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An Update of Controlled Clinical Trials**

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Fluoride Rinses, Gels and Foams: An Update of Controlled Clinical Trials

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Key Words

Caries · Fluoride · Prevention · Root caries · Schoolchildren

Abstract

Aim: The aim of this conference paper was to systematically review the quality of evidence and summarize the findings of clinical trials published after 2002 using fluoride mouth rinses, fluoride gels or foams for the prevention of dental caries. **Methods:** Relevant papers were selected after an electronic search for literature published in English between 2003 and 2014. The included papers were assessed for their risk of bias and the results were narratively synthesized due to study heterogeneity. The quality of evidence was expressed according to GRADE. **Results:** A total of 19 papers were included (6 on fluoride mouth rinse, 10 on fluoride gel and 3 on fluoride foam); 6 had a low risk of bias while 2 had a moderate risk. All fluoride measures appeared to be beneficial in preventing crown caries and reversing root caries, but the quality of evidence was graded as low for fluoride mouth rinse, moderate for fluoride gel and very low for acidulated fluoride foam. No conclusions could be drawn on the cost-effectiveness. **Conclusions:** This review, covering the recent decade, has further substantiated the evidence for a caries-preventive effect of fluoride mouth rinse, fluoride gel and foam, previously established in systematic reviews. The

lack of clinical trials free from bias is, however, still a concern, especially for fluoride mouth rinses and fluoride foam. There is also a scientific knowledge gap on the benefit and optimal use of these fluoride supplements in combination with daily tooth brushing with fluoride toothpaste.

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There is a broad consensus that fluoride prevents caries in children and adults of all ages [Griffin et al., 2007; Marinho, 2009; Gibson et al., 2011]. In this context, self-applied and professional supplements play a significant role. Fluoride mouth rinse has a long tradition as a school-based measure worldwide, but the procedure is also commonly recommended for domestic use for subjects at caries risk, e.g. patients with fixed orthodontic appliances and vulnerable elderly [Rugg-Gunn and Bánóczy, 2013]. Systematic reviews have established a caries-preventive fraction of 24–29% when fluoride mouth rinses are compared with placebo in permanent teeth in schoolchildren and adolescents, as well as for root caries reversal/arrest in older adults [Marinho et al., 2003a; Twetman et al.,

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2004]. The quality of evidence was, however, rated as limited [Twetman et al., 2004]. Fluoride gels are professionally applied in trays and display a preventive fraction of 21% compared with placebo [Marinho et al., 2003b]. Neutral or acidulated fluoride foam is a professional option to gel but less studied in clinical trials. An updated systematic review of topical fluorides for caries with clinical recommendations has recently been released by the ADA Center for Evidence-Based Dentistry [Weyant et al., 2013]. The strength of the clinical recommendations were moderate for the daily or weekly use of fluoride mouth rinses in school-aged children, while the use of gels and foams was questioned, especially for coronal caries in adults and root caries. Since the methodology in systematic reviews might differ with respect to inclusion criteria and quality assessment, continuous updates and critical appraisals of the literature may be of importance in order to reinforce evidence and identify possible knowledge gaps. The aim of this conference paper was to examine and summarize the findings of controlled clinical trials published after 2002 using fluoride mouth rinses, fluoride gels or foam for the prevention of dental caries.

Methods

Search Strategy and Inclusion Criteria

The systematic reviews from the Cochrane Library and The Swedish Council of Technology Assessment in Health Care formed the basis for this paper. Three sources were searched from 2003 throughout January 2015 for reports on controlled clinical trials: PubMed, the Cochrane Library and the Trip Database. The key words were 'fluoride mouth rinse', 'fluoride mouth wash', 'fluoride gel', 'fluoride foam' and 'incipient lesions', 'caries', 'dental decay', 'root caries' in various combinations. The full search strategy is shown in online supplement 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000439180). The abstract list, containing 219 hits, was independently assessed by the two authors and papers of potential relevance were selected. Diverging opinions were solved in consensus. To be considered for inclusion, a full description of a controlled clinical trial (randomized or non-randomized) including more than 40 subjects in each arm was needed. Furthermore, a caries end point (prevalence, incidence, increment, progression, regression) expressed with continuous or categorical data from a clinical and/or radiographic examination was required. In addition, health-economic evaluations were included. Only papers published in English were accepted. Multi-content rinses, gels and foams, such as fluoride combined with antibacterial agents, were disregarded in this review. Likewise, papers describing in situ studies, artificial caries lesions and mouth rinses, gels or foam application as part of a comprehensive preventive programme (except fluoride toothpaste) were not taken into account. The reference lists of accepted papers and systematic reviews were hand-searched for additional literature.

Table 1. Quality of evidence according to GRADE [Guyatt et al., 2011]

High (⊕⊕⊕⊕): based on high- or moderate-quality studies containing no factors that weaken the overall judgment
Moderate (⊕⊕⊕○): based on high- or moderate-quality studies containing isolated factors that weaken the overall judgment
Low (⊕⊕○○): based on high- or moderate-quality studies containing factors that weaken the overall judgment
Very low (⊕○○○): the evidence base is insufficient when scientific evidence is lacking; quality of available studies is poor or studies of similar quality are contradictory

Data Extraction

Key data from the accepted studies were extracted independently by both authors and compiled in tables. Due to the low number and diversity of the included studies, a narrative descriptive synthesis was carried out. When possible, the effect of the selected measures was calculated as the difference between caries increment or prevalence in the control group and the experimental group divided by the increment or prevalence in the control group. This preventive fraction was expressed as percent.

Quality Assessment

The quality of the selected publications was assessed according to predetermined criteria for methodology and performance. The criteria from the Cochrane handbook for interventions [Higgins et al., 2011] was used and the risk of bias for each paper was graded as 'low', 'moderate' or 'high'. The quality of evidence was rated with the GRADE tool [Guyatt et al., 2011] in four categories, as shown in table 1. Studies describing a cost analysis of the various programmes were not quality assessed.

Results

In total, 19 publications describing 17 clinical trials were accepted and quality assessed, as presented in figure 1. In addition, 4 papers on health economy were included. Excluded clinical studies with caries and/or lesion remineralization as end points are listed in the online supplementary material with the main reason for exclusion (online supplements 2 and 3).

Fluoride Mouth Rinse

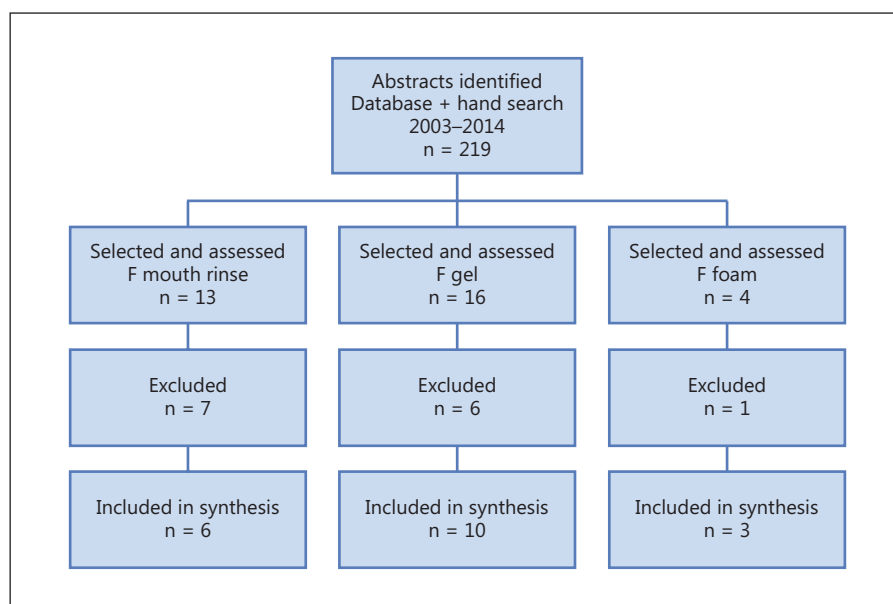
Fluoride mouth rinses are typically based on neutral sodium fluoride solutions ranging from 0.05 to 0.2% (225–1,000 ppm) and intended for subjects 6 years of age and over. In Europe, amine and stannous fluoride formulations are also available. The conclusions from the Cochrane review were based on 34 trials [Marinho et al., 2003a]. In the

Table 2. Summary of controlled clinical trials on the effect of fluoride mouth rinses

First author [year]	Design	Number; duration	Age, years	Intervention; frequency; concentration	Control	Preventive fraction	Risk of bias
<i>School-based rinsing</i>							
Moberg Sköld [2005]	RCT	269; 3 years	13–16	SB FMR; 1/14 days; 0.2% NaF	no FMR	41% ^a	moderate
Levin [2009]	cohort	1,333; –	5, 11	SB FMR; 1/14 days; 0.2% NaF	no FMR	OR 0.79 ^b	high
Chen [2010]	CCT	270; 3 years	8–9	SB FMR; 1/week; 0.2% NaF	no FMR	RR 48% ^c	high
Takeuchi [2012]	CCT	109; 6 years	10	SB FMR; 1/week; 0.2% NaF	no FMR	51%	high
<i>Root caries</i>							
Wyatt [2004]	RCT	247; 2 years	83 (mean)	FMR; 1/day; 0.09% NaF	placebo	24% ^d	high
Petersson [2007]	RCT	100; 1 year	55–81	FMR; 2/day; 250 ppm AmF	placebo	57% ^e	high

PF = Preventive fraction; SB = school-based; FMR = fluoride mouth rinse; CCT = controlled clinical trial.

^a Proximal surfaces from bitewing radiographs. ^b Odds for a tooth being decayed (95% CI 0.65–0.96). ^c Risk of developing caries (95% CI 0.26–0.85). ^d Most pronounced in reversing and preventing root surfaces. ^e Root caries reversals.

**Fig. 1.** Flowchart of the literature.

present review, 6 further studies were included, of which 4 dealt with schoolchildren and 2 with the management of root caries (table 2). The studies were small- to medium-sized and performed in Canada, Scotland, Sweden, Malaysia and the Kingdom of Tonga. One study was rated as being of moderate risk of bias while the rest were assessed

with high risk. The school-based programmes utilized weekly or bi-weekly 0.2% NaF rinses compared with no rinses and the results were generally in favour of the rinses. Notably, the results obtained in the Swedish study were obtained in a 'low to medium caries risk area' with self-reported use of fluoride toothpaste twice daily and annual

Table 3. Summary of controlled clinical trials on the effect of fluoride gels applied in trays

First author [year]	Design	Number; duration	Age, years	Intervention; frequency	Control	Preventive fraction	Risk of bias
van Rijkom [2004]	RCT	773; 4 years	4–6	NaF gel ^a ; bi-annual	placebo	26% ^b	low
Truin [2005a]	RCT	773; 4 years	4–6	NaF gel ^a ; bi-annual	placebo	22% ^c	low
Truin [2005b]	RCT	594; 4 years	9–11	NaF gel ^a ; bi-annual	placebo	18%	low
Jiang [2005a]	cluster RCT	661; 24 months	6–7	APF gel ^d ; bi-annual	no gel	37% ^b	high
Ferreira [2005]	RCT	307; 3 months	12	APF gel ^d ; weekly	placebo	n.s. ^e	high
Truin [2007]	RCT	517; 4 years	9–11	NaF gel ^a ; bi-annual	placebo	23% ^f	low
Andruskeviciene [2008]	RCT	411; 3 years	3	APF gel ^d ; 3/year	no gel	60%	high
Ersin [2008]	RCT	99; 2 years	11–13	NaF gel ^a ; bi-annual	OHE ^g	n.s.	high
Stokes [2011]	RCT	1,075; 2 years	12–13	NaF gel ^a ; 2/week, in school	NaF gel, 1/week, domestic	14–26%	low
Agrawal [2011]	cluster RCT	257; 1 year	9–16	APF gel ^d ; bi-annual	OHE	61% ^h	high

^a 1% NaF gel. ^b Dentin caries only. ^c Re-analysis of van Rijkom et al. [2004] including initial lesions. ^d 1.23% APF gel. ^e No significant difference, white spot lesion arrest. ^f Re-analysis of Truin et al. [2005b] including initial lesions. ^g Oral health education programme. ^h Incipient lesions only, no significant effect on DMFS.

applications of a fluoride varnish [Moberg Sköld et al., 2005]. Another interesting observation from Scotland was that the mean prevalence of cavitated lesions was higher for non-rinsing subjects than for fluoride rinsers in all socio-economic categories [Levin et al., 2009]. One study in adults investigated daily rinses with 0.09% NaF in institutionalized elderly and the net incidence of both crown and root caries was significantly reduced over a 2-year period [Wyatt and MacEntee, 2004]. A second adult study evaluated the effect of twice-daily amine fluoride rinses as an addition to the daily use of fluoride toothpaste on the reversal of primary root caries lesions [Pettersson et al., 2007] and the rinses seemed to boost the arresting effect. The overall caries-preventive effects in the recent studies were mainly of the same magnitude as those suggested in previous systematic reviews. The quality of evidence, however, was still to be regarded as low (⊕⊕○○).

Fluoride Gel

In the USA, flavoured acidulated phosphate fluoride (APF) gels and foams were the most widely used office-

applied topical agents from the late 1960s until the 2000s, when they gradually were replaced by fluoride varnishes [Newbrun, 2011]. The systematic review by Marinho et al. [2003b] was based on 23 studies and this updated literature search revealed 10 additional fluoride gel publications from 8 clinical trials published after 2002 (table 3). All study groups consisted of children; 4 trials employed a neutral sodium fluoride gel and 4 an APF gel. The risk of bias was contrasting; 5 papers had a low risk and 5 had a high risk. The outcome was generally beneficial for the sodium fluoride gel with a preventive fraction around 18–26%, albeit some authors concluded that this reduction was ‘not clinically relevant’ [van Rijkom et al., 2004; Truijn and van ’t Hof, 2005a]. Two studies displayed non-significant differences between the test and control groups; in 1 study, the APF gel applications were additional to supervised tooth brushing with fluoride toothpaste [Ferreira et al., 2005] and the other compared sodium fluoride gel applications with a comprehensive oral health programme in children [Ersin et al., 2008]. The most recent contribution [Stokes et al., 2011] showed a small advan-

Table 4. Summary of controlled clinical trials on the effect of APF foam (1.23%, pH 3.5) applied in trays

First author [year]	Design	Number; duration	Age, year	Intervention; frequency	Control	Preventive fraction	Risk of bias
Jiang [2005a]	cluster RCT	661; 24 months	6–7	APF foam; bi-annual	no treatment	41% ^a	high
Jiang [2005b]	cluster RCT	392; 24 months	3–4	APF foam; bi-annual	placebo	24%	moderate
Jiang [2013]	RCT	100; 18 months	10–20	APF foam; bi-monthly	placebo	76% ^b	low

^a Limited to smooth surfaces on 1st permanent molars. ^b Increment of white spot lesions adjacent to fixed orthodontic brackets.

tage of twice-weekly supervised brushing with a self-applied high-fluoride gel (12,500 ppm) on the increment of dentin lesions in comparison with a once-weekly domestic use. Collectively, the included trials on fluoride gel provided evidence of moderate quality ($\oplus\oplus\oplus\circ$) that professional and self-applied fluoride gels are associated with a clear reduction in caries increment in the young permanent dentition. There was no information retrieved to question the safety of fluoride gels.

Fluoride Foam

The APF foam has the same fluoride concentration (12,300 ppm) and pH as APF gels. Typically, the foam is professionally applied in a trimmed sponge-lined tray and the patient is asked to keep biting in the tray for 4 min while leaning forward. The advantage with the foam compared with the gel is that only one fifth of the amount by weight is needed for an adequate coverage of the teeth. Three studies from China involving children and adolescents were included and summarized in table 4. The preventive fraction was 24% in the primary dentition [Jiang et al., 2005b], 41% for smooth surfaces of first permanent molars [Jiang et al., 2005a] and 76% concerning the increment of white spot lesions around orthodontic brackets [Jiang et al., 2013]. Notably, no preventive effect was displayed in fissures located on occlusal surfaces. Furthermore, in all study groups, the tooth-brushing habits were highly irregular and less than 50% used fluoride toothpaste. Although the external validity was limited, it seems that professional applications of fluoride foam may have a caries-preventive potential of the same magnitude as fluoride gel. The quality of evidence must, however, be regarded as very low ($\oplus\circ\circ\circ$) due to the small number of studies available and the fact that all originate from one single research group.

Cost Efficacy

The literature concerning health-economy was scarce and not more than 4 relevant papers were identified. In a Swedish study, the ‘natural course’ of proximal caries progression was modelled during 4–8 years after 3-year school-based fluoride varnish and fluoride mouth rinse programmes in schoolchildren [Sköld et al., 2008]. The results suggested that the fluoride varnish strategy had a better outcome at 50% lower costs. On the other hand, school-based fluoride mouth rinse programmes may be cheaper than supervised tooth-brushing programmes [Chen et al., 2010]. In Chile, Mariño et al. [2012] compared the costs required to prevent 1 carious tooth among schoolchildren with various preventive measures and found that salt fluoridation was the most cost-effective, with APF gel ranked as the least cost-effective. Furthermore, fluoride varnish applications were found to take less time and resulted in fewer signs of discomfort than foam in high-risk children [Hawkins et al., 2004]. Although the above-mentioned cost analyses may not fully mirror all direct, indirect and tangible costs of caries prevention, the data might be helpful and suggestive to policymakers and community oral health planners.

Discussion

This 12-year update revealed only 19 ‘new’ clinical trials concerning fluoride mouth rinse, fluoride gel and foam, which certainly indicates that these research areas are far from being ‘hot topics’. An explanation could be that the caries-preventive effect of fluoride is already so obvious that further studies are a waste of time and money. However, a main concern was that the scientific

quality of many of the recent studies was suboptimal and, thus, very little was added to our evidence-based knowledge. This was especially true for fluoride mouth rinses since this is a procedure that is widely recommended in textbooks and by professionals, especially for patients with increased risk [Weyant et al., 2013]. It can be argued that fluoride mouth rinses are out of topic for this conference since they seldom are 'beyond' 1,000 ppm F. On the other hand, there are still some diverging opinions whether or not school-based fluoride rinses are beneficial in populations with regular use of fluoride toothpaste [Twetman et al., 2004; Moberg Sköld et al., 2005; Marinho, 2009] or whether this measure only 'pays off' in vulnerable risk groups. Levin et al. [2009] did not demonstrate a socioeconomic gradient of efficacy, while Divaris et al. [2012] found the most substantial caries-preventive benefits from long-term fluoride mouth rinse participation were obtained in high-risk schools. A recent systematic review has suggested that root caries patients can benefit from fluoride mouth rinses compared with a placebo rinse but the conclusion was based on very few well conducted RCTs [Wierichs and Meyer-Lueckel, 2015].

The relatively low interest in fluoride gels and foams may be understood in the light of the global increase in fluoride varnishes, with subsequent research attention. The results from the trials included in this review underlined that the preventive fraction from the gels and foams generally is inferior to that of fluoride varnish [Marinho et al., 2013], although no recent head-to-head comparisons seemed to be available. For the individual patient, however, a variety of professional fluorides is essential in order to meet personal preferences, flavour and convenience of application. Such factors, along with costs and reimbursement systems, are likely to be more important for the patient than minor differences in effectiveness. The lack of gel and foam data covering adults and vulnerable elderly was striking, as well as the shortage of benefit-harm assessments and economical evaluations. Elderly patients often have an impaired saliva function due to aging and polypharmacy and perceive tooth brushing as physically difficult. In these cases, fluoride mouth rinses and self-applied fluoride gels or foams could be an option that merits further clinical research.

This update was conducted mainly in accordance with the methodology suggested by Siwek et al. [2002] and the literature search was made to overlap the Cochrane reviews summarized by Marinho [2009] and the systematic review of Twetman et al. [2004]. The English language

restriction may have overlooked foreign clinical reports, although this risk might be small according to previous experiences [Morrison et al., 2012]. Another possible shortage was that in situ studies and investigations reporting surrogate end points, e.g. fluoride levels in saliva and plaque after applications, were disregarded. Such studies can never build evidence but indicate how effective a particular regimen can be. For example, Zero et al. [1988] reported fluoride mouth rinsing to be superior to fluoride tooth brushing when it came to residual levels in saliva. This could indicate that tooth brushing with its partial plaque removal should be followed by a fluoride rinse for the remineralization of caries lesions, as suggested by ten Cate [2013].

In conclusion, this review, covering the recent decade, has further substantiated the evidence base for a caries-preventive effect of fluoride mouth rinse, fluoride gel and foam that has previously been established in systematic reviews. The quality of evidence according to GRADE could, however, not be altered. The lack of clinical trials free from bias is still a concern, especially for fluoride mouth rinses and fluoride foam. There is also a scientific knowledge gap on the benefit and optimal use of these fluoride supplements in combination with daily tooth brushing in adults and the elderly.

Disclosure Statement

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