

## **A Clinical Evaluation of Fluoride and Non-Fluoride Agents in Carious Lesions of Permanent Dentition - A Systematic Review”**

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### **I. Background**

Dental caries, also known as tooth decay or a cavity, is an infection, bacterial in origin, that causes demineralization and destruction of the hard tissues of the teeth (enamel, dentin and cementum). It is a result of the production of acid by bacterial fermentation of food debris accumulated on the tooth surface [1]. Dental caries and its consequences pose important and uncomfortable problems not only in developing countries but also in all industrialized countries since 1970s. Even increase in prevalence has been occurred in some countries [2]. In general, dental caries levels vary considerably between and within different countries, but population groups in the lower socio-economic status (SES) have higher caries levels than those in the upper SES and these differences are consistent in industrialized and urbanized developing countries. For treatment of dental caries there should be a balance between de-mineralization and re-mineralization that normally happen in the mouth. Sometimes, weak organization of tooth structures and alterations in diet, oral hygiene or bacterial activity can lead to the predominance of de-mineralizing agents, resulting in initial lesion formation and tooth decay. Dental caries will progressively develop in enamel and dentin as a result of frequently episodes of PH drop in the biofilm exposed to sugar [3]. Early diagnosis and the right approach can stop the progressive destruction and sometimes it is possible to repair and completely heal lesions. This applies to non-cavitated white spot lesions, where the right therapeutic protocols based on fluoride and non-fluoride agents can really halt/reverse the caries process. In the last decade there has been a veritable explosion of interest in technologies which may have value for re-mineralization of enamel and dentine. A number of re-mineralization techniques have been tried out. The right approach is always based on the right interpretation of the pathological situation and knowledge about how these commonly available bioactive products work. Though there are many reviews in caries reduction and re-mineralization of initial carious lesion in primary dentition, there are no systematic reviews on caries reduction and re-mineralization of initial carious lesion in permanent dentition.

### **AIM**

The aim of this systematic review was to evaluate the effect of fluoride and non-fluoride agents in initial carious lesions of permanent dentition.

The primary objective was to evaluate whether non-fluoride agents are better than fluoride.

The secondary objective was to evaluate which re-mineralizing agent is the best for re-mineralizing initial carious lesion of permanent dentition.

### **STRUCTURED QUESTION:**

1. Are non-fluoride agents better than fluoride?
2. Which agent is the best for initial carious lesion of permanent dentition?

### **PICO ANALYSIS**

- **Population-** Patients with dental caries
- **Intervention-** Different non-fluoride agents
- **Comparison-** placebo and fluorides
- **Outcome-** Caries reduction and/or Re-mineralization.

## II. Materials And Methods

### Sources Used

For identification of studies included or considered for this review, detailed strategies were developed for the database searched.

### Searched Databases

- PUBMED ( from January 1984 to June 2012)
- PUBMED Advanced Search ( from January 1984 to June 2012)
- MEDLINE
- COCHRANE DATABASE OF SYSTEMATIC REVIEWS

No limits and language restriction were applied during electronic search to include all possible clinical trials. No time restriction was applied.

Reference list of the reviews were also checked for possible additional studies.

### Hand Search

The following journals were hand searched:

- Operative dentistry
- Quintessence International
- International Dental Journal
- Caries research
- Journal Dental Research
- Journal Clinical Pediatric Dentistry

### SEARCH METHODOLOGY

SEARCH	QUERY	ITEMS FOUND
<a href="#">#61</a>	Search (((#56) AND #57) AND #58) AND #59) AND #60	<a href="#">79</a>
<a href="#">#60</a>	Search (((((#50) OR #51) OR #52) OR #53) OR #54) OR #55	<a href="#">57654</a>
<a href="#">#59</a>	Search ((((((((((((((((((#31) OR #32) OR #34) OR #33) OR #35) OR #36) OR #37) OR #38) OR #39) OR #40) OR #41) OR #42) OR #43) OR #44) OR #45) OR #46) OR #47) OR #48) OR #49	<a href="#">170509</a>
<a href="#">#58</a>	Search (((((#24) OR #25) OR #26) OR #27) OR #28) OR #29	<a href="#">1858587</a>
<a href="#">#57</a>	Search (((((((#16) OR #17) OR #18) OR #19) OR #20) OR #21) OR #22) OR #23) OR #30	<a href="#">14736</a>
<a href="#">#56</a>	Search ((((((((((((((#1) OR #2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15	<a href="#">12287</a>
<a href="#">#55</a>	Search caries prevention	<a href="#">13972</a>
<a href="#">#54</a>	Search demineralization	<a href="#">4482</a>
<a href="#">#53</a>	Search remineralization	<a href="#">1969</a>
<a href="#">#52</a>	Search reduction in sensitivity	<a href="#">38239</a>
<a href="#">#51</a>	Search reduction in progression of caries	<a href="#">55</a>
<a href="#">#50</a>	Search reduction in caries	<a href="#">1515</a>
<a href="#">#49</a>	Search fluoride infiltration	<a href="#">77</a>
<a href="#">#48</a>	Search fluoride mouth rinse	<a href="#">203</a>
<a href="#">#47</a>	Search fluoride varnish	<a href="#">685</a>
<a href="#">#46</a>	Search sodium mono fluorophosphatate	<a href="#">1600</a>
<a href="#">#45</a>	Search fluoride tooth pastes	<a href="#">60</a>
<a href="#">#44</a>	Search fluoride gels	<a href="#">941</a>
<a href="#">#43</a>	Search fluoride dentifrices	<a href="#">2837</a>
<a href="#">#42</a>	Search stannous hexa fluoride zirconate	<a href="#">0</a>
<a href="#">#41</a>	Search acidulated phospho fluoride	<a href="#">0</a>
<a href="#">#40</a>	Search sodium fluoride	<a href="#">9256</a>

SEARCH	QUERY	ITEMS FOUND
#39	Search <b>stannous fluoride</b>	<a href="#">1150</a>
#38	Search <b>sulfuryl fluoride</b>	<a href="#">39</a>
#37	Search <b>sodium fluoro silicic acid</b>	<a href="#">7</a>
#36	Search <b>fluorosilicic acid</b>	<a href="#">30</a>
#35	Search <b>cryolite</b>	<a href="#">62</a>
#34	Search <b>salt water fluoridation</b>	<a href="#">251</a>
#33	Search <b>school water fluoridation</b>	<a href="#">872</a>
#32	Search <b>community water fluoridation</b>	<a href="#">658</a>
#31	Search <b>placebo</b>	<a href="#">155560</a>
#30	Search <b>xylitol</b>	<a href="#">2699</a>
#29	Search <b>split mouth study</b>	<a href="#">1471</a>
#28	Search <b>controlled clinical trial</b>	<a href="#">172924</a>
#27	Search <b>randomised controlled trial</b>	<a href="#">405927</a>
#26	Search <b>randomised clinical trial</b>	<a href="#">402055</a>
#25	Search <b>clinical study</b>	<a href="#">1442892</a>
#24	Search <b>clinical trial</b>	<a href="#">867955</a>
#23	Search <b>pit and fissure sealant</b>	<a href="#">2748</a>
#22	Search <b>proenamel</b>	<a href="#">3</a>
#21	Search <b>enamelon</b>	<a href="#">19</a>
#20	Search <b>novamin</b>	<a href="#">44</a>
#19	Search <b>casein phosphopeptide amorphous calcium phosphate</b>	<a href="#">134</a>
#18	Search <b>nano-hydroxyapatite</b>	<a href="#">252</a>
#17	Search <b>composite resin restoration</b>	<a href="#">9102</a>
#16	Search <b>preventive resin restoration</b>	<a href="#">257</a>
#15	Search <b>small caries lesion</b>	<a href="#">111</a>
#14	Search <b>white spot lesion</b>	<a href="#">1759</a>
#13	Search <b>pit and fissure caries</b>	<a href="#">1786</a>
#12	Search <b>caries initiation</b>	<a href="#">282</a>
#11	Search <b>early childhood caries</b>	<a href="#">636</a>
#10	Search <b>early caries</b>	<a href="#">2151</a>
#9	Search <b>management of enamel caries</b>	<a href="#">196</a>
#8	Search <b>management of dental caries</b>	<a href="#">2862</a>
#7	Search <b>caries management</b>	<a href="#">2912</a>
#6	Search <b>early caries lesion</b>	<a href="#">207</a>
#5	Search <b>dental caries lesion</b>	<a href="#">1720</a>
#4	Search <b>enamel caries</b>	<a href="#">5566</a>
#3	Search <b>initial dental caries</b>	<a href="#">1053</a>
#2	Search <b>initial caries</b>	<a href="#">1095</a>
#1	Search <b>incipient caries</b>	<a href="#">323</a>

## **INCLUSION CRITERIA**

### **Criteria for considering studies for this review**

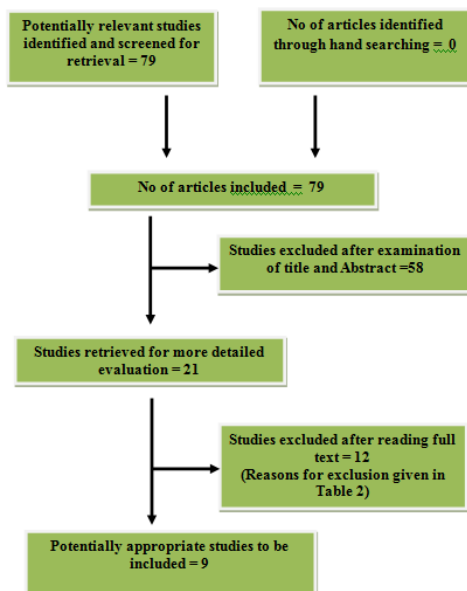
- In-vivo human studies
- In situ studies
- Fluorides
- Non-fluorides

**EXCLUSION CRITERIA**

The following studies were excluded

- Reviews
- Case reports/case series
- Animal studies
- In vitro studies
- Studies on primary teeth

**CHART 1: SEARCH FLOW CHART**



**TABLE 1: VARIABLES OF INTEREST**

S. No	Variables Of Interest
1	Clinical evaluation based on <ul style="list-style-type: none"> <li>• Lesion size</li> <li>• Lesion number</li> </ul>
2	DMFT / DMFS scores
3	Radiographic Evaluation
4	Caries Prevalence
5	Mineral Content

**III. Results**

**Description of Studies**

The search identified 79 potential publications out of which 58 were excluded after reviewing the title or abstract. Full articles were obtained for 21 studies, 12 of these publications were excluded after reading the full text. Therefore a total of 9 publications fulfilled all criteria for inclusion.

**TABLE 2: REASONS FOR EXCLUDING ARTICLES**

S.No	Author and year	Reason for exclusion
1.	Splieth et al. 2011	Age of population not applicable to this SR
2.	Tagliaferro EP et al 2011	Age of population not applicable to this SR
3.	Tripod D et el 2011	Dental sealants
4.	Behnan et al 2010	In- Vitro study
5.	Ferracane J et el 2011	Sealant
6.	Uysal T et al 2010	In-vitro study
7.	Trairatvorakul C et al 2010	In-vitro study
8.	James P et al 2010	Review
9.	Simrtvir M et al 2010	Age of population not applicable to this SR

10.	Hiiri A et al 2006	Review
11.	Ekstrand KR et al 2010	Age of population not applicable to this SR
12.	Milgrom P et al 2009	Age of population not applicable to this SR
13.	Tolvanen M et al 2009	Age of population not applicable to this SR
14.	Milgrom P et al 2009	Early childhood caries
15.	Hermosillo VH et al 2009	ART
16.	Souse RP et al 2009	Restorative materials
17.	Reynolds EC et al 2008	Review
18.	Cenci MS et al 2008	Restorative materials
19.	Gomez S et al 2008	Dental sealants
20.	Kumar VL et al 2008	In-vitro
21.	Hausen H et al 2007	Age of population not applicable to this SR
22.	Sudjalim TR et al 2007	In-vitro
23.	Armfield JM et al 2007	Dental sealants
24.	Salar DV et al 2007	Dental sealants
25.	Thorild I et al 2006	Age of population not applicable to this SR
26.	Hiiri et al 2006	Review
27.	Rodrigues JA et al 2005	In-vitro
28.	Bravo M et al 2005	Age of population not applicable to this SR
29.	Dulgergil CT et al 2005	ART
30.	Ei-Housseiny AA et al 2005	Sealant Retention
31.	Chadwick BL et al 2005	Age of population not applicable to this SR
32.	Kallestall C et al 2005	Age of population not applicable to this SR
33.	Vehkalahti MM et al 2004	Not applicable
34.	Sintes JL et al 2002	Age of population not applicable to this SR
35.	Hara AT et al 2002	Restorative Materials
36.	Donly KJ et al 2002	Restorative Materials
37.	Tseveenjav B et al 2002	Preventive practice
38.	Ceballos L et al 2001	Restorations
39.	Newbrun E et al 2001	Review
40.	Rosier RG et al 2001	Review
41.	Isokangas P et al 2000	Age of population not applicable to this SR
42.	Kleber CJ et al 1999	Orthodontic patients-only fluoride.
43.	Wolinsky LE et al 1999	In-vitro
44.	Bynum AM et al 1999	In-vitro
45.	Donly KJ et al 1999	Restorative materials
46.	Gaffer A et al 1998	Animal study
47.	Bravo M et al 1997	Age of population not applicable to this SR
48.	Glass RL et al 1997	Age of population not applicable to this SR
49.	Bravo M et al 1997	Age of population not applicable to this SR
50.	Simons D et al 1997	Age of population not applicable to this SR
51.	Bravo M et al 1996	Age of population not applicable to this SR
52.	Roberts AJ et al 1995	Review
53.	Seppa L et al 1995	Age of population not applicable to this SR
54.	Suhonen J et al 1994	In-vitro
55.	Geiger AM et al 1992	Orthodontic patients- only fluoride.
56.	Manning RH et al 1992	Chewing gums
57.	Triolo PT et al 1991	Restorative materials
58.	Haugejorden O et al 1991	Age of population not applicable to this SR
59.	Petersson LG et al 1991	Age of population not applicable to this SR
60.	Petersson LG et al 1991	Age of population not applicable to this SR
61.	Nord A et al 1991	Age of population not applicable to this SR
62.	Stephen KW et al 1990	Age of population not applicable to this SR
63.	Raadal M et al 1990	Restorative materials
64.	Jensen ME et al 1990	In-vitro
65.	Stephen KW et al 1989	Age of population not applicable to this SR
66.	Holm GB et al 1984	Age of population not applicable to this SR
67.	Bagrarmian RA 1982	Age of population not applicable to this SR
68.	Stephen KW et al 1977	Age of population not applicable to this SR
69.	Bagrarmian RA 1976	Age of population not applicable to this SR
70.	Maiwald HJ 1974	Not applicable

RESULTS

TABLE 3: GENERAL INFORMATION OF SELECTED ARTICLES - METHODOLOGY

S. No	Reference	Study Description	Sample Size	Materials used	
				Controls Employed	Test Group
1.	Gianmaria F et al 2011	In-situ study	40 Teeth.	Placebo	CPP-ACP
2.	Altenburger MJ et al 2010	Randomised controlled trial.	32 patients.	NaF-1450ppm	CPP-ACP
3.	Najibfard K et al 2011	Randomized controlled trial, double blind, crossover, in-situ study.	30 patients.	1100ppm F	5% nHAP, 10% nHAP,
4.	D.L.Bailey et al 2009	Randomized clinical trial.	45 patients	Placebo	CPP-ACP, fluoride mouth rinse and fluoride tooth paste.
5.	Aya nakamura et al 2009	In-vivo study	101 patients	Fluoride mouth rinse.	Fluoride mouth rinse + targeted sealant application
6.	E.C.Reynolds et al 2008	Randomized, double blind, 3way cross over design- in-situ study	14 patients	Placebo	1100ppm NaF, 2800ppm NaF, 2% CPP-ACP, and 2% CPP-ACP plus 1100 ppm NaF.
7.	Andersson A et al 2007	Randomized, in-vivo study.	26 patients	0.05% sodium fluoride mouth wash combined with fluoride dentifrice	CPP-ACP
8.	Santiago S et al 2005	In-vivo study	50 patients	Fluoride varnish	Sealant. Sealant and Fluoride varnish,
9.	Selwitz RH et al 1995	In-vivo study	416 patients	Fluoride	Dental Sealant + Fluoride.

TABLE 4: GENERAL INFORMATION OF SELECTED ARTICLES - RESULTS

S. No	Reference	Test group	Variable of interest					Evaluation Period	Results
			Clinical Evaluation	Dmf/dfms	Radio graphy	Caries Prevalence	Mineral Content		
1	Gianmaria F et al 2011	CPP-ACP					Yes (SEM analysis)	1 month	Diffuse and homogeneous mineral coating, reducing the surface alterations in the de-mineralized specimens treated with synthetic CPP-ACP
2	Altenburger MJ et al 2010	CPP-ACP	Yes				Yes (Diagnodent)	22 days	Fissures treated with 1450ppm NaF along with CPP-ACP containing cream showed significantly lower laser

									fluorescence values after Day 15 (P = 0.001) and Day 22 (P < 0.001) compared to the control group(1450 NaF ppm). No significant difference in the visual classification between the two groups could be found.
3	Najibfar d K et al 2011	5% nHAP, 10% nHAP, 1100ppm NaF					YES (MR)	28 days	No significant difference between 5% nHAP, 10% nHAP, 1100ppm NaF in mineral gain. No demineralization occurred in sound specimens exposed to 10% nHAP.
4	D.L.Bailey et al 2009	CPP-ACP, fluoride mouth rinse and fluoride tooth paste.	Yes (ICD AS-II)					3 months	Significantly more white spot lesions regressed with remineralizing cream containing (CPP-ACP) compared with placebo.
5.	Ayanakamura et al 2009	Fluoride mouth rinse+ targeted sealant(FMR+TS), application		Yes		Yes		11 yrs	The caries prevalence and mean DMFT (SD) was 28.3%, 1.56 (3.00) in the FMR+TS group and 60.0%, 2.20 (2.44) in the FMR group, and the difference was significant.
6.	E.C.Reynolds et al 2008	placebo, 1100ppm NaF, 2800ppm NaF, 2% CPP-ACP, and 2% CPP-ACP plus 1100 ppm NaF.					Yes (EMPWDS)	14 days	Dentifrice containing 2% CPP-ACP plus 1100 ppm F was superior to all other formulations.
7.	Andersson A et al 2007	CPP-ACP. 0.05% NaF	Yes (CA)				Yes (LF)	1yr	Statistically significant difference (63% vs. 25%).in the number of sites that totally disappeared after 12 months in CPP-ACP treated teeth in clinical assessment. LF showed statistically significant difference at 6 and 12months follow-up.
8.	Santiago S et al 2005	Sealant. Sealant and Fluoride varnish, Control(fluoride varnish)			Yes			2yrs	There is no statistically significant difference between the groups.
9.	Selwitz RH et al 1995	Dental Sealant + Fluoride, Fluoride		Yes				4yrs	Pit and fissure sealants confer additional caries-preventive benefits beyond those of fluoride therapy

									alone
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**LEGEND:**

**EMPWDS** - Electron Microprobe Wavelength Dispersive Spectrometry

**CA**- Clinical Assessment

**LA**- Laser Fluorescence

**MR**-Micro Radiography

**TABLE 5: EVIDENCE LEVEL OF SELECTED ARTICLES**

S.No	Reference	Randomization	Allocation concealment	Blinding	Clear/Ec	Sample size calculation	Baseline evaluation	Level of Evidence
1	Gianmaria F et al 2011	No	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned	3
2	Altenburger MJ et al 2010	Yes	Not mentioned	Single blind	Yes	Yes	Yes	2
3	Najibfard K et al 2011	Unclear	Not mentioned	Double blind	Yes	Yes	Yes	2
4	D.L.Bailey et al 2009	Yes	No	Double blind	Yes	Yes	Yes	2
5	Ayanakamura et al 2009	No	Not mentioned	Triple blind	Yes	Not mentioned	Not mentioned	2
6.	E.C.Reynolds et al 2008	Unclear	Not mentioned	Double blind	Yes	Not mentioned	Yes	2
7.	Andersson A et al 2007	Yes	Not mentioned	Single blind	Yes	Not mentioned	Yes	2
8.	Santiago S et al 2005	No	Not mentioned	Single blind	Yes	Not mentioned	Yes	2
9.	Selwitz RH et al 1995	No	Not mentioned	Not mentioned	Yes	Not mentioned	Yes	2

**LEGEND:**

**Yes – adequately mentioned**

**No-inadequately mentioned**

**Not mentioned**

**QUALITY ASSESSMENT**

**Higgins and Green.** Cochrane reviewer’s Handbook 2009)

The quality assessment of included trials was undertaken independently as a part of data extraction process. Four main quality criteria were examined:

1. Method of Randomization, recorded as
  - a. Yes – Adequate as described in the text
  - b. No – Inadequate as described in the text
  - c. Unclear in the text
  
2. Allocation Concealment, recorded as
  - a. Yes – Adequate as described in the text
  - b. No – Inadequate as described in the text
  - c. Unclear in the text
  
3. Outcomes assessors blinded to intervention, recorded as
  - a. Yes – Adequate as described in the text
  - b. No – Inadequate as described in the text
  - c. Unclear in the text



4. Completeness of follow-up (was there a clear explanation or withdrawals and dropouts in each treatment group) assessed as:
  - a. Yes-Dropouts were explained
  - b. No-Dropouts were not explained
  - c. None -No Dropouts or withdrawals

Other methodological criteria examined included:

1. Presence or absence of sample size calculation
2. Comparability of groups at the start
3. Clear inclusion/ exclusion criteria
4. Presence/ absence of estimate of measurement error.

**RISK OF BIAS IN INCLUDED STUDIES**

The assessments for the four main methodological quality items are shown in table 1. The study was assessed to have a “High risk” of bias if it did not record a “Yes” in three or more of the four main categories, “Moderate” if two out of four categories did not record a “Yes”, and “Low” if randomization assessor blinding and completeness of follow – up were considered adequate.

**TABLE 6: RISK OF BIAS FOR SELECTED ARTICLES - MAJOR CRITERIA**

S.No	Reference	Method of randomization	Allocation Concealed	Assessor Blinding	Dropouts Described	Risk of Bias
1	Gianmaria F et al 2011	No	No	No	No	High
2	Altenburger MJ et al 2010	Computer generated randomization list	No	Yes	Yes	Low
3	Najibfard K et al 2011	Randomized clinical trial	No	Yes	Yes	Moderate
4	D.L.Bailey et al 2009	Computer generated random permuted block schedule	Yes	Yes	Yes	Low
5	Aya nakamura et al 2009	Not mentioned	No	Yes	Yes	Moderate
6	E.C.Reynolds et al 2008	Randomized cross over study.	No	Yes	No	High
7	Andersson A et al 2007	Randomization with dice	No	Yes	Yes	Low
8	Santiago S et al 2005	Randomize controlled trial	No	Yes	Yes	Moderate
9	Selwitz RH et al 1995	Controlled clinical trial	No	No	Yes	High

**TABLE 7: RISK OF BIAS FOR SELECTED ARTICLES - MINOR CRITERIA**

S.No	Reference	Sample Justified	Baseline comparison	I/ E Criteria	Method Error
1.	Gianmaria F et al 2011	No	No	Yes	No
2.	Altenburger MJ et al 2010	Yes	Yes	Yes	No
3.	Najibfard K et al 2011	Yes	Yes	Yes	No
4.	D.L.Bailey et al 2009	Yes	Yes	Yes	No
5.	Aya nakamura et al 2009	No	No	Yes	No
6.	E.C.Reynolds et al 2008	No	Yes	Yes	No
7.	Andersson A et al 2007	No	Yes	Yes	Yes
8.	Santiago S et al 2005	No	Yes	Yes	No
9.	Selwitz RH et al 1995	No	Yes	Yes	No

**TABLE 8: SUMMATION TABLES FOR INDIVIDUAL PARAMETERS**

**A. Clinical evaluation of re-mineralization**

S. No	Comparison	No of studies	Effective method	No difference between groups
1	CPP-ACP, control (NaF)	3	2(CPP-ACP)	1

**B. Dmft / dmfs scores**

S. No	Comparison	No of studies	Effective method	No difference between groups
1	Fluoride mouth rinse +targeted sealant and fluoride mouth rinse	2	2 (Fluoride mouth rinse + targeted sealant)	-

**C. Radiographic evaluation**

S.No	Comparison of no of studies	No of Studies	Effective method	No difference between groups
1	Sealant, Sealant and Fluoride Varnish and Control (Fluoride Varnish) (3 groups)	1	-	1

**D. Caries prevalence**

S.No	Comparison of no of studies	No of studies	Effective method	No difference between groups
1.	Fluoride mouth rinse +targeted sealant, fluoride mouth rinse	1	1 (Fluoride mouth rinse + targeted sealant)	-

**E. Mineral content**

S. No	Comparison of no of studies	No of studies	Effective Method	No difference between groups
1	CPP-ACP And placebo	2	2 (CPP-ACP)	-
2	5% nHAP, 10% nHAP 1100ppm NaF, 10% nHAP intra oral.	1	-	1
3	Placebo, 1100ppm NaF, 2800ppm NaF, 2% CPP-ACP, 2% CPP-APP +1100 NaF.	1	1(2% CPP-APP +1100 NaF)	-
4	CPP-ACP and control (sodium fluoride)	1	1(CPP-ACP)	-

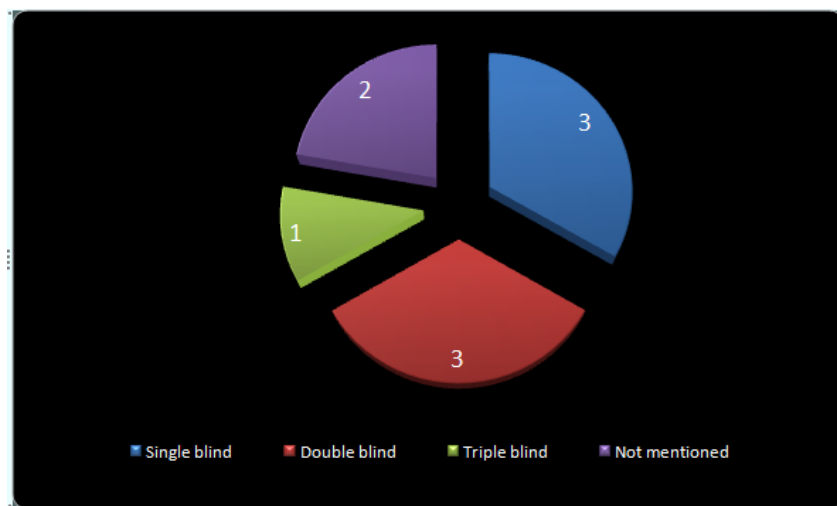
**TABLE 9: OVER ALL COMPARISON OF ALL FLUORIDE AND NON-FLUORIDE AGENTS**

Total no of studies	Fluoride more effective	Non-Fluoride more effective	Combination more effective	No difference
9	-	2	4	3

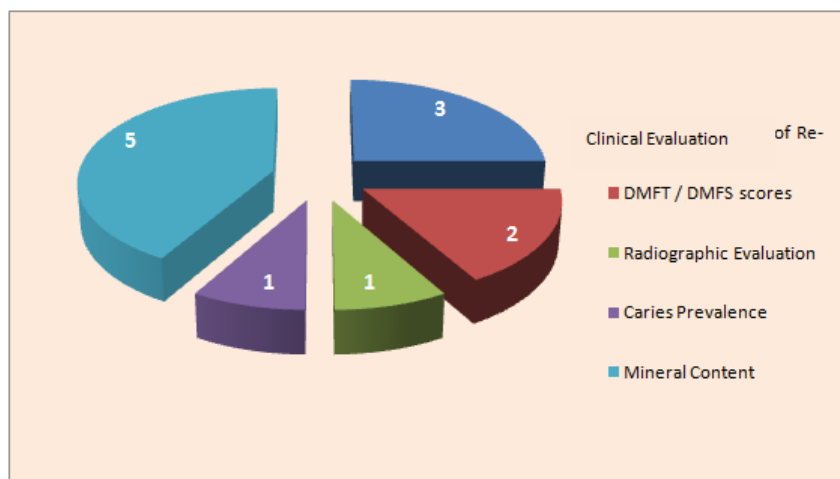
**TABLE 10: SUMMATION TABLE FOR BLINDING**

Total no of studies	No of studies blinding done	Single blind	Double blind	Triple blind	Not mentioned
9	7	3	3	1	2

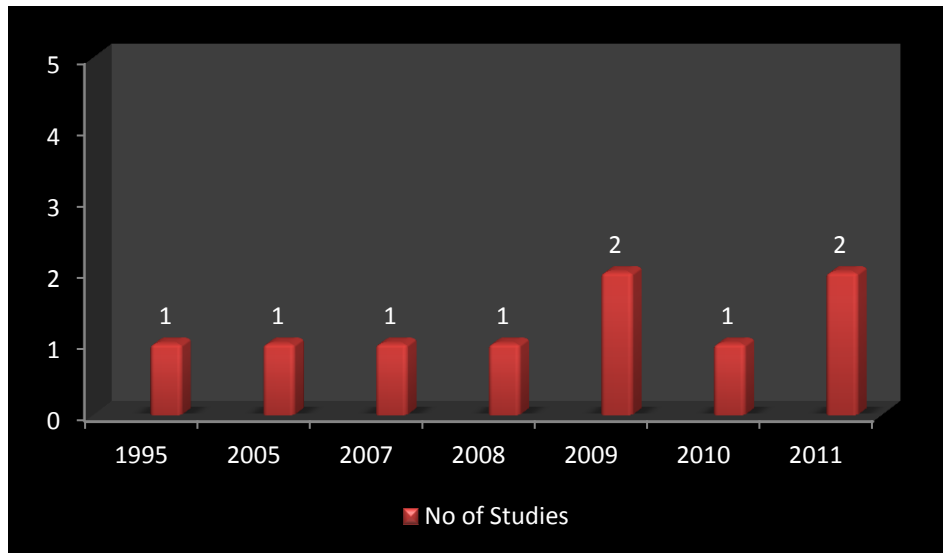
**FIGURE 1: PIE CHART FOR BLINDING**



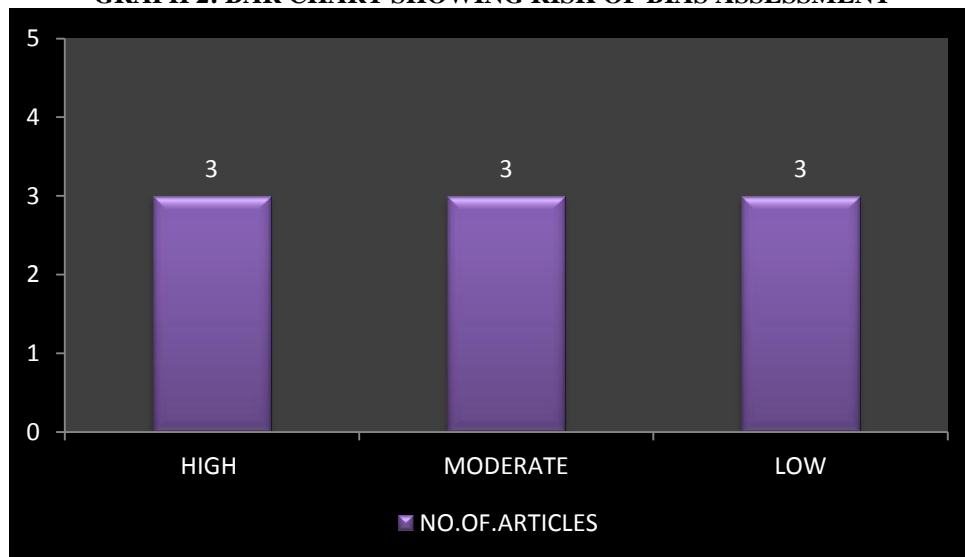
**FIGURE 2: OVER ALL COMPARISON OF VARIABLES OF INTEREST**



**GRAPH 1: YEAR OF PUBLICATION OF INCLUDED STUDIES**



**GRAPH 2: BAR CHART SHOWING RISK OF BIAS ASSESSMENT**



#### **IV. Discussion**

The search identified 79 potential publications out of which 58 were excluded after reviewing the title or abstract. Full articles were obtained for 21 studies, 12 of these publications were excluded after reading the full text. Therefore a total of 9 publications fulfilled all criteria for inclusion.

##### **Variables of Interest**

- A. Clinical evaluation
- B. DMFT / DMFS scores
- C. Radiographic Evaluation
- D. Caries Prevalence
- E. Mineral Content

##### **Accurate reporting and interpretation of results**

###### **A. Clinical evaluation**

3 articles used clinical evaluation for assessing caries progression or regression.

Of these, 1 utilized ICDAS-II preliminary plan for activity assessment. D.L.Bailey et al. 2009 [4] 80% of the lesions treated by CPP-ACP had a baseline score of 2/A whereas at the end of 12 weeks only 15% had 2/A score and 63% had become 2/I. This

was significantly more than the scores for placebo. 1.4% of the lesions had 3/A score at baseline in the group CPP-ACP, whereas only 0.5% of the lesions had 3/A scoring at the end of 12 weeks.

A study by Altenburger et al 2010 [2] evaluated 2 groups one CPP-ACP and a placebo, there was no significant difference between the two groups.

A study by Andersson et al 2007[7] showed that more sites became invisible in the CPP-ACP group than fluoride mouth rinse group. After 3months, the proportion of sites scored as 0 and 1 was 55% in CPP-ACP group compared with 18% in fluoride mouth-wash group. The corresponding values after 12months were 64% and 23% respectively, a difference that was statistically significant. Approximately about 10% of sites remained unchanged, with highest score (4) one year after the study began. The visual evaluation suggested an aesthetically more favorable outcome for amorphous calcium phosphate treatments.

#### **B. DMFT / DMFS scores**

2 articles used DMFT/DMFS scores for evaluating caries progression or regression.

A Nakamura et al 2009 [5] showed there was statistically significant difference between the groups fluoride mouth rinse plus targeted sealant (FMR+TS) and fluoride mouth rinse alone (FMR) with 1.56 in FMR + TS group and 2.20 in FMR group.

Selwitz R H et al. 1995[9] compared DMFS score in two groups, (fluoride alone, sealant and fluoride) for a duration for 4yrs in younger age (7-11yrs) group and showed that there is a decrease in the score by 67.3%. (1.5 vs. 0.4) In the same period, in older age group there was a decrease in score by 34% (6.22 vs. 4.07).

Overall reduction for both age groups was (2.1.01 vs. 2.15) respectively. Thus, Fissure sealants conferred additional caries- preventive benefits beyond those of fluoride therapy alone.

#### **C. Radiographic evaluation**

1 article used Radiographic evaluating caries progression or regression.

Santiago S et al 2005 [8] showed that there was no significant difference between sealant and fluoride varnish in controlling lesion progression both in randomized clinical trial and split mouth design. (93% of sealed vs. 88% of fluoride varnish)

#### **D. Caries Prevalence**

1 article used Caries Prevalence for assessing caries progression or regression.

A study by Aya Nakamura et al 2009 [5] showed statistically significant difference between the groups studied. The caries prevalence was 28.3% in fluoride mouth rinse plus targeted sealant (FMR+TS) group and 60.0% in fluoride mouth rinse (FMR) group.

#### **E. Mineral Content**

4 articles used Mineral Content for assessing re-mineralization and caries progression or regression.

By Najibfard et al 2011 [3] nHAP induce a consistent re-mineralization by forming a homogenous apatite layer on the de-mineralized surfaces. This layer is composed of hydroxyapatite nano-crystals which chemically bond to natural enamel crystals.

Biomimetic apatite deposition on affected sites of enamel does not only cover and protect enamel structure, but also provide minerals needed for restoring de-mineralized areas.

Progressive transfer of hydroxyapatite nano-crystals from new apatite coating to lesion maintains high concentration gradients of calcium and phosphate ions in sub-surface enamel, there by facilitating re-mineralization.

The influence of these variables on re-mineralizing efficacy of nHAP may differ with varying concentrations.

Altenberg et a 2010 [2] showed that there is statistically significant difference between the CPP-ACP and NaF group. CPP-ACP group showed statistically significant difference after 2<sup>nd</sup> and 3<sup>rd</sup> weeks compared to baseline.

Gianmaria et al. 2011 [1] showed that there is significant difference between De-mineralized specimens kept in intra-oral environment with GC Tooth Mouse (CPP-ACP), a placebo or control without any treatment. CPP-ACP showed Mineral sediment with a trend of wavy lines was clearly visible at low magnification (600x) and surfaces were covered with amorphous deposit at higher magnification (6000x) placebo showed surfaces appeared disorganized, without any distinct etching pattern control showed loss of enamel and evident holes from 5 to 25  $\mu$ m in diameter.

A study by E.C.Reynolds et al 2007 [6] showed a similar level of re-mineralization for fluoride and 2% CPP-ACP. But the dentifrice with a combination of 2% CPP-ACP and 1100ppm of fluoride was superior to all other formulations. Micro-radiography of the lesions showed fluoride ion alone tended to promote re-mineralization of surface layers, whereas CPP-ACP showed re-mineralization even in the presence of fluoride, throughout the body of lesion.

A study by Andersson et al 2007 [7] showed laser fluorescence values decreased with time and were significantly lower after 2 and 6 months compared with baseline in both CPP-ACP and fluoride group. However no significant differences were disclosed between the two treatment regimes, either at baseline or at any of the follow-ups.

## **DEFENDING OF RESULTS**

### **A. Clinical evaluation**

CPP-ACP has been shown to localize and stabilize calcium and phosphate ions at the tooth surface in a bio-available form that can promote re-mineralization of enamel sub-surface lesions. Visual evaluation by Anderson et al 2007 [7] showed esthetically more favorable outcome for CPP-ACP due to a optical phenomenon. But in the light of previous findings by Reynolds et al 2003, the milk-protein based formulation augments the natural salivary healing process and nano-crystals of ACP are small enough to access de-mineralized areas underneath already re-mineralized surface zone. Therefore a deep progression of favorable aesthetic appearance is possible.

### **B.DMFT / DMFS scores**

Selwitz et al 1995 [9] showed that magnitude of reductions in caries experience, particularly among younger children(7-11), after 4yrs of participation in combined fluoride and sealant program strongly suggests that dental sealants conferred additional benefits beyond those of fluoride procedure alone. Data analyses depicted for the 14-17-yr-olds included findings for early erupting teeth, which were at risk for caries for a much longer period prior to the opportunity for sealant placement than the corresponding teeth in the younger children, Pit and fissure sites on first molars in the older children had been in the mouth for 6 or 7yr prior to sealing. Many of these teeth may have decayed or have been restored prior to the sealant placement phase of the study. Thus, the opportunity to demonstrate caries protection in these teeth would have been reduced. Additional analysis of data for the older age group revealed that reductions in DMFS scores averaged only 30,5% for early erupting teeth, whereas late erupting teeth showed a larger reduction of 43.7%.

### **C. Radiographic evaluation**

Santiago S et al in 2005 [8] showed that physical barrier of resin tags of maximum 6 $\mu$ m in length may act as a protection against exposure of acids produced by bacteria. This decreases the no. of micro-organisms in the lesion under the sealant.

### **D.Caries Prevalence**

Selwitz et al 1995 [9] and Rippa et al did surveys on combined fluoride and sealant application have suggested greater effectiveness for the combination than fluoride application alone.

The precise reason for secular decline in dental caries observed in western industrialized countries has not been established, it might be because of available fluoride in environment. The preventive factors could be change in diet, oral health care practices. It is also expected that caries reduction would expect largely on smooth surfaces with additional fluoride rather than on pit and fissures. Pit and fissure sites on first molars in the older children had been in the mouth for 6 or 7 yr prior to sealing. Many of these

teeth may have decayed or have been restored prior to the sealant placement phase of the study. Thus, the opportunity to demonstrate caries protection in these teeth would have been reduced. The older age group revealed that reductions in DMFS scores averaged only 30.5% for early erupting teeth, whereas late erupting teeth showed a larger reduction of 43%. The secular decline in caries attributed to pit and fissure surfaces was based on assumptions that a) the reduction in caries observed on approximal surfaces in the older children was due entirely to a secular influence and b) the secular trend attributed to approximal surfaces would be manifest equally as much on pit and fissure surfaces. It is possible, however, that some other factor such as a shift in examiner diagnosis or a change in approach to treatment of inter-proximal caries may have influenced the findings observed on approximal surfaces [9].

#### **E. Mineral content**

Altenberger et al. 2010 [2] proved the presence of calcium and phosphates in CPP-ACP to increase the concentration of calcium in organic residues, serving as a reservoir during re-mineralization.

Of the 9 articles 4 studies show that a combination of fluoride and non-fluoride is significantly better than either alone. Of this 1 is an in-situ study. Out of these 4 studies one RCT showed the combination to be better only when the mineral gain was considered (LF). When clinical evaluation was performed no difference could be seen between the combination and either alone. 3 studies showed no difference between the two (fluoride and non-fluoride). All of them were clinical studies. Of these, 1 study showed statistical difference between the groups (CPP-ACP vs. NaF) when clinical examination was performed at 12 months. Whereas, mineral gain assessment using Laser Fluorescence (LF) showed no statistical difference between the groups at both 6 months and 12 months evaluation. 2 studies showed non-fluoride agents (CPP-ACP) better than placebo. Of the 2 studies one is in-situ and the other clinical study. Of the 4 studies showing combination better, two are long term and two are short term. Of the 3 studies showing no difference between the groups, two are long term and one is short term. Of the 2 studies showing non-fluoride to be better one is long term and the other short term. Of the 4 studies showing combination to be better both the long term studies had a greater sample size than the short term study. Of the 3 studies showing no difference between the groups 2 had moderate and one small sample size. Both the studies showing non-fluoride to be better had small sample size.

#### **Reporting on the Quality of Evidence**

Nine trials were included in this review. 8 studies has a level of evidence 2. 1 study had a level of evidence 3. All the studies are clinical studies with high level of evidence. Risk of bias of included studies such as Gianmaria et al 2011 and E.C.Reynolds et al 2008 is high, Najibford et al 2011; Nakamura et al 2009 are moderate, where as Altenburger MJ et al 2010 and D.L.Bailey et al 2009 have low risk of bias. (Table 5 & 6)

#### **INFERENCE**

Combination of fluoride and non-fluoride agents like CPP-ACP and Sealant are better in controlling caries progression and promoting re-mineralization of initial caries lesions in permanent dentition.

There is no evidence to suggest non-fluoride agents are better than fluoride in controlling caries progression and/or re-mineralization of initial carious lesions in permanent teeth.

#### **Report of Outlier Data**

No outlier data obtained.

### **V. Summary**

The aim of this systematic review was to evaluate the effect of fluoride and non-fluoride agents in initial carious lesions of permanent dentition. The primary objective was to evaluate whether non-fluoride agents are better than fluoride. The secondary objective was to evaluate which re-mineralizing agent is the best for re-mineralizing adult initial carious lesion.

The databases PUBMED CENTRAL AND MEDLINE were searched for the related topic until July 2012. The search identified 79 potential publications out of which 70 were excluded after reviewing the title, abstract or text. A total of 9 publications fulfilled all criteria for inclusion.

The review identified 9 trials, and after carefully analyzing the merits of each publication on the basis of randomization, sample size, quality, follow-up duration and methodology, it is concluded that non-fluoride agents are not better than fluoride. The combination of fluoride and non-fluoride agents like CPP-ACP and sealant appears to be the best in re-mineralizing initial carious lesions of permanent dentition.

## VI. Conclusion

Within the limited information gained from the systematic review it is concluded that non-fluoride agents are not better than fluoride. The combination of fluoride and non-fluoride agents like CPP-ACP and sealant appears to be the best for controlling caries progression and promoting re-mineralization of initial carious lesion in permanent dentition. Long term randomized controlled trials comparing the efficacy of newer non-fluoride agents like nHAP and CPP-ACP with fluoride are strongly recommended.

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