Topical Iodine And Fluoride Varnish Effectiveness In The Primary Dentition: A Quasi-Experimental Study

Peter M. Milgrom DDS
Professor of Dental Public Health Sciences and Director of the Northwest Center to Reduce Oral Health Disparities, University of Washington, Seattle

Ohnmar K. Tut BDS, MPhil
Preventive Services Dentist, Ministry of Health, Republic of the Marshall Islands, Majuro

Lloyd A. Mancl, PhD
Research Associate Professor of Dental Public Health Sciences, University of Washington, Seattle

Corresponding Author: Dr. Peter Milgrom, University of Washington, Box 357475, Seattle, WA 98195-7475; telephone 206 685 4183; fax 206 685 4258; email dfrc@u.washington.edu

Reprint requests should be addressed to Dr. Peter Milgrom, University of Washington, Box 357475, Seattle, WA 98195-7475; telephone 206 685 4183; fax 206 685 4258; email dfrc@u.washington.edu

Word Count:
Abstract= 197
Text=2023
Number of tables=1
Number of figures=1
Number of References=27

Topical Iodine And Fluoride Varnish Effectiveness In The Primary Dentition: A Quasi-Experimental Study

ABSTRACT

Objective: Combining fluorides with antimicrobials may be of value because fluorides alone do not provide complete protection. The aim of this quasi-experimental study was to compare the effectiveness of combined topical treatment with polyvinylpyrollidone iodine (PVP-I) and 5% sodium fluoride varnish (FV) with FV alone. ***Methods***: 172 children 12-30 months of age received either combined or single therapy in Majuro, RMI between June 2008 and March 2009. Children received a mean of 2.5 treatments in the PVP-I combined group (range 2-3) and 2.8 treatments in the FV group (range 2-4). Children were examined. ***Results***: The proportion of children with any new decayed primary teeth was 40.7% (N=81) in the PVP-I combined group and 54.4% (N=90) in the FV group. Multivariate log-binomial regression was used to compare the rate of any new decay between groups, controlling for the number of teeth at baseline and the number of treatment visits. The risk ratio for treatment is 0.69 (95% CI 0.51-0.94). No adverse effects were observed. ***Conclusion***: Combined treatment with PVP-I and FV reduced the rate of new tooth decay by 31% over FV. If confirmed with randomized clinical trials, combined treatment offers distinct advantages over FV alone.

Key words: Oral Health, Fluoride, Fluoride Varnish, PVP-iodine, Preschool Children, Dental Caries

INTRODUCTION

The twice-yearly regimen of topical fluoride prescribed by nearly all dentists reduces new tooth decay by only about 30%, even allowing for the fact that most of these studies were not done in very high risk young children.[1] Fluoride varnish is marginally better than other forms of topical fluoride but the extra benefit of topical fluoride beyond the use of fluoridated toothpaste is not a lot.[2] Three studies have recently been published further raising questions about the effectiveness of fluoride varnish in the primary dentition in children at high risk. The first[3] used a community-randomized, no treatment (no varnish) controlled design in 20 First Nation communities in Northwest Ontario, Canada and neighboring city, non-Aboriginal childcare or preschool organizations. Communities were assigned to either fluoride varnish applied in the community setting once every four months or no treatment. Children were six months to five years of age at enrollment (14% < 1 year old, 25% 1 year old). The study reported an 18 percent reduction when Aboriginal communities with and without treatment were compared and a 24 percent reduction when all children were included. The study reported a relative risk of new dfs of 1.96 (95% CI = 1.08-3.56) for the control compared to the treatment group. Thus, both groups continued to develop new tooth decay in spite of the fluoride treatments.

The second study[4] was a one-group observational investigation, in which American Indian preschoolers received fluoride application at the 9, 12, 15, 18, 24, and 30 month well child visits and the results were compared to a "historical control" of non-study preschool children from the same community who had dental assessments at an age comparable to the study children (mean 52.8 months). The author reported that children who received four or more fluoride varnish treatments during the study period had 15.4 dmfs (95% CI 10.8-20.4) versus 23.6 dmfs (95% CI 19.5-25.8) for the comparison children, a 35 percent

reduction in decayed surfaces. Children who received one, two, or three treatments during the study period (21 months) showed no significant difference in dmfs from the comparison children.

The final study[5] was a two-arm randomized clinical trial that tested whether an intensive fluoride varnish regimen (three applications/two weeks) applied annually had an equivalent effect on caries progression in the primary dentition compared to single applications applied semi-annually. All participants (n=600; mean age =55.3 [SD=4.6] months) received three varnish applications (active varnish or placebo) at semi-annual visits over three years. The standard group received one active and two placebo treatments each six months. Children were assessed clinically at baseline and 12, 24 and 36 months after the initiation of the study. The mean numbers of new decayed in primary tooth surfaces observed over three years were 9.8 (SD=8.6) and 7.4 (SD=7.7) in the intensive and standard groups, respectively. The adjusted rate ratio was 1.13 (95% CI 0.94-1.37, p=0.20). Thus, intensive treatment with fluoride varnish was not equivalent to biannual treatment and tooth decay continued to develop in both conditions.

Increasing the frequency of application has not resulted in major reductions in tooth decay progression in children at high risk for decay.[6] Biologically, the mechanism of remineralization has limits with repeated exposure of teeth to acid degradation because of a carbohydrate-laden diet.[7-9] This is true whether or not there is fluoride in the drinking water.

There are several studies of the utility of antiseptic agents to inhibit caries in older individuals.[10,11] The rationale is based on findings that show that children with a lot of tooth decay are much more heavily infected with cariogenic organisms that once thought.[12-14] PVP-iodine interferes with the ability of *S. mutans* to bind to tooth surfaces by disrupting the expression and production of glucosyltransferase.[15] Thus, PVP-iodine makes it more difficult for the organism to maintain its place in the biofilm next to the tooth, which is required for the bacterial acids to damage the tooth surface. The *in vitro* and *in vivo* iodine antiseptic literature on dental caries of three decades ago was promising, but most human studies were very small.[16,17] There has been a recent series of pilot and small scale clinical studies of utility of PVP-I in young children, some with established active ECC, with strongly encouraging data.[18-22] One quasi-experimental study compared three applications of either FV alone or FV plus PVP-I children 60 to 83 months of age and found the proportion of caries free permanent molars was greater in the combined treatment group; however, decay continued to develop in the primary teeth in both groups.[22]

The purpose of this study was to compare the effectiveness of combined treatment with PVP-I followed by FV with treatment with FV alone. The hypothesis tested was that combination treatment was more effective in preventing new decayed teeth an FV alone.

METHODS

Design

The study employed a quasi-experimental design with two groups of children.

Setting

The study was conducted on Majuro atoll in the Republic of the Marshall Islands (RMI). The Ministry of Health was a participant in the Pacific Islands Early Childhood Caries Prevention Project conducted by the University of Washington. RMI is also a grantee of the Targeted State Maternal and Child Oral Health Service Systems program. The University of Washington Institutional Review Board approved the evaluation.

Participants

The children (N=172) were part of an ongoing public health intervention program conducted by the Ministry of Health and were 12-30 months (average 20 months) at the start of the study. In this isolated population, nearly half of children have tooth decay by 36 months of age and their are few dental resources.[23] Parents gave their permission for the children to be part of the program. Special educational materials designed for populations with low health literacy were used to inform parents.

Treatments

Children in one community (Laura) received the combination treatment and children seen at the main hospital dental clinic received FV alone. Every child within the particular setting received the same treatment. The goal was to provide

three treatments per year. Children received a mean of 2.5 treatments in the PVP-I combined group (range 2-3) and 2.8 treatments in the FV group (range 2-4). Differences were due to attendance.

Combined PVP-iodine and FV. PVP-iodine (1% active iodine, Allegiance Health Corporation, McGaw Park, IL), approved by the FDA for topical use in the mouth, was applied at the well child visits along with fluoride varnish. The children were seated in a portable dental chair or on the clinician's lap in the knee-to-knee position. Clinically, the teeth were dried with gauze and then painted with about 0.2 ml PVP-iodine. The exact amount applied clinically was not standardized. Figure 1 shows the clinical application. After application, the excess iodine was wiped from the teeth and coated with fluoride varnish at the same visit.

Fluoride Varnish. Varnish (Cavity Shield, OMNII Oral Pharmaceuticals, West Palm Beach, Fl) was applied at approximately the same intervals as the combined treatment. The teeth were wiped with cotton gauze and the varnish applied with a disposable brush. The parent was asked not to allow the child to eat, or brush their teeth for one hour.

Fluoridated Toothpaste. The children in both groups were given toothbrushes (Colgate-Palmolive, Looney Tunes 3-8 years, New York, NY) and fluoridated toothpaste (My First Colgate, 0.34% sodium monofluorophosphate, Australia) as part of the RMI dental public health program.

Clinical Examinations and Measures

A single trained examiner examined children clinically in June 2008 and March 2009. The examiner knew that one group was receiving the new treatment but was not aware which group has received the combined treatment and which group only FV. Caries prevalence is very high in this population and progresses rapidly.[23] The primary clinical evaluation outcome of the study was the number of decayed (d) deciduous teeth defined as a cavitated tooth. The examiner (OKT) was trained to the World Health Organization diagnostic protocol, and examined the teeth visually using a disposable dental mirror and artificial light. Compared to a gold standard examiner (PM), the examiner previously demonstrated excellent reliability for caries diagnosis (ICC=.96-1.00).

Statistical Analysis

De-identified data were provided for the analysis. The data were cleaned and entered into SPSS Version 16 for Mac. To assess the outcome the d component of the WHO assessment scheme at the first examination was subtracted from d component at the second examination and dichotomized as either with or without new decay. Multivariate log-binomial regression with robust standard error estimates was used to compare the rate of any new decay between groups, controlling for the number of teeth at baseline and the number of treatment visits.[24]

RESULTS

Participation

All of the children were examined both time points in both cohorts. One child was lost to follow-up. Boys and girls were equally distributed in both groups. The socioeconomic characteristics of the two groups of children were quite similar (per capita income around $2500).

Caries Level

The mean (SD) number of decayed teeth at the initial examination was 2.4 (SD=3.3) in the PVP-I combined treatment group and 2.7 (SD=4.1) in the FV alone group. (Wilcoxon rank sum test, p-value = 0.61). The mean (SD) number of teeth at baseline was 17.1 (SD=4.4) in the PVP-I combined treatment group and 15.1 (SD=5.3) in the FV alone group (Wilcoxon rank sum test, p-value = 0.0053)

The proportion of children with any new decayed primary teeth was 40.7% (N=81) in the PVP-I combined group and 54.4% (N=90) in the FV group. The risk ratio for treatment is 0.69 (95% CI 0.51-0.94). Combined treatment with PVP-I and FV reduced the rate of new tooth decay by 31% over FV. Table 1 gives the results of the regression analysis, controlling for both the number of teeth at baseline and number of treatments. Adjusting for base-line decay did not change the results (data not shown).

Adverse Effects

None of the children experienced any side effects secondary to PVP-iodine treatment. There was no staining of the teeth in the PVP-iodine plus fluoride cohort. There were also no adverse effects unrelated to the treatments.

DISCUSSION

The results are generally consistent with earlier pilot studies children suggesting that combination treatment with antiseptics and fluoride varnish are more effective than fluoride treatments alone. However, the results contrast those of our earlier retrospective cohort study of children in transitional dentition where the combined treatment benefited erupting permanent molars but did not appear to protect the already infected and extensively damaged primary dentition.[22] Application of PVP-I topically before fluoride varnish is clinically simple, quick, and inexpensive. None of the previous studies or this one reported any side effects. The results of this study are important because rates of tooth decay are so high in many at-risk populations.

Limitations

The study used a quasi-experimental design in which children were not randomly assigned to treatments. Two locations were arbitrarily chosen by the dental program to be test area and other control area based on staff and resource availability. Nevertheless, these results improve on our previous work[22] on older children because time effects are controlled. The earlier study had compared results from two different school years widely separated while in this study both

groups were studied in the same period. Also, in this study the examiner was blind to the treatments the children received whereas the examiner in the earlier study was aware of the treatments. The follow-up period was only one school year. The examinations were a routine part of an on-going dental public health program conducted by the RMI government. However, in this case the examiner was unaware of which area had been assigned to particular treatments. The follow-up period was short but new lesions develop quickly in this high risk population. Nevertheless, these limitations impact the generalizability of the results.

While the findings should be interpreted with caution, the results, taken along with earlier studies, are significant and argue persuasively for randomized clinical trials of combination treatment in children at high risk for tooth decay. Such studies need to follow the children for a longer time and should be focused on children with erupting teeth where the antimicrobial effect is maximized. Similarly studies are needed to prevent relapse in children with severe Early Childhood Caries who are treated. Xylitol, with specific activity against *Streptococcus* mutans, is also a candidate for combination treatment in addition to PVP-iodine.[25-26] A recent review of prevention technology since the Surgeon General's report made the same call.[27]

Acknowledgements

This project was supported, in part, by Head Start Innovation and Improvement Project Grant No. 90YD0188 from the Office of Head Start, Agency for Children and Families, Grant No. U54DE019346 from NIDCR, NIH (UW), and Grant No: H47MC08647, Targeted State Maternal and Child Oral Health Service Systems, from HRSA (RMI).

REFERENCES

1. Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride varnishes for preventing dental caries in children and adolescents. *Cochrane Database of Systematic Reviews* 2002, Issue 1. Art. No.: CD002279. DOI: 10.1002/14651858.CD002279. Accessed September 3, 2007, http://doi.wiley.com/10.1002/14651858.CD002279.
2. Marinho V CC, Higgins JPT, Sheiham A, Logan S. Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews: Reviews 2004 Issue 1. DOI: 10.1002/14651858.CD002781.pub2. http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007868/Frame.html. Accessed June 25, 2010.
3. Lawrence HP, Binguis D, Douglas J, McKeown L, Switzer B, Figueiredo R,

Laporte A: A 2-year community-randomized controlled trial of fluoride varnish to prevent early childhood caries in Aboriginal children. Community Dent OralEpidemiol. 2008 Dec;36(6):503-516.

4. Holve S: An observational study of the association of fluoride varnish applied during well child visits and the prevention of early childhood caries in American Indian Children. Matern Child Health J 2008 Jul;12 Suppl 1:64-67.
5. Weinstein P, Spiekerman C, Milgrom P. Randomized equivalence trial of intensive and semiannual applications of fluoride varnish in the primary dentition. Caries Res. 2009;43(6):484-90.
6. Seppä, L. Studies of fluoride varnishes in Finland. Proc Finn Dent Soc 1991;87(4):541-7.
7. Tinanoff N, Daley NS, O'Sullivan DM, Douglass JM. Failure of intense preventive efforts to arrest early childhood and rampant caries: three case reports. Pediatr Dent 1999 May-Jun;21(3):160-3.
8. Featherstone JD. The science and practice of caries prevention. J Am Dent Assoc 2000 Jul;131 (7):887-99.
9. Featherstone JD. Delivery challenges for fluoride, chlorhexidine and xylitol. BMC Oral Health. 2006;15;6:Suppl1:58.
10. Köhler B, Andréen I. Influence of caries-preventive measures in mothers on cariogenic bacteria and caries experience in their children. Arch Oral Biol. 1994 Oct;39(10):907-11.

11. Zickert I, Emilson CG, Krasse B. Effect of caries preventive measures in children highly infected with the bacterium Streptococcus mutans. Arch Oral Biol. 1982;27(10):861-8.
12. Marsh PD, Featherston A, McKee AS, Hallsworth AS, Robinson C, Weatherall JA, Newman HN, Pitter AF. A microbiological study of early caries of approximal surfaces in schoolchildren. J Dent Res. 1989 Jul;68(7):1151-4.
13. Marchant S, Brailsford SR, Twomey AC, Roberts GJ, Beighton D. The predominant microflora of nursing caries lesions. Caries Res. 2001 Nov-Dec;35(6):397-406.
14. Aas JA, Griffen AL, Dardis SR, Lee AM, Olsen I, Dewhirst FE, Leys EJ, Paster BJ. Bacteria of dental caries in primary and permanent teeth in children and young adults. J Clin Microbiol. 2008 Apr;46(4):1407-17. Epub 2008 Jan 23.
15. Tam A, Shemesh M, Wormser U, Sintov A, Steinberg D. Effect of different iodine formulations on the expression and activity of Streptococcus mutans glucosyltransferase and fructosyltransferases in biofilm and planktonic environments. J Antimicrob Chemother. 2006 May;57(5):865-71.
16. Tanzer JM, Slee AM, Kamay B and Scheer ER. In vitro evaluation of three iodine-containing compounds as antiplaque agents. Antimicrob Agents Chemother. 1977;12:107-13.
17. Caufield PW, Wannemuehler YM. In vitro susceptibility of *Streptococcus*

mutans 6715 to iodine and sodium fluoride, singly and in combination, at various pH values. Antimicrob Agents Chemother. 1982 Jul;2(1):115-9.

18. Tinanoff N, O'Sullivan DM. Early Childhood caries: overview and recent findings. Pediatr Dent. 1997;19:12-6.
19. Zahn L, Featherstone JDB, Gansky SA, Hoover CI, Fujino T, Berkowitz RJ, DenBesten PK. Antibacterial treatment needed for severe early childhood caries. J Pub Health Dent. 2006;66:174-9.
20. Amin MS, Harrison RL, Benton TS, Roberts MC, Weinstein P. Effect of povidone-iodine on *Streptococcus mutans* in children with extensive dental caries. Pediatr Dent. 2004;26:5-10.
21. Lopez L, Berkowitz RJ, Spiekerman C, and Weinstein P. Topical antimicrobial therapy in the prevention of early childhood caries: a follow-up report. Pediatr Dent. 2002;24:204-6.
22. Tut OK, Milgrom PM. Topical iodine and fluoride varnish combined is more effective than fluoride varnish alone for protecting erupting first permanent molars: A retrospective cohort study. J Pub Health Dent. 2010 Mar 10 [Epub ahead of print].
23. Tut OK, Greer MHK, Milgrom P. Republic of the Marshall Islands: Planning and implementation of a dental caries prevention program for an island nation. Pacific Health Dialog. 2005;12(1):118-23.
24. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005;162:199-205.
25. Ly KA, Riedy CA, Milgrom P, Rothen M, Roberts MC, Zhou L. Xylitol

gummy bear snacks: a school based randomized clinical trial. BMC Oral Health. 2008 Jul 25;8:20.

26. Milgrom P, Ly KA, Tut OK, Mancl L, Roberts MC, Briand K, Gancio MJ. Xylitol pediatric topical oral syrup to prevent dental caries: A double blind, randomized clinical trial of efficacy. Arch Pediatr Adolesc Med. 2009 Jul;163(7):601-7.

27. Milgrom P, Zero DT, Tanzer JM. An examination of the advances in science and technology of prevention of tooth decay in young children since the Surgeon General's Report on Oral Health. Acad Pediatr. 2009;9(6):404-9.

Figure 1: Clinical photograph showing application of topical PVP-I in a preschool child.

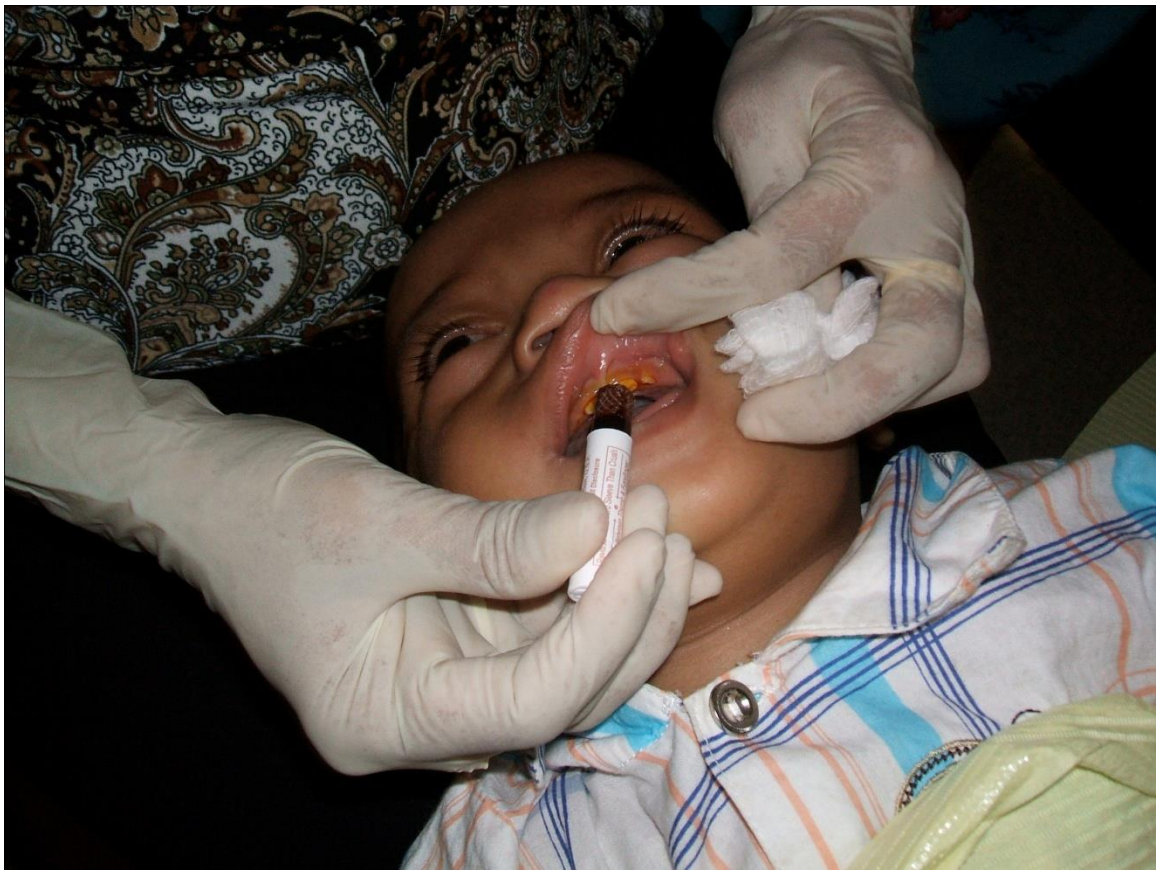

Table 1: Log-binomial regression results comparing combined treatment with PVP-I and fluoride varnish versus fluoride varnish alone in preschoolers

Variables	Risk Ratio	95% Confidence Interval	P-value
Bivariate:			
Treatment (1 vs 2)	0.75	0.54-1.30	0.079
Multivariate:			
Treatment (1 vs 2)	0.69	0.51-0.94	0.020
No. teeth at start	1.08	1.02 – 1.04	0.0003
No. treatments	1.02	0.76 – 1.37	0.90