

Effectiveness of Fluoride Varnish in Prevention of Early Childhood Caries in 3-4 Years Old Children – A 36 Month Prospective Community Based Randomized Controlled Trial

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Background: Evidence for the benefit of applying Fluoride Varnish FV to permanent teeth is generally very positive. However, the caries-inhibiting effect of FVs on primary teeth is still debatable. Aim: To assess the effectiveness of fluoride varnish in prevention of early childhood caries in children over the period of 3 years in high fluoride areas. Study design: A double-blind cluster-randomized controlled trial was undertaken amongst 3-4 years old children. The varnish application was done at three points in the intervention group. Results: Experimental group showed significantly lesser increment in mean ICDAS score than control group at both 12 month and 36 months. Preventive fraction was 72.4% at 12 months and 18.2% at 36 months. Multiple linear regression showed that at 12 months, intervention was the significant predictor with varnish group having 0.140 (95% CI 0.175–0.230) lower net caries increment. At 36 months, baseline ICDAS score and intervention were the significant predictors. Conclusion: This study suggests that fluoride varnish is an effective and a safe mode of prevention of early childhood caries in children residing in high fluoride zone. However, the overall effect is influenced by the baseline caries status.

Keywords: Fluoride varnish, early childhood caries, randomized controlled trial.

INTRODUCTION

Early childhood caries (ECC) is one of the major oral disease burdens across the world irrespective of the nation's economy and health care system. ECC result in gross destruction and cavitation in the primary teeth of young children and further leads to pain, infection and loss of function if not intervened in time.^{1,2} It is the most common chronic dental disease that can be present in preschool children and may develop with the first primary tooth in oral cavity.³ Primary maxillary central incisors are at greater risk of involvement because of their early eruption followed by primary molars.^{2,4}

The problem is more critical in the developing countries.⁵ A recent systematic review conducted by Ganesh *et al*⁶ revealed an alarming prevalence rate of 49.6% of ECC in India. Treating the teeth of such mammoth amount of young population is not only a difficult and exhausting but also a financial burden. With the meagre percentage of total national gross domestic product (GDP) spent in India on health care system and negligible amount on oral health care, it becomes imperative to endeavor on prevention rather than cure of such diseases. Moreover, to bring about any reforms upstream, there should be corresponding evidence of improvisation downstream.

Dental caries is multifactorial i.e. those related to the agent, host or substrate. These factors are intermingled with one leading to the other. So, a well-planned, systematic and integrated approach is

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required for the prevention. The various interventions used for ECC prevention are dental health education, counseling, dietary interventions, fluorides and a visit to health care personnel (e.g. dentists, dental hygienists, health visitors).⁷ Among the fluoride therapies Fluoride varnish (FV) is the most suitable for this age children as it can be applied quickly causing less patient discomfort and hence greater patient acceptability.⁸

Evidence for the benefit of applying FV to permanent teeth is generally very positive.^{9,10} However, the caries-inhibiting effect of FVs on primary teeth is still debatable. There are many systematic reviews conducted over time to pool the evidence for the effectiveness of FV in reducing caries in the primary dentition. Petersson *et al*¹¹ and Carvalho *et al*¹² reported inconclusive evidence of caries preventive effect of fluoride varnish in primary dentition in their respective reviews. However, Marino *et al*^{13,14} suggested a substantial effect in inhibiting caries in primary teeth in both of her systematic reviews. Twetman *et al*¹⁵ reported that fluoride varnish may result in a reduction in ECC incidence to some extent but it is still inconclusive because of a low level of evidence. Recently, Sousa *et al*¹⁶ conducted another review on the subject and showed that the effectiveness of fluoride varnish is lower as per recent trials probably due to selection bias in older trials or more modes of fluoride exposure of children in recent times. One recommendation which was invariably common to all the reviews was the need for more clinical randomized clinical trials with better methodological quality. There is a further need to analyze the long term effects of fluoride varnish. Moreover, considering the role of existing fluoride at a place, the effectiveness in high fluoride regions may not be at par with optimal or non-fluoridated areas as there is a continuous fluoride exposure occurring through, dentifrice, food and water.

The recommended frequency of varnish application may vary from 1-4 times per year, but in the majority of public health programs, it rarely adheres to the desired need as it largely depends upon various factors such as geographical location, funding, existing other fluoride sources and willingness of participants. Therefore, it is important to identify the effectiveness of varnish application in real-life scenarios.¹⁷

Therefore, in the paucity of results of long term effectiveness of community-based fluoride varnish application in high fluoride areas in the prevention of ECC, the present study was undertaken with a pragmatic approach to assess the effectiveness of fluoride varnish in prevention of early childhood caries in 3-4 years old children in Rohtak district; Haryana, over the period of 3 years.

MATERIALS AND METHOD

Trial Design

A 36 months, **double-blind cluster-randomized controlled trial** in community settings was conducted at Anganwadi centers (AWCs) and schools of Rohtak district amongst 3-4 years old preschool children living in high fluoride from August, 2015 to December, 2018. Children were randomly assigned by using the lottery method. The present study followed the guidelines of CONSORT statement for randomized controlled trials. The trial has been registered in Clinical Trial Registry – India (CTRI) with CTRI number CTRI/2015/10/006288.

Sample Size

The sample size was calculated to estimate a clinical difference of 0.9 with a pooled deviation of 3 at 80% power & a 95% significance level. As it was cluster trial the average cluster size was fixed at 8 and a design effect of 1.3 was calculated. The final sample size based on cluster design and 10% attrition rate was 256 children for each group.

Randomization

The study used cluster randomization. Rohtak was randomly selected from 5 block divisions of Rohtak district. 67 clusters were systematically selected from the list of 285 schools with the preschool facility and 1004 Anganwadi centers (AWCs). At each cluster a second examiner examined all the children at the center & selected eight participants systematically among the eligible participants. The participants were then randomized with block randomization using sequentially generated envelopes. The envelope was selected and opened by the Anganwadi worker in front of the second examiner. The participant were then sent to the principal investigator one by one leading to allocation concealment. The current study regions vastly comprised of high fluoride zones with fluoride level of above 2ppm in drinking water.

Participants

Children who were permanent residents and not likely to migrate from that area, having high caries risk and whose parents gave informed consent, were included in the study. Caries risk assessment was done using American Dental Association Caries risk assessment tool. Children with history of allergy to fluoride varnish, any long term medication or systemic diseases, congenital and developmental anomalies, reduced mouth opening, having stomatitis or gingivitis were excluded from the study.

Intervention

Fluoritop SR™, ICPA Health Products Ltd, (22600 ppm fluoride) between 0.3 and 0.5 ml (2–5 drops) was applied to all teeth. Teeth were first dried with the help of cotton swabs followed by application of fluoride varnish using disposable plastic brushes to all surfaces of fully or partially erupted teeth, even if they had caries. Varnish was first applied to mandibular molars followed by mandibular incisors, maxillary molars & maxillary incisors. Excess varnish on the soft tissues was removed with gauze and the caretaker was asked to ensure that the child was kept abstained from drinking any liquid for the following 30 minutes and having solid food for the entire day. Parents or caregivers were also given a pamphlet with post fluoride application instructions. The varnish application was done at three points i.e. at baseline, 6 months and 12 months in the intervention group. While in the control group, teeth were painted with plain water for blinding.

Data Collection

Clinical examination

Examinations were conducted by trained dentist unaware of group assignment. Calibration exercise for making a clinical diagnosis of dental caries was carried out in the department prior to the start of this study. All diagnostic criteria and uncertainties were discussed and resolved. Tooth status was assessed by careful visual and tactile inspection using a mouth-mirror and ball ended

explorer after drying. Diagnostic criteria for dental caries were based on the International Caries Detection and Assessment System (ICDAS II) criteria.¹⁸ A random sample of 10% of the study population was re-examined at the baseline and follow-up examinations to monitor intra-examiner reproducibility ($\kappa=0.82$). Parents or caretakers were advised the dental treatment for the children wherever required. When signs of reversible/ irreversible pulpitis and any other pulpal pathology were there, immediate dental treatment was recommended.

All parents were asked to complete a structured questionnaire at baseline to collect information on the child's socio-demographic background and child's oral health-related behaviour. Sugar score was calculated for the previous days using Nizel and Pappas 24 hour diet method. The socioeconomic status of participants in this study was determined by BG Prasad Scale.¹⁹

Outcomes

The primary outcome was net caries increment, as measured by change from baseline to 36 months. The caries increment at the tooth level at 12 months and 36 months were computed. Caries increment was counted if the surface status changes from 'sound or filled at baseline' to 'first visual change in enamel to clinical caries', 'missing due to carious extraction' or 'stainless steel crown' at the follow-up examination. Caries reversals (white spots or early demineralization to sound) were subtracted from the caries increment, creating a 'net' caries increment.⁸

Loss to Follow-Up

Children who did not attend their varnish application appointments and/or could not be contacted after a minimum of 2 telephone calls/home visit were considered loss to follow up. The investigators stayed in contact with teachers and anganwadi workers to report for any adverse event successive to varnish application and to arrange for follow up visits.

Statistical Analysis

The data was analyzed using SPSS 21 (Statistical Package for Social Sciences) package for relevant statistical comparison. Data analysis for comparing net caries increment between and within groups was carried out. Non-parametric Mann-Whitney U-test was used to analyze net caries increment between the groups. Linear regression was used to model the relationship between dependent (net caries increment) and independent variables (gender, SES, sugar score, brushing frequency, group) significant for $p<0.05$.

Ethical clearance was obtained from the Institution Ethics committee of vide letter no. PGIDS/IEC/2015/57 dated 19/05/2015. Permission from the concerned authorities of the selected schools was taken prior to the study. Parents were provided with the information sheet regarding the study before taking informed consent for the examination and intervention.

RESULTS

A randomized controlled trial was done in preschools and anganwadis of Rohtak district among 515 preschool children. At baseline, 256 subjects were in experimental group and 259 were in control group. Gender distribution did not have much difference with 54% males and 46% females (Table 1). Attrition rate in both groups was around 40% and 24% at 12 months and 36 months respectively

(Fig.1). The mean age of study population was 3.29 ± 0.281 years. As per socio-economic class distribution of study subjects among experimental and control group is concerned, majority of participants belonged to lower middle or lower class (Table 1). Overall in both the groups, it was observed that 44.3% children cleaned their teeth once daily, 11.8% twice daily, 26.2% sometimes and 17.9% of them never brushed their teeth. Nearly 75.5% used fluoridated toothpaste, 5% reported to use non-fluoridated toothpaste for their ward and 19.4% subjects were not using toothpaste without any significant difference among the groups. In the current study overall caries prevalence was found to be 49.9%. Most of the children existed in the "watch out" zone of sugar score. Mean ICDAS score was reported to be significantly higher in experimental group than control group at baseline (Table 1).

Table 2 depicts that there was a significant difference between the two groups in net caries increment as per protocol and intention to treat analysis. Experimental group showed significantly lesser increment in mean ICDAS score than control group at both 12 month and 36 months. Further analysis was done with respect to the number of fluoride varnish applications. Those with at least one or two applications had significantly lower new caries lesions in experimental group than in control group. However, there was no significant difference reported between the two groups with third application (Table 3). Preventive fraction i.e. the proportion

Table 1: Baseline demographic details and oral hygiene knowledge and practices

	Experimental Group	Control Group	P value
Gender (n) (Male/ Female)	139/117	139/120	$p>0.05$
Parent's age (mean±sd) (father's/mother's)	31.81±4.629/ 27.85±4.268	31.68±5.179/ 27.66±4.426	$p>0.05$
Socio-economic status n(%)			
Upper	29(11.3)	26(10.0)	$p>0.05$
Upper middle	43(16.7)	35(13.5)	
Middle	38(14.8)	45(17.3)	
Lower middle	80(31.2)	83(32.0)	
Lower	66(25.7)	70(27.0)	
Frequency of brushing teeth n(%)			
Once daily	105(41.0)	123(47.4)	$p>0.05$
Twice daily	32(12.5)	29(11.1)	
Sometimes	76(29.6)	58(22.3)	
Never brushed teeth	43(16.7)	49(18.9)	
Type of toothpaste used n(%)			
Fluoridated	196(76.5)	193(74.5)	$p>0.05$
Non-Fluoridated	14(5.4)	12(4.6)	
No Toothpaste	46(1.7)	54(20.8)	
Sugar score n(%)			
Excellent (<5)	10(3.9)	11(4.24)	$p>0.05$
Good (6-10)	15(5.8)	17(6.5)	
Watch out (>10)	231(90.2)	231(89.1)	
Caries at baseline (mean±sd)	3.898 ± 4.912	0.741 ± 2.011	$P<0.05$

sd=standard deviation

of caries in the subjects that was averted due to varnish application was 72.4% at 12 months and 18.2% at 36 months.

A multiple linear regression was calculated to predict net caries increment based on gender, SES, brushing frequency, sugar score, baseline caries and intervention at 12 and 36 months. Both adjusted and unadjusted models were assessed. At 12 months, intervention was the significant predictor with varnish group having 0.140 (95%

CI 0.175–0.230) lower net caries increment. At 36 months, baseline ICDAS score and intervention were the significant predictors where participant's caries score increased 0.182 (95% CI 0.68 – 0.374) with each unit increase in baseline ICDAS score and varnish group had 0.154 (95% CI 0.129 – 0.495) lower increment than control (Table 4).

Figure. 1: Flowchart of recruitment and follow-up visits of study participants

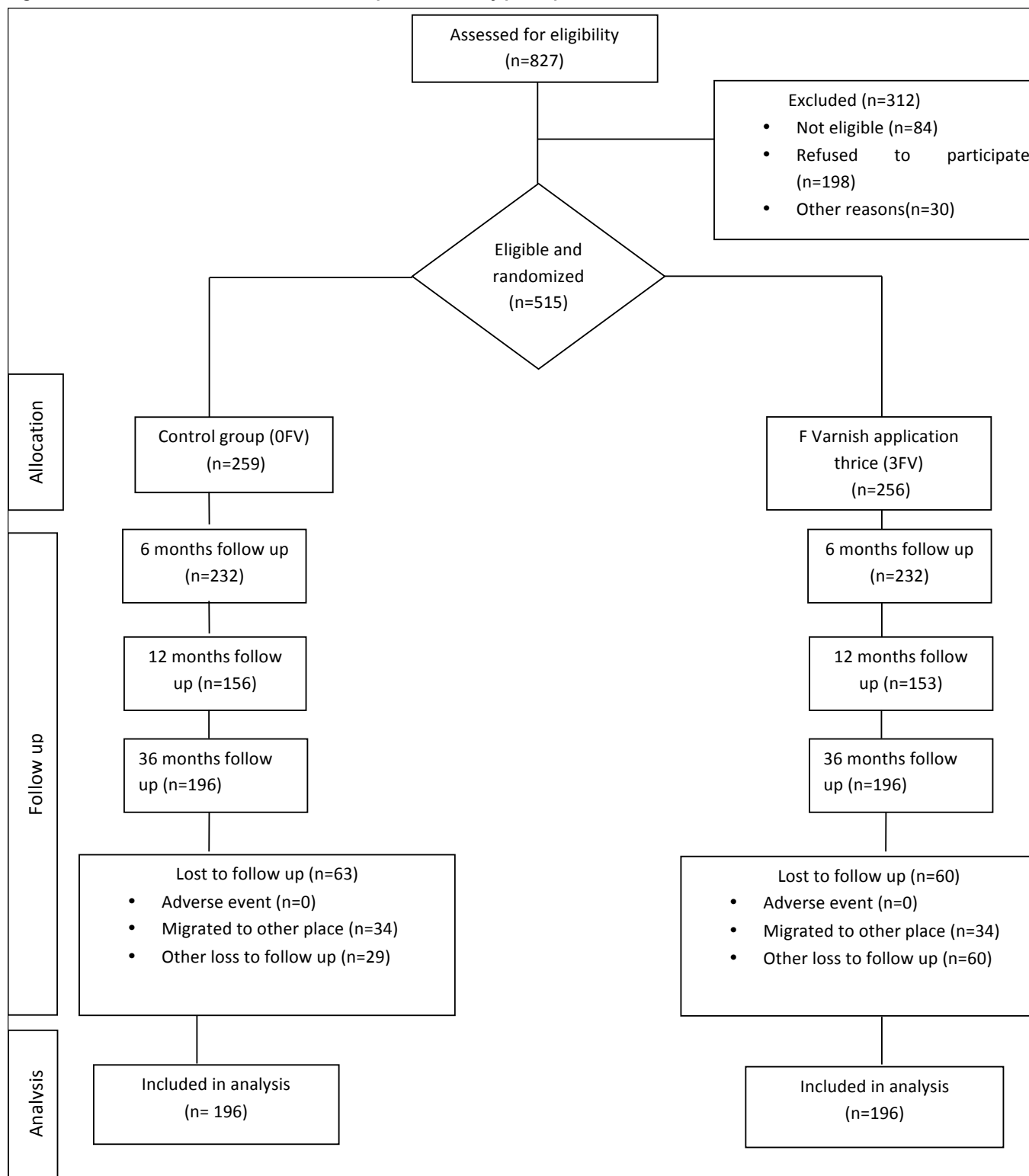


Table 2: Net caries increment at 12 months and 36 months

Period	Experimental Group	Control Group	P value	Experimental Group	Control Group	P value
	PPT			ITT		
AT 12 MONTHS (mean $\pm$ sd)	0.594 $\pm$ 4.130	2.153 $\pm$ 4.586	P<0.05	0.355 $\pm$ 3.202	1.297 $\pm$ 3.708	P<0.05
AT 36 MONTHS (mean $\pm$ sd)	5.408 $\pm$ 7.608	6.612 $\pm$ 6.731	P<0.05	4.140 $\pm$ 7.038	5.003 $\pm$ 6.506	P<0.05

PPT= per protocol; ITT= intention to treat; sd=standard deviation

Table 3: Net Caries Increment over 36 month time period with number of fluoride varnish applications

Number of varnish applications	Experimental Group	Control Group	P value
At least once (mean $\pm$ sd)	5.40 $\pm$ 7.60	6.61 $\pm$ 6.73	P<0.05
At least twice (mean $\pm$ sd)	5.69 $\pm$ 7.72	6.69 $\pm$ 6.69	P<0.05
All three times (mean $\pm$ sd)	7.09 $\pm$ 6.91	6.61 $\pm$ 6.73	p>0.05

sd=standard deviation

Table 4: Unadjusted and adjusted models for demographic and health related characteristics and net caries increment at 12month and 36 month

At 12 month								
Variables	Unadjusted model				Adjusted model			
	SE	P-value	95% CI		SE	P-value	95% CI	
Gender	.040	.508	.487	-.646, 1.353	.045	.505	.432	-.596, 1.390
Males								
Females(ref)								
SES	.060	.292	.290	-.264, .883	.057	.303	.338	-.306, .886
Upper class								
Middle class								
Lower class (ref)								
Sugar score	.017	.560	.770	-.938, 1.26	.021	.559	.712	-.893, 1.306
Excellent								
Good								
Watch out (ref)								
Brushing frequency	.038	.512	.501	-.662, 1.35	.011	.530	.851	-.943, 1.143
More than once								
Less than once (ref)								
Group	-.176	.497	.002	-2.53, -.581	-.140	.540	.023	-.230, -.175
Varnish								
Control (ref)								
Mean dental caries at baseline	-.144	.061	.011	-.276, .036	-.098	.066	.109	-.237, .024
At 36 month								
Variables	Unadjusted model				Adjusted model			
	SE	P-value	95% CI		SE	P-value	95% CI	
Gender	.036	.730	.475	-.914, 1.959	.023	.717	.642	-1.076, 1.743
Males								
Females(ref)								
SES	.070	.424	.168	-.248, 1.419	.050	.441	.339	-.445, 1.288
Upper class								
Middle class								
Lower class (ref)								
Sugar score	-.012	.852	.812	-1.877, 1.472	-.032	.837	.518	-2.187, 1.103
Excellent								
Good								
Watch out (ref)								
Brushing frequency	.075	.732	.139	-.353, 2.524	.064	.759	.223	-.566, 2.420
More than once								
Less than once (ref)								
Group	-.084	.726	.098	-2.63, 0.22	-.154	.778	.005	-3.74, -0.68
Varnish								
Control (ref)								
Mean dental caries at baseline	0.12	.086	.017	0.036-0.376	.182	.093	.001	.129, .495

DISCUSSION

The current study was a longitudinal study having pragmatic approach with three varnish applications amongst the children residing in high fluoride regions with final follow up done at 36 months. It revealed that three varnish applications at three points at six months interval bring about significant decrease in net caries increment for both short and long period of time. This result is in accordance to Autio-Gold *et al*²⁰ and Divaris *et al*²¹ where reduction in caries risk and arresting of early enamel lesions was observed respectively with fluoride varnish application in high risk population. Unconventionally, Autio-Gold *et al*²⁰ applied varnish twice at interval of four months in schools where the drinking water contained 0.8ppm fluoride. Whereas, Divaris *et al*²¹ tested biannual fluoride application for two years but with varying water fluoride concentration i.e. more or less than 0.6ppm and showed maximum varnish effectiveness on sound tooth surfaces. However, results in the present study are in contrast to few recent and contemporary trials.^{22,23} This is perhaps due to vast difference in fluoride concentration in drinking water in the regions of studies. Study regions in the current study majorly consisted of drinking water with fluoride level of above 2ppm²⁴ while that conducted by Muñoz-Millan *et al*²³ was amongst the children without the access to fluoridated drinking water.

Weintraub *et al*²³ reported reduction in caries increment with fluoride varnish, but children with caries at baseline were excluded. In the present study, both groups had substantial caries experience at baseline; so net caries increment over three years was estimated. Besides, net caries increment gives the real picture of fluoride effectiveness in limiting caries as it accounts for reversal of white lesions to sound surface as well.

Similar scenario was observed amongst the participants in the study by Lawrence *et al*⁸ where there was 18% reduction in net dmfs increment with fluoride varnish. In this study sub group analysis showed that effectiveness of fluoride varnish depends on caries at the baseline similar to current findings as the only predictor influencing net caries increment significantly in the present study was caries experience at baseline. Sugar score association with net caries increment was assessed; which was found to be insignificant in contrast to Arruda *et al*¹⁰ This can be attributed to the fact that the study areas were situated in high fluoride zone which reduces the effects of sugar. Further, the diet consumed is generally fibrous in nature which has its own cleansing effect.

Prevented fraction at 36 months in the present trial corroborates to the findings of that of Munoz-Millan *et al*²³ (18.9%) and Lawrence *et al*⁸ (18.3%). However, it is much below to that reported by Oliveira *et al*²⁶ (28.6%), Weintraub *et al*²⁵ (53%) and Marinho *et al*¹³ (33%). This was perhaps due to the difference in baseline characteristics of the population. Drastic change in preventive fraction from 72.4% at 12 months to 18.2% at 36 months shows that until varnish was being applied, prevention of caries due to FV was higher but over the time, its effect reduced and caries being irreversible increased.

More number of fluoride varnish applications is considered to improve the carious lesions.^{8,10,25} A quarterly application is indicated in the high-risk category. However, Holve *et al*²⁷ found no additional benefit in decrease in mean dmfs score with greater number of applications. The current study too somewhat hints similar outcomes as those who received at least one or two applications had significant difference in net caries increment than those with all three applications.

The high drop-out rate in this study was similar to that reported by Weintraub *et al*²⁵, Muñoz-Millan *et al*²³ owing to migration of the participants to other places, dropping out from the schools or non-willingness to participate in between the study period. Probably, this represents the real-life situation in communities with lower dental access and where perceived oral health needs are low and primary dentition doesn't get much attention as it is considered a transition to the successors.

Intention to treat (ITT) works on the principal that once randomized always analyzed and is considered as a standard for analysis of clinical trials especially following CONSORT guidelines. It prevents exaggerated estimates due to intervention. This study used last observation carry forward approach for ITT. Authors recommend that both PP and ITT should be reported for a better interpretation in RCTs. This study found varnish intervention to be effective in both scenarios. No adverse effects were reported on trial participants.

To the best of the author's knowledge, this is the first study conducted in this high fluoridated region with three years of follow up. There are a few other studies with 3 years of follow up; but included other interventions along with varnish application thereby clouding the pure effect of fluoride varnish on caries. Results of the present study can be generalized owing to substantial sample size, sound methodology and use of pragmatic approach.

A high difference in baseline caries status is an important limitation of this study. Adaptive randomization can be used in future studies. In this study, application was done at the nearest centers which were generally within half a kilometer range. Anganwadi workers directly contacted the participants and the principal investigator contacted via telephone but the desired compliance was not achieved. A more intensive approach can be used to prevent drop outs. Bi-annual fluoride applications could be preferred over quarterly applications.

CONCLUSION

This study suggests that fluoride varnish is an effective and a safe mode of prevention of early childhood caries in children residing in high fluoride zone. However, the overall effect is influenced by the baseline caries status. Despite considering the fact that there must be fluoride exposure from other sources like water, food and possibly fluoridated tooth paste in both groups, fluoride varnish is an effective means of preventing early childhood caries in high risk children residing in high fluoride areas.

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