Fluoride toothpaste efficacy and safety in children younger than 6 years: A systematic review

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J. Timothy Wright, DDS, MS; Nicholas Hanson, MPH; Helen Ristic, PhD; Clifford W. Whall, PhD; Cameron G. Estrich, MPH; Ronald R. Zentz, RPh, DDS

ABSTRACT

Background. The authors conducted a systematic review to assess the efficacy and safety of fluoride toothpaste use in children younger than 6 years.

Methods. The authors defined research questions to formulate a search strategy. They screened studies, extracted data and assessed risk of bias systematically. They conducted meta-analyses to determine the effects of brushing with fluoride toothpaste.

Results. Use of fluoride toothpaste brushing had a statistically significant effect on mean decayed, missing and filled primary tooth surfaces and decayed, missing and filled primary teeth for populations at high risk of developing caries (standard mean difference [95 percent confidence interval {CI}], −0.25 [−0.36 to −0.14] and −0.19 [−0.32 to −0.06], respectively). The effects of using different fluoride concentration toothpastes on caries varied. Study findings showed either a decrease in the odds of having fluorosis (odds ratio [OR] [95 percent CI] = 0.66 [0.48-0.90]) when the use of fluoride toothpaste was initiated after 24 months or no statistically significant difference (OR [95 percent CI] = 0.92 [0.71-1.18]). Beginning use after 12 or 14 months of age decreased the risk of fluorosis (OR = 0.70 [0.57-0.88]).

Conclusions. Limited scientific evidence demonstrates that for children younger than 6 years, fluoride toothpaste use is effective in caries control. Ingesting pea-sized amounts or more can lead to mild fluorosis.

Practical Implications. To minimize the risk of fluorosis in children while maximizing the caries-prevention benefit for all age groups, the appropriate amount of fluoride toothpaste should be used by all children regardless of age. Dentists should counsel caregivers by using oral description, visual aids and actual demonstration to help ensure that the appropriate amount of toothpaste is used.

Key Words. Caries; fluoride; fluorosis; toothbrushing; toothpaste; infant care.

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Use of fluoride toothpaste has been recommended for more than 50 years to prevent and control dental caries. Recommendations for its use with infants and children have been modified during this time in an effort to maximize the caries-preventive effect and minimize the risk of dental fluorosis. Children younger than 5 years tend to swallow toothpaste while brushing.[1] Older children are more able to spit out toothpaste consistently after brushing. Many researchers have found that brushing with fluoride toothpaste reduces dental caries in school-aged children, but fluoride toothpaste use at an early age can be associated with dental fluorosis.[2] Even though more than 25 percent of children have or had dental caries by the time they enter kindergarten,[3] few studies have addressed the effects of brushing with fluoride toothpaste in children younger than 6 years.

The lack of information regarding safety and efficacy of fluoride toothpaste for children younger than 6 years has resulted in inconsistent messaging within the dental community regarding the recommended use of fluoride toothpaste for young children. The required

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U.S. Food and Drug Administration (FDA) labels on fluoride toothpaste in the United States state that a pea-sized amount should be used for children younger than 6 years and that a dentist should be consulted regarding use in children younger than 2 years. Several organizations now recommend using a smear of toothpaste—or an amount the size of a grain of rice—in children younger than 2 years and then a pea-sized amount starting at age 2 years.[4-6] The Canadian Dental Association[5] recommends using a small amount of fluoride toothpaste (a portion the size of a grain of rice) for children younger than 3 years who are at risk of developing caries, and then a pea-sized amount for children aged 3 to 6 years. The U.S. Department of Health and Human Services[6] recommends using a smear of fluoride toothpaste for children younger than 2 years and a pea-sized amount for children older than 2 years. The American Dental Association (ADA) currently recommends brushing with water for children younger than 2 years, and then using a pea-sized amount of toothpaste for children from 2 to 6 years of age.[7] Thus, health care professionals and caregivers of children receive conflicting and inconsistent recommendations and messaging regarding the use of fluoride toothpaste for children. The goal of this investigation was to evaluate the evidence regarding the benefit of fluoride toothpaste use in caries prevention and control, and the risk of developing dental fluorosis associated with fluoride toothpaste use in children younger than 6 years.

METHODS

Research questions, search strategy and inclusion criteria. The ADA Council on Scientific Affairs proposed the following research questions: "Does the use of fluoride toothpaste by children 6 years of age and younger affect caries rates?" and "Does the use of fluoride toothpaste by children 6 years of age and younger affect fluorosis rates?" We formulated a search strategy on the basis of the two research questions, and we conducted a MEDLINE search from the date of online availability until April 25, 2012. eTable 1 (available as supplemental data to the online version of this article at http://jada.ada.org/content/145/2/182/suppl/DC1) shows the full search strategy.

We excluded the following types of studies and publications from this systematic review: in vitro studies, animal studies, studies published in languages other than English, case reports, narrative reviews, medical record reviews, meeting abstracts, historical articles, editorials, letters and commentaries. Accepted studies included those in which researchers recorded exposure to fluoride toothpaste in children 6 years or younger and reported outcomes of interest (that is, caries and fluorosis) in participants over time.

Data collection. Two people (either N.H. and C.G.E. or H.R. and C.G.E.) independently screened each abstract according to the exclusion and inclusion criteria. After abstract screening, we recalled relevant studies for full-text review. On full-text review by H.R. and N.H., we made final decisions to include or exclude studies. Bibliographies of included studies were also hand searched (by N.H.) for relevant studies not yet identified.

Two of the authors (H.R. and N.H.) extracted qualitative and quantitative data and checked them for consistency. The same two authors assessed articles for risk of bias via a standardized form and in duplicate. (eTables 2-5 [(available as supplemental data to the online version of this article at http://jada.ada.org/content/145/2/182/suppl/DC1] provide more information on the domains that they assessed.) Any discrepancy that occurred during the data collection process was settled by means of third-party adjudication.

Statistical analysis. We used standard mean difference (SMD) to assess the treatment effect of fluoride toothpaste on caries. We compared mean scores for decayed, missing and filled primary tooth surfaces (dfms) and decayed, missing and filled primary teeth (dmft) between treatment and control groups. We used odds ratio (OR) to assess the treatment effect of fluoride toothpaste on fluorosis. We dichotomized cases of fluorosis as present or absent. We did not address severity of fluorosis in this review. All meta-analyses regarding caries outcomes and fluoride toothpaste use in this review are the authors' work. The meta-analyses regarding fluorosis and fluoride toothpaste use in this review were conducted by Wong and colleagues,[8] but during the review process we updated some meta-analyses with additional studies that Wong and colleagues[8] did not include (either because they were not published at the time or for other reasons). We extrapolated missing standard deviations (SDs) when possible. In two studies,[9,10] information was not available to allow calculation of SDs according to group; however, it was possible to calculate the SD for the difference in means between the groups. The authors did not provide exact details on randomization, but they stated that the studies were randomized.[9,10] With the assumption that the studies were randomized appropriately, we applied the calculated SDs for analysis.

Caries outcome. We used statistical software (Stata SE Version 12.1, StataCorp, College Station, Texas) to calculate estimates of treatment effects (SMD). We assessed heterogeneity by visually inspecting forest plots and calculated it with the Higgins Index (I^2). We used a random-effects model for all caries-related meta-analyses. We did not assess publication bias owing to the lack of data.

Fluorosis outcome. We used an existing system-

ABBREVIATION KEY. **ADA:** American Dental Association. **dmfs:** Decayed, missing and filled surfaces (primary). **dmft:** Decayed, missing and filled teeth (primary). **FDA:** Food and Drug Administration. **RCT:** Randomized controlled trial.

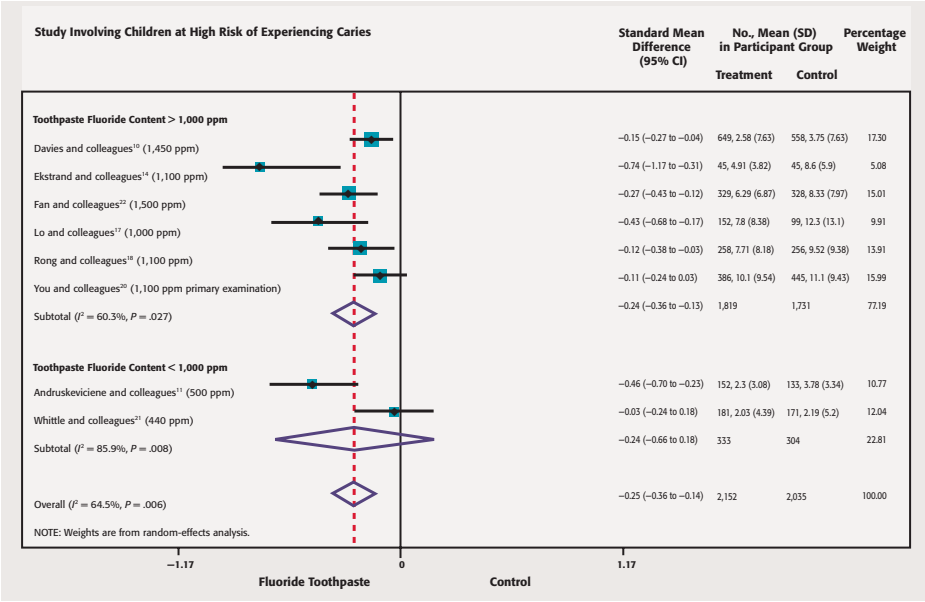

Figure 1. The effect of brushing with fluoride toothpastes (< 1,000 parts per million fluoride and > 1,000 ppm fluoride) on caries (decayed, missing and filled primary tooth surfaces) in children younger than 6 years who are at high risk of developing caries. CI: Confidence interval. SD: Standard deviation.

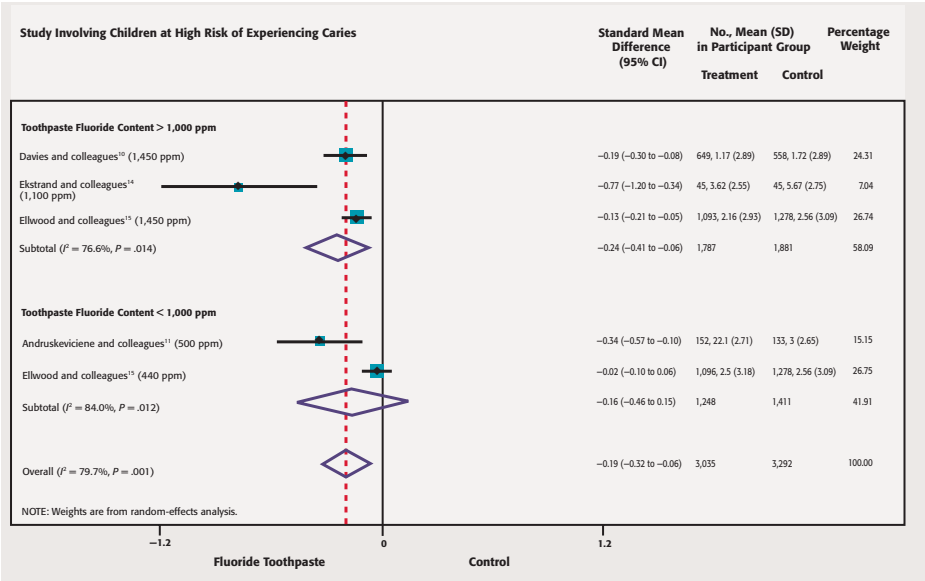

Figure 2. The effect of brushing with fluoride toothpastes (< 1,000 parts per million fluoride and > 1,000 ppm fluoride) on caries (decayed, missing and filled primary teeth) in children younger than 6 years who are at high risk of developing caries. CI: Confidence interval. SD: Standard deviation.

atic review titled "Topical fluoride as a cause of dental fluorosis in children"[8] as the foundation for our analysis regarding fluorosis. Statistical methods are described in detail in that review. In most cases, we made no changes or updates to the existing meta-analyses. However, we added studies to two previously conducted meta-analyses from the existing topical fluoride systematic review[8] and re-analyzed them by using statistical software (Stata SE Version 12.1). We used an inverse fixed-effect model for both. We assessed heterogeneity by visually inspecting forest plots and calculated it by using the Higgins Index (I^2). We did not assess publication bias owing to the lack of data.

RESULTS

The search generated 2,732 abstracts, with 402 studies recalled for full-text review. After further review, we included 14 clinical caries trials, as well as a systematic review, a case-control study and a cross-sectional study about fluorosis, yielding 17 studies for inclusion in this systematic review. The eFigure (available as supplemental data to the online version of this article at http://jada.ada.org/content/145/2/182/suppl/DC1) is a study attrition flowchart. We also hand searched bibliographies of included studies for relevant studies that were not already included. We did not select or weight studies by risk of bias for analysis; instead, we included in our meta-analyses all studies that met the inclusion criteria. eTable 6 (available as supplemental data to the online version of this article at http://jada.ada.org/content/145/2/182/suppl/DC1) provides details regarding the included prospective controlled studies of caries.

Caries. This review included 14 clinical trials of caries that varied in design and approach[9-22] (eTable 6). Risk-of-bias assessments of these studies revealed many flawed domains (eTables 2-5). Random allocation was unclear in more than one-half of the studies. The overall risk of bias for these 14 studies as a group is high. Study participants ranged in age from 1 to 4 years at the start of a given study. Study duration ranged from one year to five years. Fluoride toothpaste concentration, brushing frequency and length of brushing time

differed according to study; however, all participants were supervised throughout the studies. These studies were conducted in different countries (most of which were not the United States); investigators reported some study populations as having a high risk of experiencing caries, and we identified others as having high risk factors (low socioeconomic status and active carious lesions). The main outcomes of interest were dmft and dmfs.

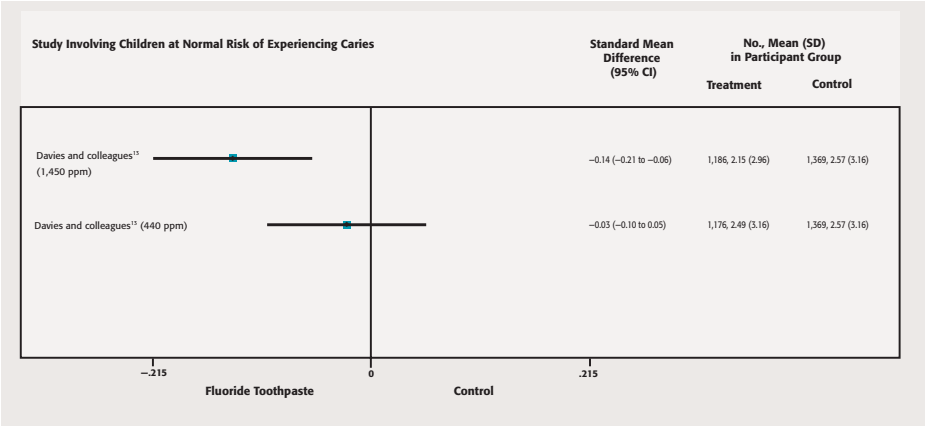

Figure 3. The effect of brushing with fluoride toothpastes (1,450 parts per million fluoride and 450 ppm fluoride) on caries (decayed, missing and filled primary teeth) in children younger than 6 years who are not at high risk of developing caries. CI: Conficence interval. SD: Standard deviation.

Fluoride toothpaste versus control or placebo. We included eight studies[10,11,14,17,18,20-22] to determine the effect of brushing with fluoride toothpaste on dmfs. Researchers in six of the studies[10,14,17,18,20,22] evaluated toothpaste that ranged in fluoride ion concentration from 1,000 to 1,500 parts per million. Figure 1[10,11,14,17,18,20-22] shows that in these high-risk populations, brushing with fluoride toothpaste resulted in a statistically significant difference in mean dmfs (SMD [95 percent confidence interval {CI}], −0.25 [−0.36 to −0.14]), whereas for the two studies in which participants used toothpastes with less than 1,000 ppm fluoride,[11,21] the findings were less consistent compared with those in control groups not using fluoride toothpastes. Similarly, Figure 2[11,13-15] depicts a statistically significant difference in mean dmft among high-risk populations that brushed with fluoride toothpaste (SMD [95 percent CI], −0.19 [−0.32 to −0.06]) compared with results in control groups. One study[13] (depicted in Figure 3) addressed fluoride toothpaste's effect on dmft in a population with a normal caries risk and involved two active treatment groups. The group that brushed with high-fluoride-concentration toothpaste (1,450 ppm) had a statistically significantly lower mean dmft compared with results in a control group. However, results for the group that brushed with low-fluoride-concentration toothpaste (440 ppm) did not differ significantly from those of the control group.

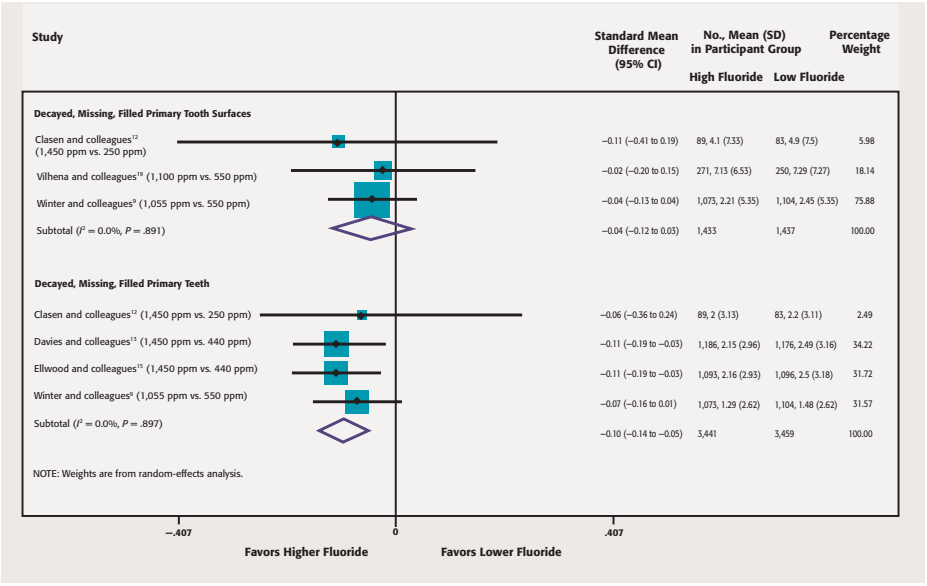

Figure 4. The effect of brushing with high-concentration versus low-concentration fluoride toothpaste on caries (decayed, missing and filled primary tooth surfaces and decayed, missing and filled primary teeth) in children younger than 6 years. CI: Confidence interval. SD: Standard deviation.

High fluoride concentration versus low fluoride concentration. Individual results of head-to-head comparisons of toothpastes with different fluoride concentrations varied. Our meta-analysis of these studies showed no statistically significant difference between brushing with toothpastes with high (1,055-1,450 ppm) or low (250-550 ppm) fluoride concentration in terms of dmfs (SMD [95 percent CI], −0.04 [−0.12 to 0.03]). However, these high-fluoride-concentration toothpastes did have a statistically significant effect on dmft compared with low-fluoride-concentration toothpastes (SMD [95 percent CI], −0.10 [−0.14 to −0.05]) (Figure 4). Eleven of the 12 studies included in this review in which researchers evaluated

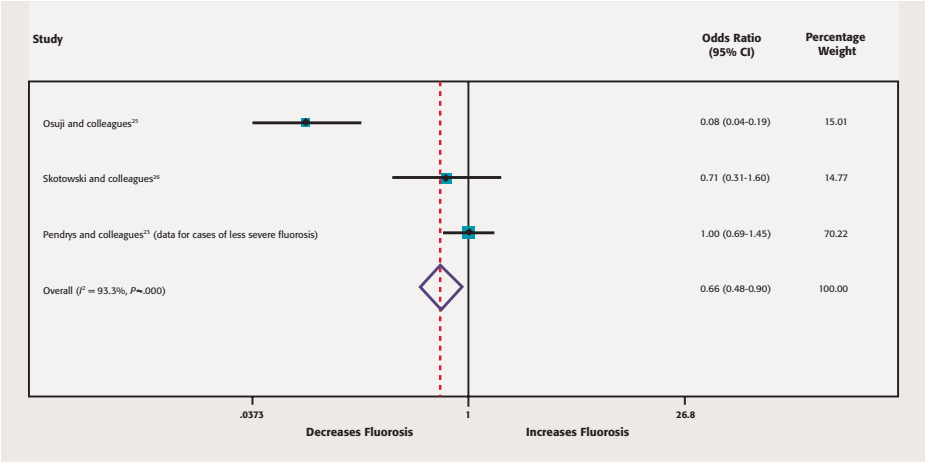

Figure 5. The effect of initiating brushing with fluoride toothpaste after 2 years of age versus before 2 years of age on the development of fluorosis. CI: Confidence interval.

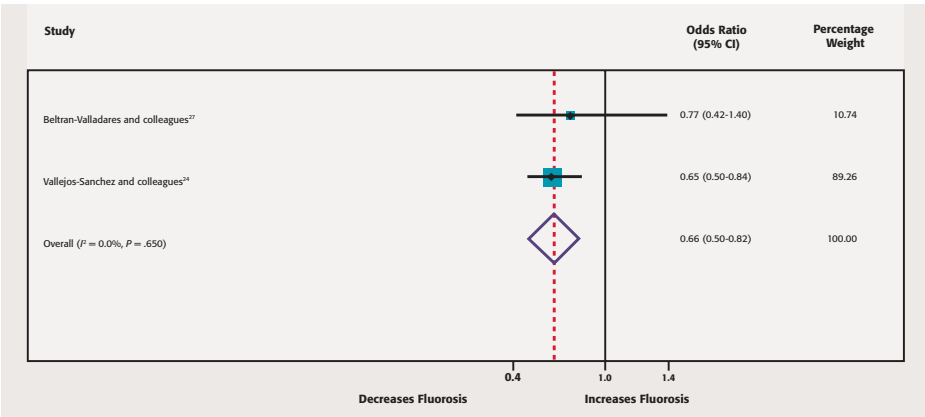

Figure 6. The effect of brushing with fluoride toothpaste fewer than seven times per week versus one or more times per day on the development of fluorosis. CI: Confidence interval.

toothpastes with 500 ppm fluoride or more produced statistically significantly lower mean caries, and 100 percent of the tested toothpastes with less than 500 ppm fluoride failed to produce a statistically significant difference compared with that in control participants not using fluoride toothpaste (Figures 1 through 3). The investigators in these studies did not compare toothpastes with different fluoride concentrations with each other, as did the investigators in the studies in Figure 4.[9,12,13,15,19]

We also reviewed an additional study[16] whose investigators did not measure fluoride toothpaste efficacy according to dmfs or dmft. The authors of that study reported that low versus high fluoride concentration did not affect lesion progression (new lesions) in children with no caries experience (P = .28), but they did find a favorable effect for toothpastes with higher versus lower fluoride concentrations in children with active lesions (P = .0052).

Dental fluorosis. A 2010 Cochrane systematic review regarding fluoride toothpaste use and dental fluorosis—a review that included randomized controlled trials (RCTs), quasi-RCTs, cohort studies, case-control studies and cross-sectional surveys—addressed the same research question regarding dental fluorosis as that posed in this study.[8] The authors of that 2010 review used meta-analyses as the foundation for the following results and conclusions related to dental fluorosis. In our literature search, we found only two studies[23,24] (one case-control and one cross-sectional) that met the inclusion criteria that were not included in the 2010 review. We conducted new meta-analyses including the additional data in these two studies.

Inception of brushing with fluoride toothpaste. Our meta-analysis of three case-control studies (Figure 5[23,25,26]) showed that beginning to brush with a fluoride toothpaste after 24 months of age decreased the odds of having dental fluorosis (OR [95 percent CI] = 0.66 [0.48-0.90]) compared with initiation of fluoride toothpaste use before 24 months of age. The direction and statistical significance of our finding did not differ from those in the previously conducted meta-analysis,[8] whereas the addition of the study by Pendrys and colleagues[23] did decrease the magnitude of effect twofold.

Brushing frequency (times per day). The overall pooled effect of these cross-sectional studies was a decreased risk of developing fluorosis that was not statistically significant in the population brushing fewer than two times per day (OR [95 percent CI] = 0.88 [0.71-1.08]). However, when we assessed brushing frequency on the basis of daily versus less than daily brushing, we did find statistical significance. Figure 6[24,27] summarizes the meta-analysis regarding brushing fewer than seven times per week compared with more than one time per day. The overall effect of the results of these two cross-sectional studies is significant and indicates that less brushing with fluoride toothpaste decreases the odds of developing dental fluorosis.

Toothpaste amount (applied to brush). Our meta-analysis of three cross-sectional studies showed that

use of a small amount of toothpaste compared with a medium or large amount was not significantly associated with fluorosis (OR [95 percent CI] = 0.92 [0.67-1.28]).

Fluoride concentration. In general, there was a tendency for fluorosis to decrease with use of toothpaste containing lower fluoride concentrations, but the pooled effect was not significant (OR [95 percent CI] = 0.79 [0.61-1.02]).

DISCUSSION

Although there are many studies in school-aged children in which investigators evaluated the effectiveness of fluoride toothpaste in preventing and controlling caries, there are fewer studies in children younger than 6 years.[2] There also is limited scientific evidence regarding the effectiveness and risk of fluorosis associated with using different amounts of fluoride toothpaste (smear versus pea-sized) in children younger than 3 years. This systematic review yielded 17 clinical trials that met the inclusion criteria. The results of our analysis of studies in which investigators evaluated fluoride toothpaste use in children younger than 6 years show that it is effective in reducing dental caries in primary teeth. The results may not be generalizable to all children, because the majority of the studies were conducted in populations at high risk of experiencing caries and in different countries. The magnitude of the effect varied between populations, which were heterogeneous, but it often was statistically significant. Another systematic review regarding fluoride toothpaste use and caries prevention in young children[28] was published after our systematic review had been completed. The results of that review are consistent with ours and indicate that fluoride toothpaste is effective in reducing dental caries in young children.

Investigators have evaluated the caries-prevention effectiveness of over-the-counter fluoride toothpastes with differing fluoride concentrations. Toothpastes with varying fluoride concentrations have been found to be significantly different in their effectiveness in preventing caries in permanent teeth when evaluated in older (adolescent) populations.[29] It is less certain, because of the limited range of fluoride concentrations in studies in children 6 years and younger, if the differing concentrations of fluoride in toothpaste are a significant factor for caries prevention. However, our results suggest that toothpastes with 500 ppm fluoride or more have a greater effect on caries reduction compared with toothpastes below this concentration in children 6 years or younger.

Another critical factor related to fluoride toothpaste use in children younger than 6 years is its association with the potential risk of development of dental fluorosis.[30] The permanent incisors are of critical importance to dental esthetics and are undergoing crown formation from around birth to four years of age.[31] Most cases of fluorosis associated with fluoride toothpaste use are mild.[32,33]

According to our findings, higher concentrations of fluoride in toothpaste increase the odds of developing dental fluorosis (for instance, using toothpaste containing 1,100 ppm versus 440 ppm fluoride). Low-fluoride toothpastes, as described in the included studies, are not available in the North American market; however, reducing the dose of regular fluoride toothpaste when using a pea-sized amount or a smear may be equivalent to the use of low-fluoride toothpaste. Indeed, findings of a more recent evaluation suggested that children who start brushing by age 24 months but do not use more than a pea-sized amount of toothpaste do not have an increased risk of developing fluorosis.[23]

There is limited and conflicting evidence from cross-sectional studies indicating that children who begin using fluoride toothpaste as early as 12 or 14 months of age are at an increased risk of developing fluorosis compared with those who start after this age. Researchers evaluating toothpaste use and fluorosis in this age group did not quantify the amount of toothpaste used. Evidence from additional case-control studies also showed that earlier use of fluoride toothpaste increases the risk of fluorosis development (Figure 5).

The results of our meta-analysis indicate that children who brush more than one time per day as opposed to less than once per day are at greater risk of developing fluorosis (Figure 6). This is different from the conclusion by Wong and colleagues[8] that brushing more than one time per day as opposed to less than once per day was not associated with risk of developing fluorosis, on the basis of one cross-sectional study. Our meta-analysis includes an additional study[24] and pools from a larger sample and indicates that brushing frequency is a risk factor for developing fluorosis. Confounding this issue, Wong and colleagues[8] also found that brushing more than twice per day does not appear to increase the risk of developing fluorosis. Thus, the relationship between brushing frequency and risk of developing fluorosis remains unclear.

Investigators in several cross-sectional studies in the Wong and colleagues[8] review reported conflicting evidence regarding an association between the amount of toothpaste used and fluorosis. The toothpaste amount was defined as a small amount versus a medium or large amount. The overall pooled effect of the meta-analysis of these studies was not significant. The amount of toothpaste used does not appear to be associated with dental fluorosis, according to the results of Wong and colleagues.[8] However, the actual amount of toothpaste used was not well-quantified in these studies, and it seems contradictory that toothpaste amount is not a significant risk factor for developing fluorosis. The concentration of fluoride in the toothpaste, frequency of brushing and amount of toothpaste used are the primary determinants driving fluoride exposure related to fluoride toothpaste use. The current evidence is inconsistent regarding the

related risk of fluorosis development associated with each of these factors.

Investigators in several observational studies included in this review measured the outcome of fluorosis differently. As such, they used multiple scales to record the severity of fluorosis. The majority of reported cases were mild[24] and may not be of clinical concern. These cases can be of esthetic concern, although there is evidence that adolescents do not report a more negative perception of their dental appearance in the presence of fluorosis.[34] Our review does not address the severity of dental fluorosis. The mere presence or absence of fluorosis at any level was the outcome of interest for most studies and their subsequent meta-analyses. In light of this, oral health care providers should discuss with caregivers the risk of developing fluorosis versus the benefit of reducing the risk for developing dental caries when providing oral health education.

The studies included in this systematic review were at a relatively high risk of bias owing to the study designs (eTables 2-5 [available as supplemental data to the online version of this article at http://jada.ada.org/content/145/2/182/suppl/DC1] show the results of the risk-of-bias assessment). To address the lack of high-quality evidence and gaps in the evidence, well-designed RCTs are needed. Specifically, investigators in future studies should address the optimal amount, frequency and timing of fluoride-toothpaste use in children 1 to 3 years of age to maximize caries prevention and minimize fluorosis. In addition, a validated risk assessment tool that identifies young children who likely will develop caries is needed.

Although it is limited, there is scientific evidence that fluoride toothpaste is effective in caries control and that ingesting pea-sized amounts or more can lead to mild fluorosis. To minimize the risk of developing fluorosis in children while maximizing the caries-prevention benefit for all age groups, the appropriate amount of fluoride toothpaste should be used by all children, regardless of age. Parental brushing and close supervision along with close attention to the amount of toothpaste dispensed for each use are necessary to minimize toothpaste consumption in children younger than 6 years. It is especially critical that dentists provide counseling to caregivers involving the use of oral description, visual aids and actual demonstration to help ensure that the appropriate amount of toothpaste is used. Study findings indicate that caregivers apply up to twice the recommended amount of toothpaste, making it essential that they are well educated regarding how to use fluoride toothpaste appropriately.[35]

Given that low-fluoride toothpastes are not commercially available in the United States and have been considered but not included in the FDA's final monograph for anticaries drug products,[36] limiting the amount of toothpaste used by young children is necessary. To help ensure appropriate use of fluoride toothpaste, caregivers of children younger than 6 years should consult their dentist or physician to discuss the benefits and risks of using fluoride toothpaste and be instructed in dispensing the recommended amount.

CONCLUSIONS

The results of this study demonstrate that for children younger than 6 years, fluoride toothpaste use is effective in caries control. However, ingesting pea-sized amounts or more can lead to mild fluorosis. Considering the best available evidence and the continued high caries rate in children, an appropriate amount of fluoride toothpaste should be used by children of all ages. ■

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