Efficacy of silver diamine fluoride as a topical fluoride agent compared to fluoride varnish and acidulated phosphate fluoride gel: An *in vivo* study

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ABSTRACT

Silver diamine fluoride (SDF) is already proven as an antibacterial agent *in vitro*. The present study was formulated to compare the efficacy of SDF as a topical fluoride agent *in vivo* with Fluoride Varnish and Acidulated phosphate fluoride (APF) Gel. A total of 123 children comprised of 82 boys and 41 girls were included in the study for a period of 18 months. Children were divided into three different groups - Group 1: SDF; Group 2: Fluoride Varnish; Group 3: APF Gel. All Subjects were evaluated through decayed, missing, and filled surface (dmfs) + DMFS index at 6th, 12th and 18th months as well as fluoride content in enamel at 6th month of follow-up. Significant increase in fluoride content of enamel was found in Group 1 when compared with Group 2 and 3, whereas no significant difference was found between Group 2 and 3. Reduction in dental caries found in all groups but inter group comparison shows no significant difference. *In vivo* application of SDF on enamel significantly increases fluoride content in enamel as compared to Fluoride Varnish and APF Gel and can be used effectively as topical fluoride agent.

Key words: Caries prevention, Enamel biopsy, Silver diamine fluoride, Topical fluoride agent

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INTRODUCTION

Dental caries is still one of the most common chronic dental diseases affecting various age bars in all countries and all populations with varying degree of severity. Treatment of the dental caries may require advanced skills of clinicians and high cost of general anesthesia for patient management.[1] In 1941 Bibby began era of topical fluorides with the use of a solution of 0.1% sodium fluoride (NaF).[2] Subsequently over the years various other topical fluoride agents have been evolved, which in sequential order are Stannous Fluoride (SnF_2) (1947), Acidulated Phosphate Fluoride (APF) (1963), Varnish containing Fluoride (1964) and Amine Fluoride (1967). Fluorides have been proved to be the single most effective weapon in still limited arsenal of anticaries agents in last 60 years. Studies also conclude that caries preventive effects of fluoride are almost exclusively topical.[3,4] Fluoride exerts its caries-protective properties in several ways. Fluoride concentrated in plaque and saliva can inhibit demineralization of dental hard tissue. Fluoride has also been shown to inhibit the process by which cariogenic bacteria metabolize carbohydrates to produce acids, and thus affect the bacterial production of adhesive polysaccharides.[5] Fluoride taken up along with calcium and phosphate by demineralized dental hard tissue forms a crystalline structure (remineralization) that is more resistant to the challenges of bacterial acid.[6] Until date, fluoride Varnish and 1.23% APF Gel were the most commonly used professionally applied topical fluoride (PATF) agents,[7] still none of them have proved completely satisfactory.

Silver diamine fluoride (SDF) (38% w/v) (Molecular formula: Ag $(NH_3)_2F$. E.g. Saforide solution [J Morita

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Company, JAPAN]) was introduced in Japan in 1970's. Since then it was used in Japan as an effective caries arresting agent.[8] Many *in vivo*[9-11] as well as *in vitro* trials[12,13] were done to evaluate its caries arresting potential and antibacterial effect. Until date, no *in vivo* study has been reported to check its efficacy as a topical fluoride agent when applied on enamel surface.

Aims and objectives

Keeping the above mentioned discussion in mind this study was formulated to compare the efficacy of SDF with Fluoride Varnish and APF Gel on caries prevention with the following objectives:

1. To compare increase in fluoride concentration of the enamel after application of SDF, Fluoride Varnish, APF Gel.
2. To check development of new carious lesions after application of above mentioned topical fluoride agents.

MATERIALS AND METHODS

The study was conducted in the Department of Pedodontics and Preventive Dentistry, Ahmedabad Dental College, Gandhinagar. It was a randomized, controlled, prospective *in vivo* study. Study Protocol was approved from Ethical Committee of Ahmedabad Dental College and Hospital.

A total of 419 children were screened from four primary and secondary government funded schools in Gandhinagar district, Gujarat, India. As these schools are government funded schools, children in these schools are from low socio-economic status. As they are from neighboring villages (from similar community), dietary pattern is almost similar in these children. At the time of screening type of oral hygiene practice was also evaluated, children who regularly brush their teeth twice a day with fluoridated paste were included in the study. The screening was done with mouth mirror and explorer under good illumination (Natural Day light). At the end of screening, 123 children (Boys = 82, Girls = 41) with the mean age of 8.38 ± 0.75 years were selected who fulfilled the inclusion criteria given below. Before the commencement of the study, the parents were explained the purpose of the study and informed consent was obtained for participating in the study.

Inclusion criteria

Subjects between 6 and 9 years of age (mean age 8.38 ± 0.75 years) fulfilling the following inclusion criteria were included in the study:

1. All permanent first molars fully erupted.
2. Subjects with decayed, missing, and filled surface (dmfs) + DMFS score equal to or more than one.
3. Subjects with all deciduous molars present.
4. No known history of allergy against silver particles or colophonium.

Group division

- Group 1: Children receiving application of SDF (38%w/v) (Saforide-J. Morita company, Japan) on all deciduous canines and molars and 1st permanent molars (n = 41).
- Group 2: Children receiving application of Fluoride Varnish (6% NaF, 6% CaF_2) (Bifluoride 12-Voco, Germany) on all deciduous canines and molars and 1st permanent molars (n = 41).
- Group 3: Children receiving application of APF Gel 1.23%) (Fluocal, Septodont, France) on all deciduous canines and molars and 1st permanent molars (n = 41).

Base line evaluations

- Base line fluoride content in enamel with the help of enamel biopsy.
- dmfs[14] + DMFS[15] index.

DMFS index is used to describe DMFS for permanent tooth, the components are:

D component

Used to describe (Decayed teeth) which include:

1. Carious tooth.
2. Filled tooth with recurrent decay.
3. Only the root is left.
4. Defect filling with caries.
5. Temporary filling.
6. Filled tooth surface with other surface decayed.

M component

Used to describe (Missing teeth due to caries) other cases should be excluded these are:

1. Tooth that extracted for reasons other than caries should be excluded,
2. Unerupted teeth.
3. Congenitally missing.
4. Avulsion of teeth due to trauma or accident.

F component

It is used to describe filled teeth due to caries. Teeth were considered filled without decay when one or more permanent restorations were present and there was no secondary (recurrent) caries or other area of the tooth with primary caries. A tooth with a crown placed because of previous decay was recorded in this category.

dmfs index is used to describe DMFS for primary teeth. The criteria are similar to DMFS index.

Steps for the study

Initially, full mouth ultrasonic scaling was done to remove any food debris, plaque or calculus present on the tooth surface. In addition polishing rubber cup in a slow speed hand piece were used, whereas applying a constant stream

of water. Then enamel biopsy was taken from buccal surface of mandibular permanent first molar to check baseline fluoride concentration. All carious lesions present in the mouth were restored with Intermediate Restorative Material (IRM) (Kalzinol, DPI, India). The above mentioned procedure was same for all subjects. Afterwards they were divided in to 3 different groups on a random basis using computerized randomization tables (GraphPad Software, Inc, CA, USA).

Fluoride application was done on primary canine, 1st molar and 2nd molar as well as permanent 1st molar based on the individual group. Anterior teeth were excluded because patient selected in this study have transition period for incisors at this stage and also SDF can cause staining of the tooth surfaces, so it is not indicated for anterior teeth.

Procedure for fluoride application

Application of SDF

Before starting the procedure, the whole mucosal surface in the oral cavity was covered with the Vaseline, to protect it from mild burning sensation due to SDF. Isolation of the teeth was done with the help of cotton rolls and high volume suction. Lid of the bottle was removed just before the application and drop of solution was squeezed on the cotton pellet. Then application was done for 3-4 min on all surfaces of 4 teeth in single quadrant at 1 time [Figure 1]. This procedure was repeated on all quadrants in similar manner. As per manufacturer's instructions, after 3-4 min of application the patient was allowed to clean his mouth by gargling with distilled water or normal saline.

Application of fluoride varnish and APF gel was also done as per manufacturer's instructions in their respective group [Figures 2 and 3]. Furthermore the patients were instructed not to rinse, drink or eat for at least 30 min, take liquid and semisolid diet for that day and do not brush the teeth for that day. The similar procedure was repeated in all three groups at 6th and 12th month of follow-up, when subjects received next fluoride applications.

Evaluation criteria

Fluoride analysis

Method of enamel biopsy

Fluoride content was evaluated at baseline as well as 6th month of follow-up visit just before the next application. Fluoride content was measured from buccal surface of lower 1st permanent molar. The tooth on which the biopsy had to be done was isolated with the help of cotton rolls and high volume suction to eliminate any chances of saliva contamination. Sticking plaster was used to cover the tooth to be subjected for biopsy. 4 mm/side square punch was made in the sticking plaster keeping in mind that it should be present on the buccal surface of molar [Figure 4]. A 4 mm/side non-fluoride containing square blotting paper was wetted with 5 microliters of 0.5 M perchloric acid and immediately placed on the punched window on the mesiobuccal surface of the tooth for 4 s using a timer [Figure 5]. This filter paper was then transferred to plastic tube which had 0.1 ml of double distilled water pipetted

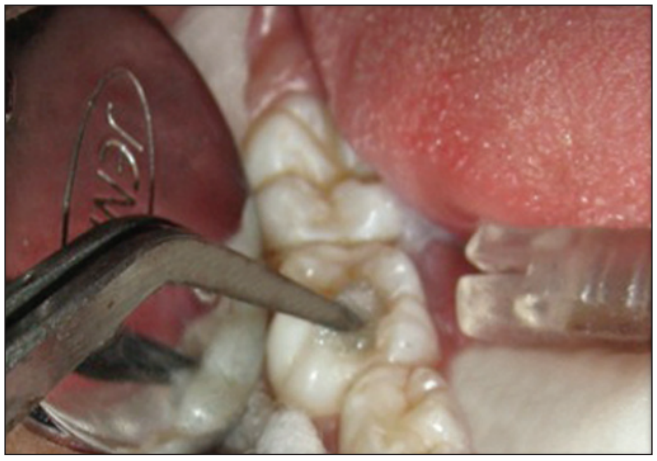

Figure 1: Application of silver diamine fluoride

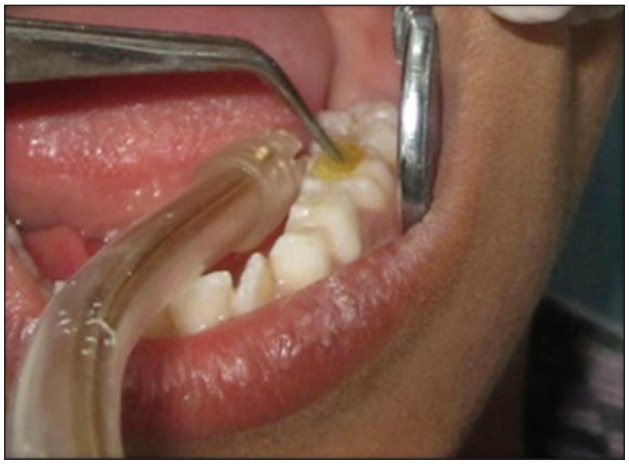

Figure 2: Application of fluoride varnish

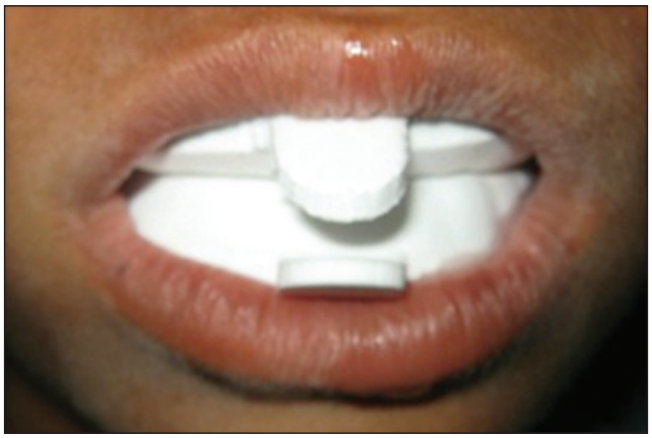

Figure 3: Application of acidulated phosphate fluoride gel

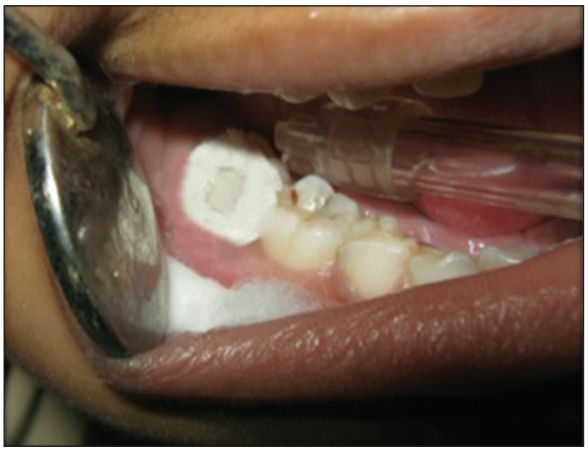

Figure 4: Sticking plaster with 4 mm^2 window

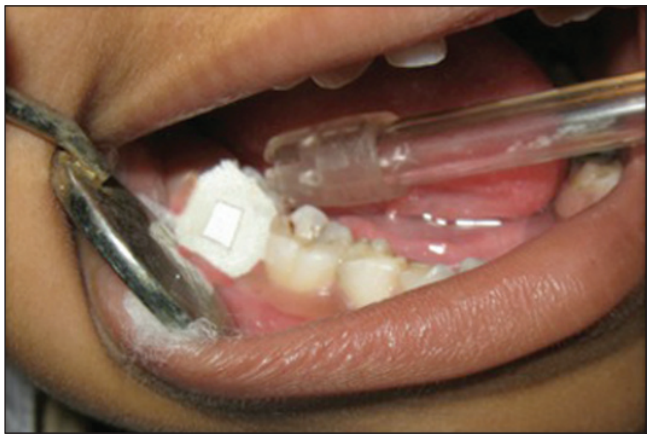

Figure 5: Enamel biopsy with blotting paper containing $HClO_4$

using a micro-pipette. Equal amount of total ionic strength adjustment buffer (TISAB-II) was added using a micro-pipette to the plastic tube, after which it was stored for 3 days to get maximum fluoride diffusion into the diluents of double distilled water and TISAB-II.[16,17] As all the patients were undergone fluoride application, the biopsy site had also received the fluoride application as all subjects received topical fluoride according to their group distribution (Either SDF or Naf Vanish or APF Gel). After 3 days of storage, the sample was stirred using a magnetic stirrer and send to laboratory for fluoride analysis.

Laboratory procedures

As the fluoride present on the tooth surface is measured in part per million (ppm), it is necessary to calculate amount of enamel mass is removed through enamel biopsy procedure. The weight and the volume of enamel removed by each acid etch and the corresponding fluoride concentration was calculated by use of the values of 2.95 for human enamel density and 37% for calcium content. Calcium content in the sample was measured using atomic absorption spectrophotometer.[18-20] From the data obtained, the depth of each biopsy was calculated by means of the following equations.[21-23]

$$\text{Mass of enamel} = \mu g\ Ca^{++} \times (1 \div 1000) \times (1 \div 1000) \times (100 \div 37)g$$

$$\text{Enamel depth of etch (cm)} = \frac{\text{Mass of enamel (g)}}{\text{Density of enamel} \times \text{biopsy area (cm}^2\text{)}} \times 10{,}000$$

Usually, concentrations of trace elements are expressed in ppm, so the following formula was used to state the ppm fluoride in the biopsy samples:

$$\text{Fluoride (ppm)} = \frac{\text{Fluoride in the aliquot } (\mu g)}{\text{Enamel in the aliquot (g)}}$$

Fluoride levels in enamel biopsy samples (aliquot) were estimated by a laboratory technician (blinded to group division) using an Ion Selective Electrode and ion analyzer ORION model 290.

Caries index

Diagnostic criteria for dental caries

A mouth mirror and sharp fine pig tailed explorer were used to detect caries under adequate light source. Baseline as well as follow-up examinations for dental caries were done by two different examiners blinded to the group division. Following criteria for the identification of dental caries were followed:

1. The lesion should be clinically visible and obvious.
2. The explorer tip can penetrate deep into soft yielding material.
3. There is discoloration or loss of translucency typical of undermined or demineralized enamel.
4. The pits and fissures were diagnosed as carious when the explorer catches or resists the removal after insertion with moderate to firm pressure.

Caries susceptibility of subject

Once the number of carious surfaces involved was determined following equation was used to measure the caries susceptibility (Richardson 1961).[24]

- There are two factors:
  a. Amount of tooth surface at risk
  b. Amount of caries developed during period of observation.
- 'b' is divided by 'a' will give measure of caries susceptibility ratio.
- Susceptibility index = susceptibility ratio × 100.
- In this study, total no. of surfaces at risk is: 76.

Statistical analysis

Estimation of sample size was based on the expected amount of increase in fluoride content in enamel on the basis of pilot study. The power of study was fixed at

80% (β = 0.20) and α = 0.05 as significance level. On the basis of difference in mean number between groups and standard deviation obtained from pilot study, the sample size was estimated to be around 110 using the nomogram given by Altman.[25] Keeping the estimated dropout rate in mind around 125 sample size was decided, among them total 123 subjects were included in the study. All the collected data were evaluated using SPSS (Software pakage for statistical analysis, IBM Corporation, Armonk, New York, US) version 13 software for windows.

RESULTS

Fluoride content in enamel

Out of 123 subjects, 115 subjects were available at 6th month. Table 1 shows mean value (at 95% confidence intervals) of fluoride on enamel surface at base line as well as at 6th month. Intra group comparison was done with the help of paired sample *t*-test. It is mentioned in Table 2. Analysis of variance test was done followed by *post hoc* test Multiple comparisons Tukey HSD for inter group comparison [Table 3].

Fluoride content in enamel was significantly increased at 6th month of follow-up in all three groups. Significant increase in fluoride content was found in case of SDF compared with Fluoride Varnish and APF Gel. No significant increase in fluoride content was found between Fluoride Varnish and APF Gel.

Development of new carious surfaces

Base line distribution of caries in different groups is mentioned in Table 3. Intergroup Comparison for baseline distribution of dmfs + DMFS shows no significant difference ($P > 0.05$) between Groups [Table 4].

Intergroup comparison

Development of new carious surfaces was evaluated by caries susceptibility index by Richardson 1961.[24] Mann Whitney test was used to compare the significant difference for new caries development between Groups [Table 5].

0-6 months: Compared to baseline, one new carious surface was found in Group 1 (SDF), six were found in Group 2 (Fluoride Varnish) and four were found in Group 3 (APF Gel).

6-12 months: Between 6 and 12 months, one was found in Group 1 (SDF), two were found in Group 2 (Fluoride Varnish) and three were found in Group 3 (APF Gel).

12-18 months: Between 12 and 18 months, No new carious surface was present in Group 1 (SDF), two were found in Group 2 (Fluoride Varnish) and two were found in Group 3 (APF Gel).

Table 1: Intra group comparison for fluoride content (ppm)

Groups	*N*	Mean	Standard deviation	*P* value
Group 1				
Fluoride at baseline	41	1,815.90	474.93	<0.001***
Fluoride at 6 months	39	5,663.08	740.09	
Group 2				
Fluoride at baseline	41	1,678.15	499.79	<0.001***
Fluoride at 6 months	37	4,903.81	756.10	
Group 3				
Fluoride at baseline	41	1,677.85	473.27	<0.001***
Fluoride at 6 months	39	4,698.31	529.88	
Overall				
Fluoride at baseline	123	1,723.97	483.27	<0.001***
Fluoride at 6 months	115	5,091.61	795.48	

Paired *t*-test. $P > 0.05$ (not significant). *$P < 0.05$ (significant). **$P < 0.01$ (highly significant). ***$P < 0.001$(extremely significant)

Table 2: Inter group comparison for fluoride content (ppm)

Dependent variable	Group		*P* value
Baseline-6 months	1	2	0.003**
	1	3	<0.001***
	2	3	0.6002

Multiple comparison Tucky HSD $P > 0.05$ (not significant). *$P < 0.05$ (significant). **$P < 0.01$ (highly significant). ***$P < 0.001$ (extremely significant). HSD: Honestly significant difference

Table 3: Baseline distribution of carious lesion

Parameter	Group	Subjects	Carious lesion	Mean	Standard deviation
dmfs	1	41	118	2.88	1.69
	2	41	108	2.63	1.95
	3	41	87	2.12	1.67
	Total	123	313	2.54	1.79
DMFS	1	41	17	0.41	0.97
	2	41	13	0.32	0.61
	3	41	8	0.20	0.51
	Total	123	38	0.31	0.72
Total	1	41	135	3.29	2.02
	2	41	121	2.95	1.84
	3	41	95	2.32	1.66
	Total	123	351	2.85	1.88

Intergroup comparison by ANOVA. $P > 0.05$-not significant. ANOVA: Analysis of variance, DMFS: Decayed, missing and filled surface

Table 4: Intergroup comparison for baseline distribution of dmfs + DMFS

Group		*P* value
1	2	0.68
1	3	0.06
2	3	0.27

Multiple comparison Tucky HSD. $P > 0.05$ is not significant. DMFS: Decayed, missing and filled surfaces. HSD: Honestly significant difference

Table 5: Caries susceptibility between study groups

Groups	0-6 months	6-12 months	12-18 months	0-12 months	0-18 months
Group 1 and 2 (*P* value)	0.28	0.52	0.29	0.19	0.09
Group 2 and 3 (*P* value)	0.31	0.30	0.14	0.13	0.06
Group 1 and 3 (*P* value)	0.91	0.69	0.59	0.87	0.90

Mann-Whitney Test. $P > 0.05$ is not significant

0-12 months: Compared to baseline, two carious surfaces were found in Group 1 (SDF), eight were found in Group 2 (Fluoride Varnish), and seven were found in Group 3 (APF Gel).

0-18 months: Compared to baseline, two carious surfaces were found in Group 1 (SDF), 10 were found in Group 2 (Fluoride Varnish), and nine were found in Group 3 (APF Gel). No statistically significant difference in number of new carious surfaces was found between any of the Group at different time period ($P > 0.05$).

DISCUSSION

The present study was conducted as a randomized, prospective *in vivo* trial with SDF as an experimental material, against Fluoride Varnish and APF Gel as comparative groups. Provided the composition of the treatment groups is similar (children from almost similar socio-economic status, food and oral hygiene habit and almost similar caries distribution [Tables 3 and 4], conclusions drawn from the trial can be mostly attributed to the administration of the treatment under consideration.

Age group selected for the study was 6-9 years, with first permanent molars fully erupted. As the second window of infectivity opens at this age,[26] first permanent molars were at highest risk to be affected by dental caries. The present study also supports the proposal by Johnston and Lewis[27] that PATFs may be practical preventive treatments that allow more high risk children (included in present study) to be intervened at early age. As it was unethical to leave the open carious lesion and proceed with study, all existing carious lesions were restored and defective restorations treated by IRM before instituting the study protocol.

An expert panel of the American Dental Association in 2006 concluded that "Fluoride varnish applied every 6 months is effective in preventing caries in the primary and permanent dentition of children and adolescents".[28] Furthermore, biannual applications of APF gel were used by Hawkins and Locker[29] and Agrawal and Pushpanjali[30] and found significant caries reduction. On the other hand, there are no published recommendations for the frequency of SDF applications. Hence, considering the frequency of application of Fluoride Varnish and APF Gel, in this study, it was intended to check the availability of fluoride in tooth structure after 6 months.

According to Mellberg *et al*., in 1983, Fluoride introduced into the oral cavity is cleared with passage of time; hence a continuous supply of fluoride is essential for anti-caries effect.[31] Therefore, retention of fluoride on tooth surface after topical application has become a major field of interest in caries research. It is important to evaluate how much fluoride is retained over a period of time on the tooth surface.

Until date there are no reported studies on measuring the concentration of fluoride on enamel surface after application of SDF *in vivo*. Fluoride content was measured at 6th month of follow-up only. Since the frequency of application of the solution was set every 6 month, it was decided to measure fluoride content at 6th month just before the next application. Present study proves that, fluoride content increased significantly in all three groups at 6th month follow-up. Factors responsible for fluoride uptake and retentions are mainly concentration of fluoride, pH of the solution and barrier coating over the solution.[31] As SDF has highest concentration of fluoride (44,800 ppm), so it can be assumed that fluoride on enamel is directly proportional to the amount of fluoride available. On the other hand APF Gel with acidic pH has increased penetration power, Fluoride Varnish with barrier coating increased the contact period of fluoride with the tooth surface.

Considering the intergroup significance, significant increase of fluoride in enamel was found in teeth of subjects who received SDF application compared to Fluoride Varnish and APF Gel. No significant increase of Fluoride in enamel was found between Fluoride Varnish and APF gel group. Two reasons could be possible explanation for this observation. First reason could be that since SDF has high fluoride content when compared with other two agents, it would deliver more fluoride. Second reason could be SDF stabilizes very fast (3-4 min of application) on the tooth surface and no additional post treatment instruction need to be mandatorily followed by patient to enhance fluoride uptake and retention on tooth surface unlike in Fluoride Varnish and APF Gel group. This result varies from the results of *in vitro* study by Delbem *et al*. in 2006.[32] They found more concentration in case of fluoride varnish compared to SDF. According to them 'the silver fluoride products are more often used in dentinal caries, which present a greater amount of protein substrate, carbonates and phosphates for

the reaction. On the other hand, the enamel is short of these substrates in comparison with dentin which may have decreased the SDF's reactivity.' In present study, since young permanent molars were included, which have more porous structure and more amount of protein content. Bruun in 1973 mentioned that the recently erupted tooth into the mouth is not yet fully mineralized and more porous, so fluoride uptake can be increased when applied at this time.[33] It can be suggested that as early as SDF application is done, better protection for the young permanent molar can be obtained.

No significant difference at baseline dmfs + DMFS scores between all three groups signifies relatively equal distribution of existing dental caries in all three groups. Although no significant reduction in development of new carious surfaces between any of the groups was found, SDF had comparatively better reduction in development of new carious surfaces because of higher uptake of fluoride in enamel. Also SDF has proven antibacterial effect;[12,13] it might be the additional factor in reduction of carious lesion.

Summarizing the discussion, it can be derived that *in vivo* biannual application of SDF on enamel provides a better caries preventive effect due to higher uptake of fluoride content contributing toward reduction in caries susceptibility as compared to other professionally applied topical fluoridated agents Fluoride Varnish and APF Gel, still additional researches are required to check the efficacy of SDF while applying on annual basis.

CONCLUSION

The following conclusions were drawn:

1. Enamel fluoride content was increased significantly even after 6 months of application of SDF compared to Fluoride Varnish and APF Gel.
2. Although not significant, SDF was more efficient in reducing the number of new carious surfaces when compared to fluoride varnish and APF Gel.

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