Comparing the Effectiveness of Topical Fluoride and Povidone Iodine with Topical Fluoride Alone for the Prevention of Dental Caries among Children: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Combined use of povidone iodine (PI) along with topical fluorides (TF) has been suggested as a promising strategy to reduce dental caries incidence and cariogenic bacterial load. However, the available literature presents mixed evidence regarding its effectiveness as compared to TF application alone.

Aim and objective: TF + PI vs TF alone in the prevention of dental caries among 1–12-year-old children assessed through caries increment and mean S. mutans and Lactobacillus counts.

Materials and methods: Five databases (Cochrane Central Register of Controlled Trials, EBSCOhost, PubMed/Medline, Scopus, and Web of Science) were searched for relevant literature. Out of 72 studies that were screened, 7 eligible studies were included out of which 4 studies were subjected to meta-analysis. The generic inverse variance test was used to assess the primary outcome reported as mean ± SD/ events occurred (caries incidence), whereas for mean post-intervention S. mutans colony count, inverse variance function was used. The Cochrane’s Collaboration tool and Modified Downs and Black scoring criteria were used to evaluate the quality of the included articles. Heterogeneity across the studies was assessed using the I² statistic. Statistical significance was set at p < 0.05.

Results: Overall, for primary and permanent dentition combined, the dental caries incidence was found to be significantly lower in the TF + PI combined therapy group as compared to TF alone [SMD −0.4 (−0.78 to −0.03), p = 0.04]. The two groups showed no significant difference with respect to post-intervention S. mutans count [SMD −0.1 (−0.57 to +0.37), p = 0.69]. No study was found that compared post-intervention Lactobacillus count between the two groups.

Conclusion: Based on the pooled analysis from the limited literature available, there is a very low quality of evidence that TF + PI combined therapy is more effective in the prevention of new caries lesions among 1–12-year-old children as compared to TF use alone. Future clinical trials with robust methodologies are recommended to generate conclusive evidence.

Clinical significance: PI application might exert an added benefit with TF in preventing the occurrence of new carious lesions among 1–12-year-old children.

Keywords: Dental caries, Lactobacillus, Meta-analysis, Mutans Streptococci, Povidone-iodine, Systematic review, Topical fluorides.

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INTRODUCTION

Dental caries is an easily preventable yet highly prevalent condition worldwide and thus constitutes a significant public health problem.¹,² The conventional restorative treatment for tooth decay exerts an enormous financial burden on an individual.³ Moreover, it has been reported that general anesthesia is usually required for treatment of severe early childhood caries, and it may increase the risk of morbidity and/or mortality.⁴ Patient-dependent behavioral modification focusing on healthy diet and good oral hygiene practices cannot be solely relied upon for prevention of dental caries. Thus, intensive preventive interventions that do not depend upon patient compliance should be adopted.⁵

The imbalance between the protective and pathogenic factors as the primary mechanism of dental caries causation is well documented in the literature.⁶ Evidence suggests that professionally applied topical fluoride (TF) is highly effective in preventing dental caries by strengthening the protective factors.³⁷ The primary mechanism of action of TF is by enhancing the remineralization process and inhibiting the demineralization process.⁸ However, it is noted that the effectiveness of fluoridated compounds is low in episodes of low pH stress and a more holistic approach is necessary to control caries progression and prevent caries occurrence effectively.⁹ To limit down the pathogenic factors, use of antimicrobial agents as an adjunct to TF therapy is implicated to be an effective caries preventive regimen.¹⁰ The water-soluble

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povidone-iodine (PI) solution is known to exert caries preventative effect owing to its long-term preferential and antimicrobial action against S. mutans due to the slow release of iodine. Various trials have assessed the added benefit of using PI in preventing dental caries but with inconclusive evidence.

In this era of evidence-based dentistry, there is a need to draw conclusive evidence regarding combined use of topical fluoride and povidone-iodine (TF + PI) over TF alone, which may alter the current clinical practices and may guide the future preventive programs. Thus, the aim of this study is to compare the effectiveness of TF + PI with TF alone for the prevention of dental caries among 1–12-year-old children.

**Materials and Methods**

The present study was registered with PROSPERO (CRD42019134530).

**Search Strategy**

Cochrane, EBSCOhost, PubMed/Medline, Scopus, and Web of Science were electronically searched in March 2019 to identify the published literature that assessed the effectiveness of TF + PI application on dental caries in children. The keywords used for literature search were “topical fluoride,” “povidone-iodine,” “dental caries,” “early childhood caries,” “Lactobacillus,” and “Mutans streptococci” along with the use of Boolean operators (AND/OR) as required. Manual search of cross-references was done to identify additional records, if any. All the records obtained were exported to the Endnote X9 software for removing the duplicates and further screening and selection based on the inclusion–exclusion criteria. Assessment of records for possible inclusion was done in two phases; the first phase included the screening of titles and abstracts and was done independently by two authors (‘NT’ and ‘SS’). The second phase involved scrutiny of the full texts and was done by two authors (‘NT’ and ‘SS’). The subgroup analysis was done for deciduous dentition14,15 and permanent dentition16,17 separately. For the post-treatment S. mutans count reported as a continuous variable, the inverse variance test was used to compare the experimental and control groups. Heterogeneity among the studies was evaluated using the I² statistic. The random effect model was used to carry out the pooled analysis. The p value <0.05 was set as the statistical significance limit.

**Results**

Through the electronic search, 120 records were identified. After removing 48 duplicate references, 72 studies were assessed for eligibility. Sixty-four were excluded after the title and abstract screening in the first phase. In the second phase, one study was excluded after full-text reading. Finally, seven articles were included in qualitative analysis out of which data from five studies were synthesized quantitatively. The systematic review process is shown in PRISMA flowchart18 (Flowchart 1).

**Study Characteristics**

Table 1 summarizes the characteristics of the seven included studies. All studies were published between 2005 and 2016 and had children at high risk of dental caries except for El-Housseiny et al.5 that included healthy children. El-Housseiny et al.5 and Zhan et al.14 used 1.23% acidulated phosphate fluoride (APF) gel and PI combined therapy; Xu et al.17 applied fluoride foam and PI; Milgrom et al.,15 Reilly et al.,19 and Tut et al.16 applied 5% sodium fluoride varnish and PI; Hashemi et al.20 applied a mixture of 0.2% sodium fluoride varnish and PI. Thus, in all the included studies, TF + 10% PI application was made in the experimental group.

None of the studies reported a low risk of bias. Xu et al.17 had an overall unclear risk of bias due to incomplete reporting of blinding and loss to follow-up of the study participants. The retrospective cohort study by Tut et al.16 was noted having a high risk of bias for all the domains except for attrition bias and reporting bias. The quasi-experimental research by Milgrom et al.15 had an overall high risk of bias. The Downs and Black quality assessment scores of the included studies ranged from 15 to 21. Three studies were graded “fair”5,14,15 and four were graded “good”.16,17 For the studies subjected to meta-analysis, the Risk of Bias Assessment is shown in Figure 1, and the Downs and Black scores are shown in Table 2.
Primary Outcome
Overall, the pooled analysis showed a lower risk of caries incidence in ‘TF + PI’ combined therapy compared to TF use alone [SMD –0.4 (–0.78 to –0.03), p = 0.04; I² = 28%, p = 0.24]. For the subgroup analysis, no significant difference is observed between the experimental and control group in deciduous teeth [SMD –0.19 (–0.65 to 0.26), p = 0.41; I² = 17%, p = 0.3], whereas, the pooled analysis is seen to significantly favor combined therapy in permanent teeth [SMD –0.71 (–1.15 to –0.28), p = 0.001; I² = 0%, p = 0.83] (Fig. 1).

Secondary Outcome
The pooled analysis of 37 participants in the ‘TF + PI’ group and 33 in the TF group from two studies was performed for mean post-intervention S. mutans counts. Although the meta-analysis was noted to favor the ‘TF + PI’ application, the difference was not significant [SMD –0.1 (–0.57, +0.37), p = 0.69, (I² = 0%; p = 0.49)] (Fig. 2).

Discussion
The present review favors ‘TF + PI’ application over TF use alone in reducing the incidence of dental carious lesions. While, Cochrane reviews suggest that TF application is effective in reducing caries incidence in children and adolescents, Buzalaf et al. have reported that although fluoride exhibits bactericidal effects on S. mutans in vitro, yet convincing evidence is lacking regarding the clinical effects of fluoride-containing oral-care products on S. mutans. Additional use of an antibacterial agent is suggested to exert an added benefit in reducing oral pathogenic bacteria. The US FDA has regarded 10% PI safe enough to be applied on the skin and mucous membrane as a presurgical disinfectant. None of the studies have reported any side effects of PI use and its use has been found to be well accepted by children.

Although the studies included in this review have used different delivery vehicles for the application of TF, yet literature concludes that there is no difference in the caries-preventive effectiveness on using fluoride in solution, gel, or varnish form. Thus, pooling of results seems to be justified irrespective of the TF delivery vehicle used. Moreover, to account for the heterogeneity across the studies, a random-effects model was used.

Among the included studies, the frequency of ‘TF + PI’ application varied from single to 12 per year. Results of a systematic review concluded that the biannual application of TF reduces the chances of new tooth decay by approximately 30%. The American Academy of Pediatric Dentistry guidelines suggests the quarterly application of fluoride varnish can significantly prevent dental caries in the high-risk group.

Hashemi et al. used a mixture of PI and 0.02% NaF solution as the active ingredients (iodine and fluoride) do not react with each other and are thus available in free form for their therapeutic action. Other studies included in the present review have applied PI solution followed by TF.

Since the Cochrane Collaboration’s tool is primarily used to assess the risk of bias of randomized controlled trials, the risk of bias evaluated for the retrospective cohort study by Tut et al. and quasi-experimental trial by Milgrom et al. holds limited relevance. To assess the quality of all the trials subjected to quantitative analysis, the Downs and Black criterion was also used as it is designed to evaluate both randomized and nonrandomized studies. This criterion has superior internal consistency, acceptable test-retest reliability, and validity (face and criterion).
Table 1: Characteristics of included studies

| Author, year          | Study design, Study location (country) | Target population | Experimental group intervention | Control group intervention | Outcome variables | Follow-up, period | Summary of findings                                      |
|-----------------------|---------------------------------------|-------------------|---------------------------------|----------------------------|-------------------|-------------------|----------------------------------------------------------|
| El-Housseiny and Farsi 2005 | Two-arm, parallel, clinical trial Saudi Arabia | 4–6-year-old healthy children | Acidulated phosphate fluoride (APF) gel and povidone iodine (PI) | Application of 10% PI solution every week for one month | dmft, S. mutans and lactobacillus count | 1, 3, 6 and 12 months | No statistically significant difference for dmft and bacterial counts. |
| Zhan et al. 2006       | Two-arm, parallel, randomized clinical trial USA | 2–6-year-old healthy children per group | Oral prophylaxis and complete restorative therapy + 2 mL PI application + 1.23% APF gel application | | Change in S. mutans, Lactobacillus count and incidence of dental caries | No statistically significant difference observed in-between the two groups |
| Xu et al. 2009         | Two-arm, parallel, randomized controlled clinical trial China | 6–9-year-old high-risk children | Fluoride foam and PI | | | |
| Tut et al. 2010        | Retrospective Cohort study USA         | 5–7-year-old high risk children | Fluoride varnish (FV) and PI | | No statistically significant difference between the groups for the outcome variables. |
| Milgrom et al. 2011    | Quasi Experimental study USA           | 1–2.5-year-old high risk children | Fluoride varnish (FV) and PI | | | 88.3% children in experimental group and 78.5% children in control group had caries-free first permanent molars |
| Hashemi et al. 2015    | Double-blind, clinical trial Iran      | 4–6-year-old high risk children | Fluoride varnish (FV) and PI | | | 41% in the experimental group and 54% in the control group had developed new decay in primary teeth |
| Reilly et al. 2016     | Single arm double baseline clinical trial USA | 6–12-year-old high risk children | Fluoride varnish (FV) and PI | | | 68% of the teeth in experimental group and 63% in control group showed carries arrest |

**Note:** dmft = decayed, missing, and filled teeth; S. mutans = Streptococcus mutans; Lactobacillus = Lactobacillus; FV = fluoride varnish; PI = povidone iodine; TF = topical fluoride; PVP-I = polyvinylpyrrolidone iodine; APF = acidulated phosphate fluoride; NaF = sodium fluoride; NaF Varnish = sodium fluoride varnish; Plaque = plaque; dmft = decayed, missing, and filled teeth; Microbiome = microbiome; plaque ecology = plaque ecology.
Topical Fluoride and Povidone Iodine Combined Therapy for Prevention of Dental Caries

Marinho et al. in a comparative analysis between fluoride varnish vs placebo or no treatment group reported a statistically significant pooled caries prevented fraction estimate of 43% in permanent teeth and 37% in deciduous teeth. This evidence having a statistically significant heterogeneity has been reported to be of moderate quality. In the present review, for the permanent teeth subgroup analysis, a statistically significant 45% risk reduction in caries increment was noted in the ‘TF + PI’ group compared to TF use alone. In deciduous teeth, however, the 21% risk reduction favoring the experimental group over TF use alone was not found to be statistically significant. Hashemi et al. using a split-mouth design in 4–6-year-old demonstrated 68% caries arrest in the combined therapy group compared to 6.3% caries arrest in the control group. PI can thus be seen to have an added benefit with TF in the prevention of dental caries, especially in the permanent teeth.

No difference was observed in-between the experimental and control groups for post-treatment S. mutans count. This could be attributed to the restorations of the caries lesions and extractions or improvement in oral hygiene practices of both the experimental group and control group population. On the contrary, Milgrom et al. found ‘TF + PI’ combined use to be more effective than TF alone in reducing bacterial count in primary teeth. The limited follow-up, small sample, along with nonrandomization limit the generalizability of this study results. Single application of 5% NaF varnish and 10% PI among high-risk children of 6–12-year-old by Reilly et al. showed a subtle change in the plaque ecology in just 1 week, although no drastic dysbacteriosis within dental plaque was noted.

Although I² statistic for the primary and secondary outcome assessment showed low/no heterogeneity, there exists some variation among the included studies with respect to variation in study design, methodology, different follow-up period, and the frequency of application of the agents. The results of this review should be interpreted cautiously. Also, it is recognized that it takes nearly 18 months before the carious lesion can be clinically detected with conventional methods. Therefore, the pooled analysis of the included studies with at least 1-year follow-up might have underreported the primary outcome in both the groups.

Furthermore, due to nonreporting of data on caries determinants such as demographic details, socioeconomic status of the study population, sugar consumption, etc., a multivariate analysis could not be used in the meta-analysis function. Given the multifactorial nature of dental caries, the odds ratio calculated might have underestimated the effectiveness of ‘TF + PI’ application. The paucity of randomized trials that assessed the caries preventive effectiveness evaluated through post-intervention Lactobacillus count also limited the pooling of the secondary outcome variable as desired. Taking the limitations into account, future randomized controlled trials with robust methodology are recommended to compare the effect of combined application of ‘TF + PI’ and TF alone.

Authors await the results of a randomized controlled trial by Milgrom et al. planned to assess the efficacy of a combination of PI and sodium fluoride dental varnish application in the prevention of new caries lesions with a 2-year follow-up (NCT03082196). Authors

Table 2: Summary chart for downs and black scoring (grading)

| Author, year       | Downs and black scores (grades) |
|--------------------|---------------------------------|
| El Housseiny et al. 2005 | 15 (fair)                        |
| Hashemi et al. 2015    | 20 (good)                        |
| Milgrom et al. 2011   | 21 (good)                        |
| Reilly et al. 2016    | 17 (fair)                        |
| Tut et al. 2010       | 18 (fair)                        |
| Xu et al. 2009        | 20 (good)                        |
| Zhan et al. 2006      | 21 (good)                        |

Fig. 1: Meta-analysis for deciduous and permanent teeth on dental caries increment
also await the results of a pragmatic, controlled trial aimed to assess the effectiveness of a specially designed oral healthcare package comprising of quarterly application of ’TF + PI’ and oral health education on oral health status among children of aged 1–6 years (CTRI/2019/02/017556).10

**CONCLUSION**

The findings of this review indicate very low-quality evidence that combined application of ‘TF + PI’ has better caries preventive effectiveness compared to TF use alone. Moreover, the limited number of studies with low internal and external validities limits the generalizability of results obtained. Therefore, future clinical trials with longer follow-up period, larger sample size, and robust methodologies are recommended in order to generate conclusive evidence.

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