Seven systematic reviews confirm topical fluoride therapy is effective in preventing dental caries

Robert J. Weyant
University of Pittsburgh
School of Dental Medicine

This review article summarizes 7 systematic reviews of topical fluoride therapy (TFT) published by the Cochrane Library all conducted by the same investigators (Marinho, Higgins, Logan, Sheiham, and Logan). Together these 7 reviews address the individual and comparative effectiveness of 4 methods of delivering topical fluoride for caries control.

**SEARCH STRATEGY**

These Cochrane reviews all employed extensive and well-documented searches using: multiple electronic data bases, reference lists of articles, hand searching of 7 journals, and personal communication with selected authors and manufacturers.

**SELECTION CRITERIA**

In all cases, selection was limited to randomized or quasi-randomized controlled trials with blind outcome assessment. Studies of individual topical fluoride treatments needed to have placebo or “no treatment” controls. Studies were limited to those examining children up to 16 years and lasting at least 1 year.

**EXPOSURE (INTERVENTION)**

Exposure to topical fluoride therapy (TFT) in the form of fluoride-containing toothpastes (dentifrice), gels, mouthrinses, or varnishes. Details are provided in Table 1.
**MAIN OUTCOME MEASURE**
Caries increment (in both permanent and deciduous teeth) expressed as preventive fraction (PF) that is the difference in caries increments between the treatment and control groups expressed as a percentage of the increment in the control group. Caries was defined as being clinically or radiographically recorded at the dentin level of diagnosis.

**OBJECTIVES**
These reviews collectively examined the following questions:
1. What is the effectiveness and safety of TFT in preventing dental caries in child/adolescent populations?
2. Is there a differential effect between any two forms of TFT?

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**TABLE 1. Summary of results from systematic reviews of 4 methods of topical fluoride therapy**

<table>
<thead>
<tr>
<th>Fluoride source</th>
<th>Subjects</th>
<th>Exposure</th>
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</thead>
<tbody>
<tr>
<td>Toothpaste (Review 1)</td>
<td>74 trials conducted between 1954 and 1994 involving 42,300 children in the age range 5–16 yr.</td>
<td>Flouride agent including any of the following: NaF; SMFP, SnF2, APF, AmF. Daily exposure, administered with a toothbrush, but toothpaste quantity rarely reported. 56 trials <em>ad libitum</em> home use; 18 trials involved supervised use at schools or institution.</td>
</tr>
<tr>
<td>Mouthrinse (Review 2)</td>
<td>36 trials conducted between 1965 and 1994 involving 15,171 children in the age range 5–15 yr.</td>
<td>Supervised use of mouthrinse in school programs. Flouride agent: NaF in 32 trials; APF in 4 trials; SnF2 in two trial; SMFP, AmF, and NH4F each tested in one. F concentration ranged from 100 ppm to 3000 ppm. Frequency ranged from 3 to 330 times/yr.</td>
</tr>
<tr>
<td>Gel (Review 3)</td>
<td>25 trials conducted between 1964 and 1996 involving 7747 children in the age range 2–15 yr.</td>
<td>14 trials involved professional applications; 11 trials used self-applied under supervision using a tray or brush. Flouride agent: APF: NaF; AmF; and SnF2. F concentration ranged from 2425 ppm to 12,500 ppm (13 trials used 12,300 F APF). Frequency ranged from 4–5 times/yr. Application time (when reported) 2–10min.</td>
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<tr>
<td>Varnish (Review 4)</td>
<td>9 trials conducted between 1973 and 1997 involving a total of 2709 children in the age range 3–15 yr.</td>
<td>Professional application of NaF based varnishes in all trials. F concentration range: 7000ppm to 56,300 ppm, using approx. 0.5mL/child. Application time ranged from 1–4 min. Application frequency 2–4 times/yr.</td>
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<tr>
<td>Meta-Analysis Estimating Pooled Effect of TFT (Review 5)</td>
<td>133 trials conducted between 1954 and 1996 involving over 65,000 children in the age range 5–16 yr. contributed data for the meta-analysis.</td>
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</tbody>
</table>
3. Are combinations of TFT better at reducing caries levels?
4. Is the effectiveness of TFT influenced by the initial level of caries severity?
5. Is the effectiveness of TFT influenced by the background exposure to fluoridated water or other sources fluoride (e.g., salt)?
6. Is the effectiveness of TFT influenced by the mode/setting of use (i.e., self-applied supervised use of TFT in preventive programs, self applied “unsupervised use of TFT at home, and operator-applied use of TFT)?
7. Is the effectiveness of TFT influenced by the form of TFT used?

### MAIN RESULTS

1. **What is the effectiveness and safety of TFT in preventing dental caries in child/adolescent populations?**

   Reviews 1 to 4 each address separately the effectiveness of the four TFT modalities. The results of these reviews are summarized in Table 1. Review 5 reports the results of a meta-analysis that determined the pooled effectiveness of TFT and is summarized in the last line of Table 1.

2. **Is there a differential effect between any two forms of TFT?**

   This question was addressed in Review 6. Using the search criteria and selection criteria listed above, trials

### TABLE 1, cont’d. Summary of results from systematic reviews of 4 methods of topical fluoride therapy

<table>
<thead>
<tr>
<th>Fluoride source</th>
<th>Results caries reduction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toothpaste (Review 1)</td>
<td>PF: 24% (95% CI: 21%–28%; P &lt; .0001). Heterogeneity: 1.6 (with caries increment of 2.6).</td>
<td>Effectiveness was greater with:</td>
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<tr>
<td></td>
<td></td>
<td>- higher baseline caries rates.</td>
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<td></td>
<td></td>
<td>- higher concentrations of fluoride used.</td>
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<td>- greater frequency of application (1 vs. 2 times/day).</td>
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<td>No association was found with background exposure to other fluoride sources.</td>
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<tr>
<td>Mouthrinse (Review 2)</td>
<td>PF: 26% (95% CI: 23%–30%; P &lt; .001). Heterogeneity: slight. NNT: 1.8 (with caries increment of 2.4).</td>
<td>No association found between initial caries severity and background fluoride exposure including toothpaste (but statistical power to detect difference in this regard was considered low and potential confounding may exist).</td>
</tr>
<tr>
<td>Gel (Review 3)</td>
<td>PF: 28% (95% CI: 19%–37%; P &lt; .001). Heterogeneity: substantial. NNT: 2 (with caries increment of 2.2).</td>
<td>Effectiveness was greater with:</td>
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<tr>
<td></td>
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<td>- greater frequency of application</td>
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<td></td>
<td></td>
<td>- higher concentration of fluoride used.</td>
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<tr>
<td></td>
<td></td>
<td>No association found between initial caries severity and background fluoride exposure including toothpaste (but statistical power to detect difference in this regard was considered low and potential confounding may exist).</td>
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<tr>
<td>Varnish (Review 4)</td>
<td>PF permanent dentition: 46% (95% CI: 30%–63%; P &lt; .0001). Heterogeneity: substantial. PF deciduous dentition: 33% (95% CI: 19%–48%; P &lt; .0001). Heterogeneity: none. NNT: 1.4 (with caries increment of 1.6).</td>
<td>No association found between initial caries severity and background fluoride exposure including toothpaste (but statistical power to detect difference in this regard was considered low and potential confounding may exist).</td>
</tr>
<tr>
<td>Meta-Analysis</td>
<td>PF pooled estimate for all TFT modalities: 26% (95% CI: 23%–29%; P &lt; .0001). Heterogeneity: substantial. NNT: 2.0.</td>
<td>Supervised use of self-applied fluoride increases the benefit. Fluoride varnish may have a greater effect, but estimate is based on few studies.</td>
</tr>
</tbody>
</table>
were selected that compared 1 form of TFT with another (head to head), during a study that lasted at least 1 calendar year. A total of 17 trials, conducted between 1962 and 1994, were included. All studies used parallel group design and lasted from 1 to 3 years, and in all but one case recruited children from school settings. From this group, 16 studies provided data for an additional meta-analysis. There was at least one trial available for each of the six possible pair-wise (head to head) comparisons.

In all cases, the pair-wise comparisons resulted in nonsignificant effect measures. In comparisons that involved more than 1 study, heterogeneity was generally found. The authors concluded that toothpastes, mouthrinses, and gels reduce decay in children and adolescents to a similar extent. There was no convincing evidence that fluoride varnishes offered a benefit over the other modalities.

It was noted that less fluoride is likely ingested with fluoride varnishes, which may reduce risk of fluorosis. It was also found that the acceptability of toothpastes was higher and thus more likely to be used on a more regular basis, thereby improving effectiveness. However, the authors also note that the number of studies for any given pairwise comparison was small and the confidence intervals for the effect sizes were large. Thus, the authors caution against drawing too strong of a conclusion from the evidence currently available.

3. Are combinations of TFT better at reducing caries levels?

This question was addressed in Review 7. The results of the studies that evaluated the effectiveness of combination therapy over single modality TFT are summarized in Table 2.

Given the widespread use of fluoride toothpaste use, the authors conducted additional analysis to determine the benefit of additional TFT beyond toothpaste use alone. The authors conclude that the simultaneous use of combined TFT use results in enhanced caries inhibiting effect compared with toothpaste alone. Based on a meta-analysis of nine studies of combined fluoride therapy comparing mouthrinses, gels, and varnishes with toothpaste versus toothpaste alone, an additional 10% (95% CI: 2–17%) reduction could be expected. This

| TABLE 2. Results of studies Preventive fraction from combined use of TFT modalities compared to use of a single TFT modality |
| --- | --- | --- | --- |
| **Flouride Source** | **Mouthrinse** | **Gel** | **Varnish** |
| Toothpaste | (5 trials) 7% nonsignificant effect favoring combined use over toothpaste alone. (4 trials) 5% nonsignificant effect favoring combined use over mouthrinse alone. | (3 trials) 14% nonsignificant effect favoring combined use over toothpaste alone. (3 trials) 10% nonsignificant effect favoring combined use over gels alone. | (1 trial) 48% reduction (95% CI: 12%–84%; P=.009) favoring combined use over toothpaste alone. NNT*: 3 (with caries increment of 0.8) (1 trial) 15% reduction (CI not obtainable) favoring the combined use over varnish alone. NNT not reported. |
| Mouthrinse | (1 trial 2%) nonsignificant effect favoring combined use over mouthrinse alone. (2 trials) 23% reduction (95% CI: 4%–43%; P=.02) favoring combined use over gel alone. NNT: 3 (with caries increment of 1.6) | No trials found | No trials found |

*Preventive Fraction defined as the difference in caries increments between the treatment and control groups expressed as a percentage of the increment in the control group.

*NNT: Number Need to Treat defined as the number of children who must receive TFT to avoid one DMFS per year in a child population with the indicated caries increment.
10% additional caries reduction benefit is characterized as “not substantial” by the authors. This level of effectiveness would correspond to a NNT of 4 with a caries increment of 2.5 or a NNT of 13 with a caries increment of 0.8.

Safety and side effects: The main safety concerns with TFT are fluorosis, oral allergy, and tooth staining. None of the reviews provided any evidence of harmful effects. However, conclusion about the safety of TFT is limited by the study designs, as most studies were not designed to specifically address safety issues. Additionally, the age range of the participants and the duration of many studies would prevent assessments of fluorosis risk. The authors caution against drawing strong conclusions about safety based on these reviews.

4. Is the effectiveness of TFT influenced by the initial level of caries severity?

Toothpaste studies showed a small but significant increase in the caries prevention in trials where participants had higher initial caries levels. Meta-analytic results estimate a 1% increase on the preventive fraction with a unit increase in the baseline caries rate. No evidence was found relating effectiveness to initial caries severity for gels, mouthrinses, or varnishes. However, the authors caution that many studies had low power to detect such a difference.

5. Is the effectiveness of TFT influenced by the background exposure to fluoridated water or other sources fluoride (e.g., salt)?

No evidence was found for any of the four TFT modalities to suggest that background exposure to fluoride such as water or salt fluoridation influenced their effectiveness. In other words, use of TFT resulted in an additional caries reduction beyond what is provided by fluoridated water or salt.

6. Is the effectiveness of TFT influenced by the mode/setting of use (i.e., self-applied supervised use of TFT in preventive programs, self-applied “unsupervised use of TFT at home, and operator-applied use of TFT)?

Greater caries prevention effect was found with self-applied, supervised use of fluoride (e.g., toothpaste or gels). Toothpaste was also found to be used more regularly, thus enhancing effectiveness. Brushing with fluoride toothpaste twice or more per day versus one per day added an additional 14% to the preventive fraction. There was some evidence that fluoride varnishes had a greater overall caries inhibiting effect, but methodological problems with the varnish studies resulting in wide confidence intervals and require caution in making this conclusion.

7. Is the effectiveness of TFT influenced by the form of TFT used?

Toothpaste studies suggest that increase in the concentration of F in toothpastes increase effectiveness. Results of a meta-analysis showed an 8% increase in the preventive fraction per 1000 ppm increase in F concentration of toothpaste. There was no difference in effectiveness detected in association with the type of fluoride contained in a toothpaste. However, the authors note that two other meta-analyses\(^1\)\(^2\) report a 7% greater caries reduction with sodium fluoride. Greater intensity (i.e., higher concentration and frequency) of self-applied gel application was also associated with lower caries increments.

**Commentary**

**CONCLUSION**

The authors conclude that children 5 to 16 years of age who regularly applied fluoride through the use of toothpastes, mouthrinses, gels, or varnishes had fewer decayed, missing, and filled teeth, regardless of whether their drinking water was fluoridated. Specific reductions in caries rates were estimated to be 24% for fluoride toothpaste, 26% for mouthrinses, 28% for gels, and 46% for fluoride varnishes. When used in combination with fluoride toothpaste, gels, mouthrinses, and varnishes decreased caries rates an additional 10% beyond the use of toothpaste alone. There was insufficient documentation about the safety or possible side effects of the 4 TFT modalities to support conclusions in this regard.

**ANALYSIS**

These reviews provide strong evidence of a significant beneficial effect of topical fluoride when delivered through toothpastes, gels, mouthrinses, or varnishes. The overall estimate of benefit of topical fluoride therapy was 26% in the permanent dentition and 33% in the primary dentition. Substantial benefits such as these suggest the importance of including TFT in any comprehensive caries control program.

Effectiveness, however, must be evaluated within the context of safety and acceptability if proper guidelines for TFT are to be developed. The primary safety concerns are fluorosis, oral allergies, and tooth staining. Importantly, the studies reviewed provided no evidence of safety problems associated with TFT. However, the authors caution that most of the trials reviewed did not address safety issues directly and as a result, their analysis of unwanted side effects is statistically under powered (i.e., would not be able to
detect differences in unwanted outcomes between treatment and control groups if they existed). Thus, the old admonition that the absence of evidence is not evidence of absence should be kept in mind, especially since there is epidemiological evidence that fluorosis is associated with exposure to topical fluorides. However, the majority of fluorosis in most children is only a minor esthetic concern. Furthermore, fluorosis risk can be reduced through parental supervision aimed at limiting the amount of fluoride ingested through parental supervision during toothbrushing during the critical permanent tooth development period from birth to about 5 years of age.

Evidence of acceptability was provided in these reviews, primarily through assessing dropout rates from study protocols. The consistent winner was toothpaste. From a cost-benefit and policy perspective, this is good news. Not only is toothpaste the most readily available form of TFT, but it can be effectively used at home in a relatively unsupervised manner.

The evidence provided in these reviews suggests the following for clinical practice:

- Topical fluoride therapy in any of the four forms appears to be safe and effective and should be encourage for all child patients.
- Based on its higher acceptability, affordable price, and ready availability for home use, fluoride toothpaste should probably be the first TFT recommendation made for most child patients.
- Based on evidence that supervision improves the effectiveness of home use of toothpaste, parents of younger children should be advised to supervise their children’s daily toothbrushing to ensure its use at least twice per day.
- Although the improvement in caries prevention is modest (10%) with combined TFT use (e.g., toothpaste and varnish) some patients, especially where there is concern over high caries risk, may benefit from two forms of TFT. Fluoride varnish applied 2 to 4 times per year may be particularly effective in this regard.

These reviews also suggest that TFT can be effectively delivered in public health prevention programs. Therefore, dentists should be encouraged to become advocates for such programs in their communities. Advocacy is particularly important for the so called “high-risk” groups, including children from poor families and certain minority groups, that not only have higher caries rates but also lower access to treatment. Thus, prevention is especially important for these children.

The extensive information contained in these 7 systematic reviews represents a tremendous effort on the part of authors, and they are to be commended for making an important and substantial contribution to our understanding of topical fluoride therapy. Collectively, these 7 reviews total 414 pages and provide a rich and highly nuanced review of the available literature. The authors have done a meticulous job of teasing out and presenting the extensive amount of information provided in the hundreds of publications that they reviewed. Thus, the reader should be aware that this review of these systematic reviews is no more than a very modest summary of the most salient points to be found in the 7 publications. Every effort was made to accurately summarize the information provided by these 7 reviews, but no summary of a few pages can completely capture the complexity of analysis provided in the full reviews. Therefore, readers wishing a fuller understanding of this area are referred to the Cochrane Library online to access the complete reviews.

**WEAKNESSES AND STRENGTHS**

A major strength of this review process was the comprehensive approach adopted in the 7 reviews. The authors did a thorough job of selecting and reviewing an extensive literature and presenting the various findings in clinically important ways.

The weaknesses in this process derive primarily from the problems inherent in the original trials. Many of the included trials were older, from a time when the approach to clinical studies was somewhat less rigorous and reporting of methodologies less detailed. As a result, such findings are less useful for systematic review. Additionally, few of the trials directly address safety and compliance issues. The authors correctly call for future studies to include assessments of both. However, given the established efficacy of TFT, it is unlikely that any future trial will ethically be able to use a placebo comparison, thus limiting conclusions regarding both efficacy and safety issues.

**REFERENCES**