervention		Reliability	Dx method	Loss to follow up	Definition outcome	Comparison	Outcome		Overall significance	Authors quality score	ADA quality score	Cochrane (risk of bias)
				Test	Control						Test	Control				
Chlorhexidine (CHX)				Gel CHX digluconate 1% + F Varnish	F Varnish		Visual + BW									
Lundstrom et al., 1987	40 (36)	1.8 years	11–15 years old	Duraphat + F TP	Duraphat + F TP	NR	Radiographs	10%	Caries incidence	BL	1.6 ± 1.2	1.6 ± 1.2	NS	Poor	Poor	Moderate
										During ortho treatment	0.4 ± 0.9	1.4 ± 2.1	NS			
Xylitol				Group1: Xylitol 422 mg, Group2: Xylitol 422 mg + 0.25 mg												
Stecksen-Blicks et al., 2008	160 (115)	2 years	10–20 years old	NaF lozenges	Not random-no treatment	Inter: Kappa: 0.85	BW Radiographs	28%	Caries incidence (ΔDSe)	BL	Group 1: 1.6 ± 1.3 Group2: 2.0 ± 2.5	Group 3: 2.0 ± 1.8	NS	Poor	Poor	Moderate
										Year 2	Group 1: 3.6 ± 4.4 Group 2: 3.7 ± 4.2	Group 3: 3.0 ± 3.8	NS			
										ΔDSe	Group 1: 2.0 ± 4.0 Group 2: 1.7 ± 3.8	Group 3: 1.0 ± 3.0	NS			
Combination				Cervitec (1% CHX 1%Thymol) once every w k for 3 weeks + F varnish every 12 weeks until debonding	Positive control: cervitec varnish and control: no treatment											
	220	72 weeks				NR	Visual	0%	Increments WS lesions	During treatmen	0.04 ± 0.20	0.08 ± 0.30	NS	Poor	Poor	High

Table 2 **Continued**

Author/ year	N	Duration	Age at start	Intervention: Test	Intervention: Control	Reliability	Dx method	Loss to follow up	Definition outcome	Comparison	Outcome: Test	Outcome: Control	Overall significance	Authors quality score	ADA quality score	Cochrane (risk of bias)
Ogaard et al., 2011			12–15 years old	Group 1: cervitec weekly for 4 weeks, Group 2: F varnish weekly for 4 weeks, Group 3: Cervitec + F varnish weekly for 4 weeks	Group 4: no treatment except restorative	Intra: kappa: 0.96			WS lesions mean difference		Group 1: 3.15 ± 2.23 Group 2: 3.45 ± 2.31 Group 3: 3.10 ± 2.59					
Guedes de Amorim et al., 2008	80	3 months	3–5 years old				Visual	5%		BL		Group 4: 3.25 ± 2.00	NS	Poor	Poor	High
										t1–t2	Group 1: −0.35 ± 0.74 Group2: −0.47 ± 0.77 Group 3: −0.55 ± 0.99	Group 4: −.21 ± 0.63	NS			
										t2–t3	Group 1: −.61 ± 1.14 Group 2: −0.58 ± 1.17 Group 3: −.85 ± 1.46	Group 4: 0.58 ± 0.77	S			
										t1–t3	Group1: −0.89 ± 1.45 Group2: −0.05 ± 1. Group3: −1.40 ± 2.21	Group 4: 0.37 ± 1.01	S			

Table 3. Summary information and quality scores for studies on CPP-ACP/CPP-ACFP (n = 6)

Author/ year	N	Duration	Age at start	Intervention		Dx method	Loss to follow up	Definition outcome	Com parison	Outcome		Overall significance	Authors quality score	ADA quality score	Cochrane (risk of bias)
				Test	Control					Test	Control				
				CPP-ACP + NaF 0.2%;900 ppm (MI paste Plus 35 ml Recaldent)	F-free paste + calcium (Ultradent 100 ml)			Lesion depth Δ F, lesion area % mm^2, integrated fluorescence loss IFL		Δ F:8.45 ± 1.17, % mm^2: 5.07 ± 5.6 9, IFL: 56.37 ± 73.05	Δ F:9.10 ± 1.75, % mm^2: 7.29 ± 7.9 1, IFL: 90.81 ± 111.28				
Beerens et al., 2010	65 (55)	3 months	12–19 years old			QLF + Visual	15.30%		BL			NS	Poor	Poor	Moderate
									6 weeks	Δ F:7.93 ± 1.34, % mm^2: 5.09 ± 6.53, IFL: 57.14 ± 86.74	Δ F:8.22±2.38, % mm^2: 5.96 ± 6.3 8, IFL: 70.17 ± 81.76	NS			
									12 weeks	ΔF:7.52 ± 1.78, % mm^2: .05 ± 6,9 8, IFL: 57.76 ± 91.73	Δ F:7.96 ± 2.76, % mm^2: 7.17 ± 7.7 6, IFL: 85.89 ± 97.82	NS			
				Brushing w/ CPP-ACP cream no F (Topacal-C-5) 3 months + F dentifrice (1000–1100 ppm)for next 3 months	0.05% NaF mouthw- ash once daily + F dentifrice for 6 month period	LF diagnodent + visual		Mean laser							
Andersson et al., 2007	26	12 months	12–16 years old				0%	Fluorescence values	BL	7.4 ± 10.2	9.4 ± 9.5		Poor	Poor	Moderate
									1 month	5.5 ± 6.7	7.6 ± 9.2	NS			
									3 months	4.9 ± 5.5	6.8 ± 8.1	NS			
									6 months	4.6 ± 5.1	6.4 ± 7.3	NS			
									12 months	4.4 ± 5.2	6.4 ± 7.5	NS			
				CPP-ACP sugar free gum (sorbitol) (54 mg) 3 times per day (10 minutes each session)	Sorbitol based sugar free gum	Standardized Bitewing Radiographs + Visual		Caries progression (OR, 95% CI)		OR: 0.82 95% CI (0.68, 0.98)					
	2720 (1)	24 months					35.70%					S	Fair	Poor	Low

Table 3 **Continued**

Author/ year	N	Duration	Age at start	Intervention		Dx method	Loss to follow up	Definition outcome	Com parison	Outcome		Overall significance	Authors quality score	ADA quality score	Cochrane (risk of bias)
				Test	Control					Test	Control				
Morgan et al., 2008			11.5–13.5 year old	CPP-ACP tooth mousse 1 g 2 times per day + F dentifrice NaF 1000 + NaF mouth rinse 900 ppm				WS regression/ stable/pro-gression (OR, 95% CI)							
Bailey et al., 2009	45	12 weeks	12–18 years old		Placebo cream	Visual ICDAS II	0%		BL to 4 weeks	OR: 1.40 95% CI (0.84, 2.34)		NS	Fair	Poor	Low
									BL to 8 weeks	OR: 1.14 95% CI (0.70, 1.87)		NS			
									BL to 12 weeks	OR: 1.67 95% CI (0.81, 3.45)		S (only for WS with severity 2–3 (OR 2.33, 95% CI:1.06, 5.14)			
				CPP-ACP-TP + FTP				Lesion depth Δ F, lesion area % mm^2		Δ F:6.68 ± 0.58, % mm^2: 0.12 ± 0.16	Δ F:7.04 ± 1.65, % mm^2: 0.19 ± 0.43				
Brochner et al., 2011	60 (50¶)	4 weeks	13–18 years old	1100 ppm	FTP 1100 ppmF	QLF + Visual	17%		BL			NS	Poor	Poor	Moderate
					Toothpaste 1450 ppmF			Incipient lesion (mean (SD) DD readings decrease)	BL	16.66 ± 1.27	16.87 ± 1.69		Poor	Poor	Low
Altenburger et al., 2010	32	3 weeks	22–31	CPP-ACP-Toothpaste		DD	0%		1 weeks	15.1	15.18	NS			
									2 weeks	12.5	14.71				
									3 weeks	10.96	14.78				

NS: non significant, WS: white spot; CPP-ACFP, casein phosphopeptide amorphous calcium fluoride phosphate; QLF, quantitative light-induced fluorescence.
¶Effective sample size for analysis.

instructions. Two studies used placebo, while the other studies used as controls F varnish, home-based flossing instructions, and flasks of 0.2% NaF. The diagnostic methods used to assess noncavitated carious lesions comprised visual criteria (Downer and ICDAS), endoscopic examination CDR-CAM, bitewing and digital radiography. All the studies except two (33, 34) reported overall significant differences between test and control groups at follow-up. In particular, Martignon et al. (36) reported that the percent of caries progression among approximal surfaces that were sealed was lower than those assigned to a home-based flossing control after 12 months (test: 27%, control: 51%) and 2.5 years (test: 46%, control: 71%). A second study conducted by the same author in 2012 (37) that evaluated infiltration and sealants versus placebo found significant differences between infiltration versus placebo (lesion progression 32% versus 70%, respectively, *P*-value: 0.001) and sealants versus placebo (41% versus 70%, *P*-value: 0.029) but no statistical difference between sealants and infiltration after a 3-year period. In another study, Paris et al. (38) reported a significant difference between infiltration versus placebo in the percentage of progression in lesion depth (test: 7%, placebo: 37%, *P*-value: 0.021). No concealment of allocation and lack of ITT were the major issues in the studies rated as 'fair'. All these studies were found to have moderate to high risk of bias except one (38) (Table 4).

Combination (n = 2 studies)

Two trials evaluated the combination of two preventive interventions to reduce early carious lesions. These studies explore the use of an antimicrobial varnish (CHX) in combination with a F varnish (39, 40). Sample sizes for the trials ranged from 80 subjects to 220 and were conducted between 12 and 72 weeks (loss to follow-up ranged from 0% to 5%). One study evaluated permanent dentition, while the other one assessed primary teeth, and they were conducted in Sweden and Brazil. Both studies used visual criteria to detect noncavitated lesions. Guedes de Amorin et al. (40) reported significant differences in WSLs mean variations between test and control between the first and third months of the study and between the third month and the baseline. The authors concluded that the combined application of CHX and F varnishes was more effective on remineralization of incipient caries than the same agents applied separately. Both studies were found to have high risk of bias (Table 2).

Discussion

Several scales have been used to assess the validity and 'quality' of RCTs (41, 42). Because there is no 'gold standard' for the 'true' validity of a trial, the possibility of validating any proposed scoring system is limited. In this review, we applied three different methods for quality assessment and found large variations in the way a study is decided to be free from bias. ADA's clinical recommendations heavily emphasize the ITT as a key criterion to rank a study 'Good' or 'Fair'. 'Intention to treat' is a strategy for the analysis of RCTs that compares patients in the groups to which they were originally randomly assigned. This is generally interpreted as including all participants, regardless of the treatment actually received, and subsequent withdrawal or deviation from the protocol (43). Clinical effectiveness may be overestimated if an ITT is not undertaken (44). This analysis is therefore most suitable for pragmatic trials of effectiveness, where the objective is to identify the utility of a treatment for clinical practice rather than for explanatory investigations of efficacy, which aim to isolate and identify the biologic effects of treatment (45). In this sense, the information from most of the trials assessed in this review is limited for making decisions about how to treat future patients. In contrast, Cochrane's quality assessment centers on the fact that ranking a study in different risk categories of bias (low, medium, high) will most likely be appropriate if only a few assessment criteria are used and if all the criteria address only substantive, important threats to the internal validity of the study and the extrapolation of the results to different populations (12). Inadequate concealment of allocation and lack of blinding are known to result in over-estimates of the effects of treatment. Hence, ranking the studies based on these two characteristics seemed to be more consistent with the consensus process undertaken by the authors and demonstrated that more than half of the trials had moderate to high risk of bias or may be categorized as 'poor'. A previous systematic review in the topic (3) concluded that the most problematic aspect among the studies assessed at that time was the lack of standardized

Table 4. Summary information and quality scores for studies on sealants/resin infiltration (n = 6)

Author/ year	N	Duration	Age at start	Intervention			Loss to follow up	Outcome					Authors quality score	ADA quality score	Coch rane (risk of bias)
				Test	Control	Dx method		Definition outcome	Com parison	Test	Control	Overall significance			
Gomez et al., 2005	50	2 years	10–20 years old	Group1: sealants (concise), Group2: sealants or F varnish	F varnish	Visual + BW radiographs	0%	Number and% enamel caries with no progression	BL	Group 1: 115 Group 2: s-38 fv-33	Group 3: 76	NR	Poor	Poor	High
									Year 2	Group 1: 107 (93%) Group 2: s-35 (92.1%) fv-29 (87.9%)	Group 3: 67 (88.2%)	NS			
Florio et al., 2001	34 (31¶)	12 months	6 years old	Group 1: Resin GI Vitremer, Group 2:2.26% F varnish Duraphat every 6 months	Flasks 0.2% NaF + 1500 ppm F TR	Visual (Downer) + endoscopic exan CDR-CAM + digital radiography	9%	% caries progression	BL	Group 1: 0%, Group 2: 5.5%	6.10%	NS	Poor	Poor	High
									12 months	Group 1: −0.35 ± 0.74, Group 2: −0.47 ± 0.77, Group 3: −0.55 ± 0.99	Group 4: −0.21 ± 0.63	NS			
Martignon et al., 2006	82 (72¶)	18 months	15–39 years old	Sealant (concise) + home - based flossing instructions	Home -based flossing instructions	BW radiography	12.20%	% caries progression	BL-18 months	43.50%	84.10%	S	Poor	Poor	High
				Sealant (single one bond)	Home - based	BW radiography + Visual (ICDAS)									

Table 4 **Continued**

Author/ year	N	Duration	Age at start	Intervention			Loss to follow up	Definition outcome	Com parison	Outcome		Overall significance	Authors quality score	ADA quality score	Coch rane (risk of bias)
				Test	Control	Dx method				Test	Control				
					flossing instructions										
Martignon et al., 2010	91 (56¶)	2.5 years	4–6 years old				38%	% caries progression	12 months	27%	51%	S	Poor	Poor	Moderate
								2.5 years Progression lesion depth	46%	71%	S			
				Resin infiltration Icon	Rlacebo: water as infiltrant instead of HCL gel	BW radiography + visual									
Paris et al, 2010	22	18 months	18–35 years old				0%		BL-18 months	7%	37%	S	Good	Fair	Low
				Group 1: infiltration Icon Group 2: sealant (prime bond NT)		Digital subtraction radiography + visual (ICDAS)				Group 1: 32% Group 2: 41%	Placebo: 70%	S (for differences between GA and Placebo, and GB and placebo. No differences between GA and GB)			
Martignon et al., 2012	39 (36¶)	3 years	16–35 years old		Placebo		5%	% lesion progression	3 years				Poor	Poor	Moderate

NS, non significant.
¶Effective sample size for analysis.

criteria for initially identifying these lesions and for assessing their progression. In this regard, there has been a progress as all the studies included in this review objectively assessed NCCIs, and the proportion of excluded studies where the definition of the caries outcome was unknown was relatively small. Slightly more than one-third of the studies included used some type of laser fluorescence method alone or in combination with visual criteria to diagnose these lesions. These findings support that some of those methods have the ability to measure demineralization and also remineralization of NCCIs, and the measures of mineral density change are primary indicators of the cumulative status of the dental caries lesion (46). The variation in clinical outcomes (caries incidence, increment in WSLs, percentage caries progression, lesion depth, lesion area, and integrated fluorescence loss among others) remains, but it is to some extent a consequence of the new detection methods that are being used in these studies. Also, the reporting of the progression and regression of initial caries lesions rather than the differences in overall caries experience is an important methodological improvement in the conduct of these trials, as previous research had demonstrated that not doing so resulted in poor results and outcomes for remineralization technologies (47).

Based on the number of studies, the quality and the findings, fluoride interventions using vehicles such as varnishes, gels, and toothpaste seem to have the most consistent benefit in decreasing the progression and incidence of noncavitated carious lesions. The interventions that relied on the use of xylitol or CHX vehicles alone or in combination with fluoride therapy are very limited in number and in the majority of the cases did not show a statistically significant reduction in noncavitated lesions. This finding is aligned with the recommendations made by a panel of experts convened by the ADA regarding the efficacy of nonfluoride agents in reducing the incidence of caries and arresting or reversing the progression of the disease (48).

On the other hand, the current evidence *in vivo* supporting the efficacy of casein derivatives has increased in number (from 2 to 6 randomized clinical trials) and in quality during the last 4 years, when the last systematic review on this area was published (49). However, only two studies in the current review reported a slowed progression of carious lesions with the use of a CPP-ACP gum and a cream (28, 29). It is worth noting that one of these studies employed one of the largest sample sizes among all the trials assessed (n = 2720) (28) and was conducted for a period of 2 years taking into consideration most of the key design and statistical aspects in clinical trials. Future studies using casein derivatives will confirm if this positive findings using gum as a vehicle may be replicated in other populations with higher risk of dental caries.

Finally, sealants and resin infiltration are nonsurgical methods that have been tested in different populations with varying levels of caries risk with a relatively higher frequency than other interventions and are pointing also to a potential consistent benefit in slowing the progression or reversing NCCIs, which supports clinical recommendations based by the ADA in 2008 (50). However, all the studies that yielded statistical significant differences between test and control groups used 'split mouth designs'. The main purpose of the split-mouth design is to remove all components related to differences between subjects from the treatment comparisons. By making within-patient comparisons, rather than between-patient comparisons, the error variance of the experiment can be reduced, obtaining more powerful statistical tests (51). NCCIs may regress, progress, or fluctuate in severity during the period of investigation independent of treatment. Early lesions that are subject to periodic variation could result in the effects of treatment being confounded by fluctuations in the disease process itself.

Conclusion

More than half of the trials assessed had moderate to high risk of bias or may be categorized as 'poor'. Based on the number of studies, the quality and the findings, fluoride interventions using vehicles such as varnishes, gels, and toothpaste seem to have the most consistent benefit in decreasing the progression and incidence of NCCIs. The studies, whose interventions relied on the use of xylitol, CHX, and CPP-ACP vehicles alone or in combination with fluoride therapy, are very limited in number and in the majority of the cases did not show a statistically significant reduction in these early lesions. Sealants and resin infiltration studies point to a potential consistent benefit in slowing the progression or reversing NCCIs.

Acknowledgements

This study was sponsored by a research grant from the Colgate Palmolive Company. Prof. Roger Ellwood is an employee of the Colgate Palmolive Company.

References

1. Autio-Gold JT, Tomar SL. Prevalence of noncavitated and cavitated carious lesions in 5-year-old head start schoolchildren in Alachua County, Florida. Pediatr Dent 2005;27:54–60.
2. Ismail AI, Brodeur J-M, Gagnon P, Payette M, Picard D, Hamalian T et al. Prevalence of non-cavitated and cavitated carious lesions in a random sample of 7–9-year-old schoolchildren in Montreal, Quebec. Community Dent Oral Epidemiol 1992;20:250–5.
3. Bader JD, Shugars DA, Bonito AJ. A systematic review of selected caries prevention and management methods. Community Dent Oral Epidemiol 2001;29:399–411.
4. Ismail AI, Sohn W, Tellez M, Amaya A, Sen A, Hasson H et al. The International Caries Detection and Assessment System (ICDAS): an integrated system for measuring dental caries. Community Dent Oral Epidemiol 2007;35:170–8.
5. Anusavice K. Efficacy of nonsurgical management of the initial caries lesion. J Dent Educ 1997;61: 895–905.
6. Buchalla W, Attin T, Shulte-Monting J, Hellwig E. Fluoride uptake, retention,and remineralization efficacy of a highly concentrated fluoride solution on enamel lesions *in situ*. J Dent Res 2002;81:329–33.
7. Longbottom C, Ekstrand K, Zero D. Traditional preventive treatment options. Monogr Oral Sci, 2009;21:149–55.
8. Longbottom C, Ekstrand K, Zero D, Kambara M. Novel preventive treatment options. Monogr Oral Sci, 2009;21:156–63.
9. Neuhaus KW, Longbottom C, Ellwood R, Lussi A. Novel lesion detection aids. Monogr Oral Sci, 2009;21:52–62.
10. Centre for Evidence-based Medicine from the University of Oxford for Prognosis; available at: http://www.cebm.net/ [last accessed 12 December 2011].
11. Center for Evidence Based Dentistry American Dental Association (ADA Clinical Recommendations Handbook) October 29, 2009.
12. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. available at: HYPERLINK "http://www.cochrane-handbook.org" www.cochrane-handbook.org [last accessed 3 December 2012].
13. Zantner C, Martus P, Kielbassa AM. Clinical monitoring of the effect of fluorides on long-existing white spot lesions. Acta Odontol Scand 2006;64: 115–22.
14. Biesbrock AR, Faller RV, Bartizek RD, Court LK, McClanahan SF. Reversal of incipient and radiographic caries through the use of sodium and stannous fluoride dentifrices in a clinical trial. J Clin Dent 1998;9:5–10.
15. Karlsson L, Lindgren LR, Trollsås K, Angmar-Månsson B, Tranæus S. Effect of supplementary amine fluoride gel in caries-active adolescents. A clinical QLF study. Acta Odontol Scand 2007;65: 284–91.
16. Feng Y, Yin W, Hu D, Zhang YP, Ellwood RP, Pretty IA. Assessment of autofluorescence to detect the remineralization capabilities of sodium fluoride, monofluorophosphate and non-fluoride dentifrices. Caries Res 2007;41:358–64.
17. Schirrmeister JF, Peter J, Jörg Altenburger M, Schulte J, Hellwig E. Effect of dentifrice containing 5000 ppm fluoride of non-cavitated fissure carious lesions *in vivo* after 2 weeks. Am J Dent 2007;20:212–6.
18. Du M, Cheng N, Tai B, Jiang H, Li J, Bian Z. Randomized controlled trial on fluoride varnish application for treatment of white spot lesion after fixed orthodontic treatment. Clin Oral Invest 2012;16:463–8.
19. Tranæus S, Al-Khateeb S, Björkman S, Twetman S, Angmar-Månsson B. Application of quantitative light-induced fluorescence to monitor incipient lesions in caries-active children. A comparative study of remineralization by fluoride varnish and professional cleaning. Eur J Oral Sci 2001;109:71–5.
20. Ferreira JMS, Aragão AKR, Rosa ADB, Sampaio FC, de Menzes VA. Therapeutic effect of two fluoride varnishes on white spot lesions: a randomized clinical trial. Braz Oral Res 2009;23:446–51.
21. Agrawal N, Pushpanjali K. Feasibility of including APF gel application in a school oral health promotion program as a caries-preventive agent: a community intervention trial. J Oral Sci 2011;53:185–91.
22. Ferreira MA, Latorre Mdo R, Rodrigues CS, Lima KC. Effect of regular fluoride gel application on incipient carious lesions. Oral Health Prev Dent 2005;3:141–9.
23. Truin G-J, Van't Hof M. The effect of fluoride gel on incipient carious lesions in a low caries child population. Community Dent Oral Epidemiol 2007;35:250–4.
24. Truin G-J, van't Hof MA. Caries prevention by professional fluoride gel application on enamel and dentinal lesions in low-caries children. Caries Res 2005;39:236–40.
25. Lundström F, Krasse B. Caries incidence in orthodontic patients with high levels of *Streptococcus mutans*. Eur J Orthod 1987;9:117–21.
26. Stecksén-Blicks C, Holgerson PL, Twetman S. Effect of xylitol and xylitol-fluoride lozenges on approximal caries development in high-caries risk children. Int J Paediatr Dent 2008;18:170–7.
27. Andersson A, Sköld-Larsson K, Hallgren A, Petersson LG, Twetman S. Effect of a dental cream containing amorphous calcium phosphate complexes on white spot lesion regression assessed by laser fluorescence. Oral Health Prev Dent 2007;5:229–33.
28. Morgan MV, Adams GG, Bailey DL, Tsao CE, Fischman SL, Reynolds EC. The anticariogenic effect of sugar-free gum containing CPP-ACP nanocomplexes on approximal caries determined using digital bitewing radiography. Caries Res 2008;42:171–84.
29. Bailey DL, Adams GG, Tsao CE, Hyslop A, Escobar K, Manton DJ et al. Regression of post-orthodontic lesions by remineralizing cream. J Dent Res 2009;88:1148–53.

30. Bröchner A, Christensen C, Kristensen B, Tranæus S, Karlsson L, Sonnesen L et al. Treatment of post-orthodontic white spot lesions with casein phosphopeptide-stabilized amorphous calcium phosphate. Clin Oral Invest 2011;15:369–73.
31. Jörg Altenburger M, Gmeiner B, Hellwig E, Wrbas K-T, Schirrmeister JF. The evaluation of fluorescence changes after application of casein phosphopeptides (CPP) and amorphous calcium phosphate (ACP) on early carious lesions. Am J Dent 2010;23:188–92.
32. Beerens MW, van der Veen MH, van Beek H, Ten Cate JM. Effects of casein phosphopeptide amorphous calcium fluoride phosphate paste on white spot lesions and dental plaque after orthodontic treatment: a 3 month follow-up. Eur J Oral Sci 2010;118:610–7.
33. Gomez SS, Basili CP, Emilson CG. A 2-year clinical evaluation of sealed non cavitated approximal posterior carious lesions in adolescents. Clin Oral Invest 2005;9:239–43.
34. Flório FM, Pereira AC, Meneghim Mde C, Ramacciato JC. Evaluation of non-invasive treatment applied to occlusal surfaces. J Dent Child 2001;68:326–31.
35. Martignon S, Ekstrand KR, Ellwood R. Efficacy of sealing proximal early active lesions: an 18-month clinical study evaluated by conventional and subtraction radiography. Caries Res 2006;40:382–8.
36. Martignon S, Tellez M, Santamaria RM, Gomez J, Ekstrand ER. Sealing distal proximal caries lesions in first primary molars: efficacy after 2.5 years. Caries Res 2010;44:562–70.
37. Martignon S, Ekstrand KR, Gomez J, Lara JS, Cortes A. Infiltrating/sealing proximal caries lesions: a 3 year randomized clinical trial. J Dent Res 2012;91:288–92.
38. Paris S, Hopfenmuller W, Meyer-Lueckel H. Resin infiltration of caries lesions; an efficacy randomized trial. J Dent Res 2010;89:823–6.
39. Øgarrd B, Larsson E, Henriksson T, Birkhed D, Bishara SE. Effect of combined application of antimicrobial and fluoride varnishes in orthodontic patients. Am J Orthod and Dentofacial Orthop 2001;120:28–35.
40. Guedes de Amorim R, Leal SC, Cristina A, Bezerra B, de Amorim FP, de Toledo OA. Association of chlorhexidine and fluoride for plaque control and white spot lesion remineralization in primary dentition. Int J Pediatr Dent 2008;18:446–51.
41. Moher D, Jadad A, Nichol G, Penman M, Tugwell T, Walsh S. Assessing the quality of domized controlled trials: an annotated bibliography of scales and checklists. Control Clin Trials 1995;16:62–73.
42. Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials: current issues and future directions. Int J Technol Assess Health Care 1996;12:195–208.
43. Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials 2000;21:167–89.
44. Lewis JA, Machin D. Intention to treat—who should use ITT? Br J Cancer 1993;68:647–50.
45. Petrie A, Bulman JS, Osborn JF. Further statistics in dentistry Part 3: clinical trials 1. Br Dent J 2002;193:495–8.
46. Pitts NB, Stamm JW. International Consensus Workshop on Caries Clinical Trials (ICW-CCT): final consensus statements—agreeing where the evidence leads. J Dent Res 2004;83:C125–8.
47. Pretty IA. Caries detection and diagnosis: novel technologies. J Dent 2006;34:727–39.
48. Rethman MP, Beltran-Aguilar ED, Billings RJ, Burne RA, Clark M, Donly KJ et al. Nonfluoride caries-preventive agents executive summary of evidence-based clinical recommendations. J Am Dent Assoc 2011;142:1065–71.
49. Azarpazhooh A, Limeback H. Clinical efficacy of casein derivatives a systematic review of the literature. J Am Dent Assoc 2008;139:915–24.
50. Beauchamp J, Caufield PW, Crall JJ, Donly K, Feigal R, Gooch B et al. Evidence-based clinical recommendations for the use of pit-and-fissure sealants. A report of the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 2008;139: 257–68.
51. Hujoel PP, DeRouen TA. Validity issues in split-mouth trials. J Clin Periodontol 1992;19(9 Pt 1):625–7.