Caries preventive effect of fluoride in milk, salt and tablets: A literature review

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Abstract

BACKGROUND: There are a number of studies in the literature about the effectiveness of fluoride in tablets, fluoride added to frequently-consumed food like milk, or to food additives like salt, in prevention of dental caries. This literature has been evaluated in different evidence based reviews. **AIM:** The scope of this paper was to identify the most recent evidence-based reviews on the effect in caries prevention from added fluoride in milk, salt and fluoride tablets/drops including newer RCT studies, and to synthesize the findings into practice guidelines. The key question was as follows: Does regular use of fluoride in milk, salt and fluoride tablets/drops prevent dental caries among children and adolescents? **METHODS:** MEDLINE, EMBASE and EBM reviews (Cochrane database of systematic reviews) were searched using modified filters from a Cochrane review. One evidence-based report on fluoridated milk was identified. Salt fluoridation was covered by three HTA reviews. One Cochrane protocol on the caries preventive effect of fluoridated salt was identified. **RESULTS:** Very few studies of good quality were identified in general. Two studies on fluoridated milk were tabulated and seven studies dealing with fluoride tablets/drops were analysed. One study showed a 78% reduction in caries in newly erupted permanent teeth among 8 year olds after 3 years with fluoridated milk. For primary teeth one study showed 31% caries reduction. The differences between fluoride-group and control were statistically significant. The reduction in caries prevalence in the fluoride tablet group compared with a negative control varied from 81% (carious surfaces in permanent teeth erupted in the study period) to 49% in DMFS for all permanent teeth. No RCT studies on fluoridated salt were identified. **CONCLUSION:** There is limited evidence that F tablets and drops are effective, and compliance is a key factor. There are good reasons to believe that fluoride in different applications and formulas does work as caries preventive agents under supervision. There is a need for new, well-designed studies within this field, but the use of negative controls without any fluoride exposure is difficult due to ethical reasons. In particular new research is needed concerning possible caries preventive effect of fluoridated milk and salt.

Introduction

Systemic fluoride supplements were developed as alternatives to addition of fluoride (F) to drinking water and the basic idea was that it should reach as many individuals in the target population as possible. The optimum F doses were based on the view that a F content of 1 mg F/L would be the ideal. Based on Dean's 21 cities studies there was a marked drop in caries experience when the F concentration increased towards 1.0-1.2 mg F/L [Burt et al., 1996]. Many studies of the caries inhibition of F supplements were initiated in the period 1960-85. Since the 1970s an increased focus has been on the risk for dental fluorosis and dosage recommendations have tended towards lower doses in many countries [Stephen, 1999].

Fluoridation of drinking water targets the whole population and is a cost-effective method [Burt, 2002]. Caries is directly related to low socio-economic status (SES). It is a challenge to tailor programs based on F supplements that target underprivileged populations. The following key question was addressed in this paper: Does regular use of F supplements such as F-milk, F-salt and F tablets/drops prevent dental caries among children and adolescents? This is the possible beneficial effect of regular exposure to F.

The ingestion of F may give rise to dental fluorosis, but it is outside the scope of this paper to cover this important topic. A recent review gives excellent information about the literature and the relationship between early exposure for F supplements and increased risk for enamel disturbances [Ismail et al., 2008]. The length of the exposure will also play a crucial role in the development of dental fluorosis. Aspects on dental fluorosis have also to be addressed in guidelines for use of F supplements.

The aim of this paper is to identify the most recent evidence based reviews on F added to consumables or F tablets/drops including newer RCT studies, and synthesize the findings into practice guidelines.

Methodology

The critical appraisal of the literature was done in accordance with SIGN methodology for appraising randomised controlled trials [The Scottish Intercollegiate Guidelines Network, 2008], (Table 1). The most recent evidence based reviews on F containing tablets or lozenges, milk and salt were

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Table 2. RCTs on caries preventive effect of fluoridated milk and fluoride tablets. The rating of evidence was completed by the author of this paper.

Author year, Country	Study type	Evidence	Length of follow-up	Patient characteristics	Number of patients at baseline and drop out %	Intervention/control group	Results
Fluoridated milk							
[Stephen et al., 1984], UK	RCT, DB	1-	5 yr data for permanent teeth	4.5-5.5 yr old children in first grade in primary schools in a low socio-economic area.	94 47 %	F-milk, 7,5 mg F/L	defs 22.1 DMFS 3.762
			3 yr data for primary teeth		93 40 %	Ordinary milk.	defs 22.1 DMFS 6.612
More details and comments: Supervised intervention in school. All children consumed 200 mL milk per day using a straw, radiographs were taken. High drop-out. Small groups.							
[Maslak et al., 2004], Russia	RCT, DB	1+	3 yr	3 yr old children in kindergartens	80 6 %	F-milk, 2,5 mg F/L	D3-4MFT 2.501 D3-4MFT 0.04 1
					100 9 %	Ordinary milk.	3.641 0.171
More details and comments: Supervised intervention in kindergartens, small groups, small drop-out. Parents knew what type of milk drunk by their child. Blinding of examiners. Clinical caries recordings only. Some details about the study is collected from the Cochrane review [Yeung et al., 2005].							
Fluoride tablets							
[Stephen et al., 1978], UK	RCT, DB	1+	3 yr	5.5-5.7 yr. Social classes IV & V (low socio-economic area)	61 11%	NaF tablet 1 mg F	DMFS increment new 1st perm molars 0.81 DMFS increment all 1. molars 3.02
					55 13%	Placebo tablet	DMFS increment new 1st perm molars 4.34 DMFS increment all 1. molars 5.96
More details and comments: Supervised intervention in school. Tablets given in schooldays (200 days per year). Radiography. Small groups. Low drop-out.							

[Poulsen et al., 1981], Denmark	RCT	1+	3 yr	7 yr old	161 23 %	NaF tablet 0.5 mg rinse placebo	DMFS increment 2.27
					160 22 %	NaF rinse 0.1 % F tablet placebo	DMFS increment 2.02
				10 yr old	177 27 %	NaF tablet 0.5 mg rinse placebo	DMFS increment 4.90
					172 30 %	NaF rinse 0.1 % F tablet placebo	DMFS increment 4.74
More details and comments: Supervised intervention in school. Tablets given in schooldays (200 days per year). Rinse every second week. Radiography of oldest group. Moderate drop-out. Same dentist performed all examinations. Another dentist examined radiographs – blinded.							
[Driscoll et al., 1979], USA	RCT, DB	1-	6 yr + 1.5 yr post treatment	Mean age 6.6 yr	345 65 % b	APF tablet Daily dosage 1 mg F	DMFS increment 7.70
					345 68 % c	Another APF tablet after ≥3 hours Daily dosage 2 mg F	7.64
					344 64 % a	Placebo tablet	11.35 2
More details and comments: Supervised intervention in school, no radiographs, and high drop-out. No tablets in weekends, holidays, or vacations (max 145 days with tablets per year). One of two dentists was randomly chosen for examination. Tablets most effective in approximal surfaces.							
[Driscoll et al., 1992], USA	RCT	1-	8 yr	5-6 yr, kindergarten or first grade school.	544 58 %	Once a week 60 s rinse 0.2% NaF	DMFS increment 3.57
					537 63 %	Daily NaF tablet 1 mg F	2.83
					559 62 %	Both procedures	2.40 2 (versus rinse)
More details and comments: Supervised intervention in school. Three examiners did the baseline examination and two examiners the 8-yr follow up. No radiographs. High drop-out.							
[Lin et al., 2000], Taiwan	RCT	1-	2 yr	22-24-month old children with cleft lip and/or palate.	46 11%	Daily NaF tablet 0.25 mg F	4.10 (versus control)
					50 20%	x2 daily fluoride drops 0.25 mg F	1.552 (versus control and tablets)
					44 23%	No fluoride supplement (control group)	dmfs increment 8.35

More details and comments: Non-supervised intervention. Non-fluoride toothpaste used in all groups. Two examiners. Small study groups. No radiographs. Compliance was checked and non-compliant participants excluded.							
[Kallestal, 2005], Sweden	RCT	1-	5 yr	12 yr old children with high caries risk.	231	Tooth-brushing group. Written instructions on when and how tooth-brushing with fluoridated toothpaste should be done.	Increment: DMFS (dentin caries) & DeMFS (enamel caries included) 4.1 & 7.0
					213	F-tablet group. 0.25 mg x 3 daily up to 16 years and thereafter 0.25 mg x 4–6 daily.	4.2 & 7.1
					228	Fluoride varnish group. 3 x during 1 week every 6 months.	3.9 & 6.5
					231	Individual programme group. Oral hygiene information and counselling in dental hygiene, teeth were professionally cleansed, and fluoride varnish was applied. Check up every 3 months, F-varnish applied each time.	3.6 & 6.0
More details and comments: The number of participants given is remaining patients after 5 yr. Average drop-out for all groups 18 %. None of the outcome differences were statistical significant.							
[Stecksen-Blicks et al., 2008], Sweden	RCT, DB	1-	2yr	10-12 yr old children with high caries risk	80 30 %	Daily dose 2.5 g xylitol in 2 tablets x3 times daily	DMFS increment approximal 2.7 DSe increment (enamel caries in approximal surfaces) 2.0
					80 26 %	Xylitol as above, but tablets did also contain 0.25 mg F	2.7 1.7
					70 9 %	reference group with no intervention or placebo	1.7 1.0
More details and comments: Supervised intervention in school. Radiographs. Two calibrated examiners evaluated the radiographs. Poor compliance. In intervention groups were 27 and 20 individuals rated as having "Good compliance" respectively.							

1P<0.05, 2P<0.01

identified using search on Medline (January 1990-October 2008). Search terms such as "fluoride tablets", "fluoride lozenges", "fluoridated salt", and "fluoridated milk" were used. In addition relevant reports by Health Technology Assessment (HTA) Agencies and the Cochrane Collaboration Oral Health Group's systematic reviews were identified and the RCT's included were examined and tabulated in Table 2. The full text of each of the papers was assessed by the author.

One Cochrane systematic review report on F-milk was identified [Yeung et al., 2005]. Salt fluoridation was covered by two HTA reviews [National Health and Medical Research Council, 2007; Swedish Council on Technology Assessment in Health Care, 2002]. One Cochrane protocol on the caries preventive effect of F-salt was identified [Gillespie et al., 2005].

For updating the evidence-based reviews identified, literature searches were performed according to the methods described in MEDLINE, EMBASE [Yeung et al., 2005] and EBM reviews (Cochrane database of systematic reviews) using the OVID search engine. For literature on F-milk the following search filter was used:

1. exp FLUORIDES/
2. FLUORIDATION.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (fluori$ or flouri$).mp.
4. or/1-3
5. exp MILK/
6. milk$.mp.
7. (schoolmilk or school-milk).mp.
8. or/5-7
9. 4 and 8
10. limit 9 to yr="2005 – 2009"
11. limit 10 to humans

This search filter was modified also to cover F-salt, F tablets/lozenges, and F-drops in separate searches. The search results were screened in OVID for a decision about papers without relevance and which papers to be read in full text. For selection of studies a longitudinal design was required with parallel groups of randomised participants. The studies needed to include one or more of the F vehicles such as milk, salt, tablets/lozenges, and drops. The search periods differed according to when the evidence-based reports were updated. All searches were updated in December 2008.

In the Cochrane review on F-milk [Yeung et al., 2005] two randomised controlled trials (RCT) were included [Stephen et al., 1984; Maslak et al., 2004]. The two RCTs were compiled and reported in Table 1. There were 27 studies excluded from the review, mainly because they did not have adequate control groups. In an Australian systematic review of the efficacy and safety of fluoridation [National Health and Medical Research Council, 2007] another two recent original publications were included, but none of these were RCTs. In the Australian review the evaluation was that "both studies provided only low levels of evidence for assessing the effectiveness of an intervention". Both studies showed positive effectiveness of F-milk in terms of caries prevention.

With respect to the possible caries preventive effect of F-salt two HTA reviews [National Health and Medical Research Council, 2007; Swedish Council on Technology Assessment in Health Care, 2002] could not identify any RCTs which aimed to examine this. In the report by the Swedish Council on Technology Assessment in Health Care (SBU) 5 studies with low evidence were tabulated, 2 studies were cross-sectional studies and 3 were controlled clinical trials. The Australian review [National Health and Medical Research Council, 2007] identified 3 recent cross-sectional studies which assessed the effectiveness of F-salt for reducing dental caries.

Studies on the caries-preventive effect of F-tablets have been identified and assessed by SBU [Swedish Council on Technology Assessment in Health Care, 2002]. The quality of evidence was graded as medium evidence in 2 studies and low in 2 others. The studies were compiled and are reported in Table 1. Moreover, 3 studies were identified in the period 2000-2008 [Kallestal, 2005; Stecksen-Blicks et al., 2008; Wennhall et al., 2008]. Results from one of the studies were reported in 2 publications, but only the most recent was considered. One paper was excluded because it was not a RCT [Wennhall et al., 2008] and the two other studies were tabulated in Table 1. Based on the literature search 2005-2008 only one RCT study on caries preventive effect of F containing drops (liquid) compared with F-tablets and a negative control, was included [Lin et al., 2000].

Supplements of F were available as chewing gum but have not been explicitly covered within this review. Very few studies are available [Swedish Council on Technology Assessment in Health Care, 2002].

With respect to studies on F-milk, one possible RCT was identified [Pakhomov et al., 2005] in the updated search. The paper was in Russian, but the English abstract indicated that the test group receiving F-milk came from different kindergarten schools than the control group. Accordingly the study design did not follow a strict RCT protocol and the study was not included.

Results

Fluoridated milk. The study of Maslak et al. [2004] had low attrition of participants during the 3 yr study period in contrast to the 5 yr follow-up study by Stephen et al. [1984]. The main results from these studies are given in Table 1 and indicate a caries preventive effect of F-milk. After 3 years, the 6 year olds using the F-milk had 76.4% ($P<0.05$) lower DMFT (permanent teeth) compared with the control group. After 5 years, a positive effect was found also in the other study included (32.2 %, P<0.05), but not after 3 years. For primary teeth a significant caries reduction was demonstrated (31.3 %, P<0.05) in the most recent study, but not in the other. The lower evidence grading of the study by Stephen et al. was based on the high attrition rate of participants.

Fluoridated salt. The 5 studies evaluated by SBU [Swedish Council on Technology Assessment in Health Care, 2002] were all rated with low evidence and SBU concluded that the scientific evidence for assessing the effect of F-salt is insufficient to draw conclusions. The results may indicate that the magnitude of the positive, preventive effect may be comparable to the effect of F drinking water. Three more recent studies were identified by the Australian HTA report [National Health and Medical Research Council, 2007]. All studies aimed to measure caries prevalence before and after introduction of F-salt [Irigoyen et al., 2000; Estupinan-Day et al., 2001; Solorzano et al., 2005]. These studies were conducted in Mexico, Jamaica and Costa Rica respectively. Comparisons of DMFT data showed a significant caries reduction during this time period. However, there was no assessment of, or adjustment for, potential confounding variables [National Health and Medical Research Council, 2007; Yeung, 2008].

Fluoride tablets/drops. One RCT study of good quality demonstrated a high caries preventive effect of F-tablets in children in permanent teeth [Stephen et al., 1978] (Table 1). The dropout rate was low. The greatest caries reduction (DMFS) was obtained for first permanent molars that erupted during the study period (81%). The corresponding reduction for all first permanent molars was 49%. However, the caries prevalence was much higher at the time when the study was carried out compared with nowadays. In another RCT study of good quality F-rinse was used by the comparison group [Poulsen et al., 1981]. There was no statistical significant difference between groups, indicating that F-rinse every fortnight might give equal caries preventive effect to daily F tablet use during school days. A comparison of F-tablets and F-drops with a negative control showed a significant effect of both methods after 2 years in a high caries risk preschool population [Lin et al., 2000]. The best caries preventive effect according to this study was obtained using F-drops twice a day (Table 1).

Discussion

The studies included in the Cochrane review on F-milk [Yeung et al., 2005] in Table 1, indicate that F-milk might be an effective intervention for caries prevention in 3 to 11 yr old children. These studies however, provide insufficient evidence to make a strong recommendation. The results from the two studies assessed could not be pooled due to different F concentrations in the milk. Stephen et al. [1984] used 3 times the concentration used by Maslak et al. [2004]. The recent Australian HTA report on F [National Health and Medical Research Council, 2007] concluded on the basis of two additional, recent studies that they provided only low levels of evidence for assessing the effectiveness of F-milk. However, both studies show consistent results that suggest that this intervention may be an effective method for preventing caries. There is need of well-designed good quality studies examining the potential caries preventive effect of F-milk.

The history of F-salt started in the 1960s in Switzerland, Hungary and Colombia [Marthaler et al., 2005]. One of the key questions when F-salt is introduced is whether there will be non-F alternatives. When most of the salt consumed is with F the caries preventive effect approximates that of F drinking water [Jones et al., 2005]. Burt [2002] argued strongly that F-water is "probably the most significant step we can take toward reducing the disparities in dental caries".

The use of F-salt is recommended by WHO as one alternative method to F-water to also target underprivileged groups with caries preventive measures [Marthaler et al., 2005]. Although no RCTs have been conducted to examine if F-salt has any caries preventive action there are several clinical and epidemiological studies that indicate an effect comparable with that of F water [Burt et al., 1996; Swedish Council on Technology Assessment in Health Care, 2002; National Health and Medical Research Council, 2007]. In the age group 0-3 yrs there is reason to believe that F-salt does not give a caries preventive effect due to the low salt consumption at this young age.

F-salt is shown to give an increase in F concentration in saliva. One study showed that 6 different baked food items prepared with F-salt gave a significant increase in salivary F concentration for up to 20 min [Macpherson et al., 2001]. Fluoridated popcorn increased F in saliva at least 30 min after consumption and probably longer [Björnström et al., 2004]. A dinner meal prepared with F containing salt increased salivary F for about 30 min [Hedman et al., 2006].

There is evidence that F-tablets may prevent caries based on 2 medium and 3 low quality RCTs (Table 1). Additionally one low quality RCT did not find any effect of tablets compared with a negative control [Stecksen-Blicks et al., 2008] and in one study no differences were found between 4 groups with different preventive programs including one using F tablets [Kallestal, 2005]. One major disadvantage with F-tablets is that the effect is dependent upon an individual's compliance that is a problem in underprivileged populations.

National disparities are seen with respect to use of F-tablets. For example Norway had a strong tradition in the use of F-tablets especially among preschool children. Among 5-year-olds a 9% increase in prevalence of caries was recorded in the period 1997 to 2000. This was associated with a reduction in the sale of F-tablets. The sale of these tablets increased after 1998 and may explain the improved caries status of these children in 2003 [Haugejorden et al., 2005].

Table 1. Grading system for recommendations in evidence based guidelines used by SIGN.
(Reprinted from [Harbour et al., 2001])

	Levels of evidence
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Table 3. Grade of recommendations concerning the use of fluoride supplements.

	Grades of recommendations
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+
Use of fluoride supplement	**Grade***
Fluoridated milk	C One RCT with evidence 1+ and one with evidence 1-.
Fluoridated salt	D No RCTs. One comparative cross-sectional study. See [Yeung, 2008].
Fluoride tablets	C Two RCT with evidence 1+ and five with evidence 1-. Best rated studies are old. Results are not uniform.

*Grade of recommendation

Findings would support that F-tablets might be useful in caries prevention. These findings should be interpreted with caution because aggregated data for a group increases the risk of ecological fallacy when making an inference on an individual level.

The lack of well-designed studies on F-drops makes it difficult to draw any conclusion, but there might be some indications that this will work in some settings [Lin et al., 2000]. There is also reason to believe that this could be an effective way to treat incipient caries, but in general there is a lack of evidence with respect to the efficacy of F in caries prevention in children younger than 3 years of age [Stephen, 1999; Ismail et al., 2008].

It is likely that there is a dose-response effect with respect to F and caries experience. This fact may deflate the results of some studies on F supplements because the doses used were far higher compared with today's recommendations. A dose-response relationship has been demonstrated both for F containing dentifrices [Stephen et al., 1988] and F containing varnishes [Weintraub et al., 2006].

In a recent Swedish study F-tablets given free of charge were part of a 2 yr intervention program for caries prevention among 3 yr old immigrant children [Wennhall et al., 2008]. This program had a significant positive caries preventive effect compared with a historical reference group. However, this study did not meet the inclusion criteria, as it was not an RCT.

All F-supplements which have been discussed in this paper, result in fluoride absorption in the gastrointestinal tract with a rise in plasma F concentration. Aspects of the toxic effects of F are not covered in this paper. The prevalence of dental fluorosis is practically dependant on the body uptake of F in preschool age and there is still a debate about the dosages and when to start with fluoride supplements [Centers for Disease Control and Prevention, 2001; Ismail et al., 2008].

The question whether pre-eruptive exposure of F has any effect on the developing tooth is examined in some analytical papers [Singh et al., 2004; Singh et al., 2007]. The results indicate that high pre-eruptive exposure of F could decrease caries susceptibility of occlusal surfaces. However, these results have been questioned [Mascarenhas et al., 2008].

In general it could be stated that a child's caries risk status needs to be considered and current exposure to F explored before recommending the use of additional F sources such as F-tablets, F-mouth rinse etc. The F containing toothpaste represents the basic caries preventive measure for all children and adolescents.

Conclusion

In Table 3 the grade of recommendation of fluoride tablets and fluoride added to frequently consumed food such as milk or as food additives such as salt are given. High caries risk and good compliance might be a premise for an effective caries prevention. Evidence based reports often contain policy recommendations which may not all be substantiated in good clinical evidence [Ismail, 1998; Limeback et al., 1998]. This is a reminder to the scientific community that there is a need for new, well-designed studies within this field.

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