

The current use of anti cariogenic agents and fluoride agents to cure white spot lesion: A systematic analysis

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Abstract

To find the best option to treat White Spot Lesion in existing caries treatments, and to identify the selected articles discussing etiology of caries along with White spot lesion. Null hypothesis was that "Only anti-cariogenic agent can cure White Spot Lesion".

PRISMA guidelines were used to conduct the systematic analysis. An electronic customized search was performed using mesh terminologies on PubMed database based on inclusion criteria that included studies with; any treatment option that can treat or prevent WSL; and minimally invasive treatment options that may be altered to treat WSL. While exclusion criteria comprised studies with treatment of rampant caries, severe early childhood caries and root caries. Inclusion criteria for etiological factors incorporated studies with factors that lead to white spot lesion or carious lesion.

Finally, therapeutic agents of dental caries were analyzed. Only the use of anti-cariogenic agent cannot cure White Spot Lesion. Hence study fails to prove the null hypothesis. Although combination of anti-cariogenic agents with a re-mineralizing agent can provide additional options for the treatment or prevention of WSL.

Keywords: White spot lesion, Fluoride, Caries, Treatment.

DOI:10.5455/JPMA.281716

Introduction

Dental caries is a disease affecting people of all ages.¹ Carious lesion has the ability to hurt the quality of life if

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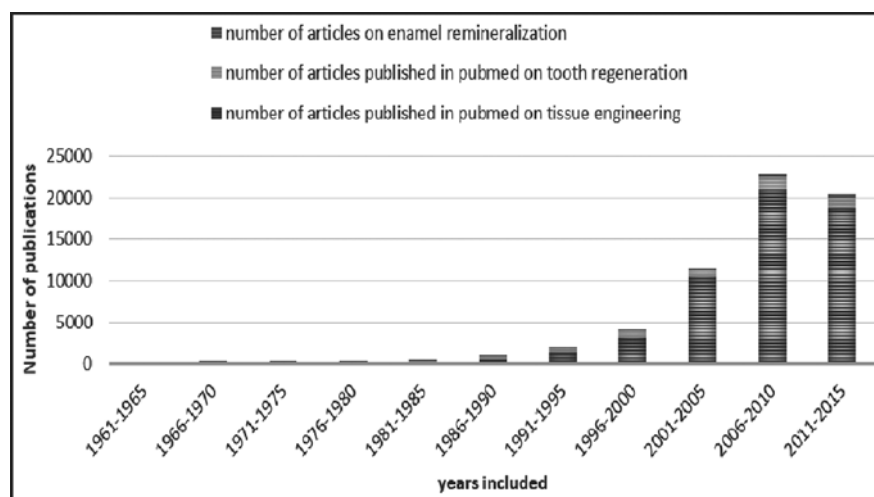


Figure-1: Trend over 50 years in literature.

left untreated.² Treatment of such lesions at the earliest possible stage with minimally invasive options is the utmost requirement. Trend from drilling of carious lesion is moving towards reversal of early form of caries. Preservation of tooth structure is forming the basis of the latest treatment options.³⁻⁶

There is a fine line to differentiate between the White Spot Lesion (WSL) and caries lesion. This study seeks to present a systematic analysis on the current trends of minimal to non-invasive treatments of dental caries. Non-invasive options of treating caries may add to or provide an alternative to re-mineralising agents that are currently being investigated for the treatment of WSL.⁷⁻⁹ WSL is considered the first step in the formation of carious lesion. PubMed medical subject heading (MeSH) terminology explains WSL tooth de-mineralisation separately from carious lesion even though it can lead to carious lesion. Considering de-mineralisation or WSL as a separate entity will clearly isolate the treatment options of WSL from dental caries.

Available non-invasive options in use for the treatment of WSL include fluoride gel application and desensitising agents.⁹ While treatment options at dental clinic include

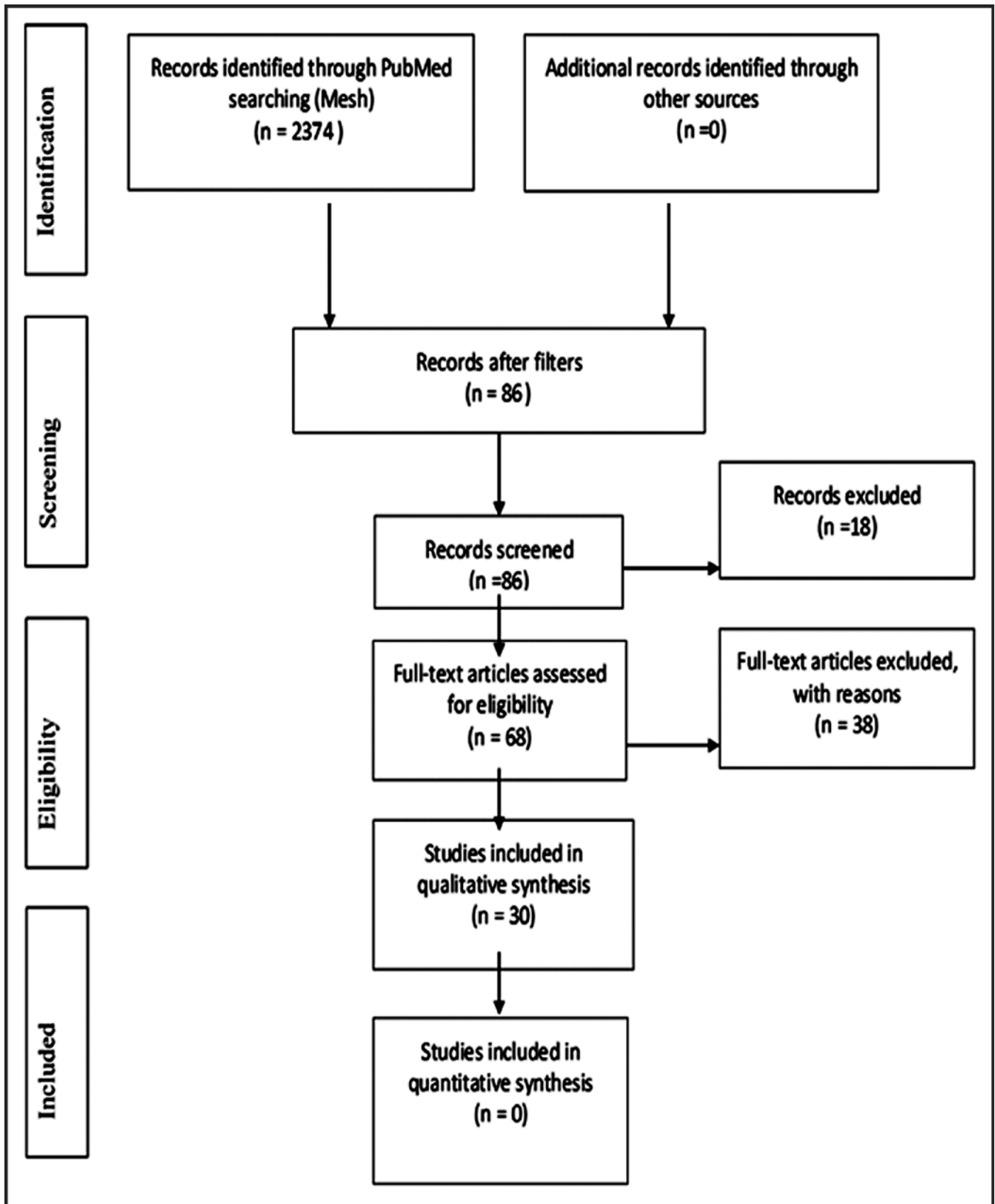


Figure-2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

filling or coating with veneers using porcelain or composite, bonding agent to correct flaw or decay, crowns or inlays and vital tooth crowning. Non-invasive treatment options in use are mostly symptomatic. On the other hand, invasive treatment options are not attractive as it involves removal of vital tooth structure.^{7,10}

Latest treatment options in literature focus on re-mineralising the WSL.^{9,11} A visible change in trend over 50 years can be seen in literature (Figure-1) which is an evidence of increasing number of research studies in this related field. Considering that present research on treating WSL is fixated on re-mineralising agents, there was a possibility of finding additional treatment options in latest research on prevention and treatment of dental caries. The current systematic review was planned to put on emphasis on the current trends in minimal to non-invasive anti-cariogenic agents that can be used to treat WSL.

Methodology

The PubMed database in conjunction MeSH terminologies was used to harvest articles most relevant to the search. The search string formulated after 'key word' optimisation for maximum relevant search results was:

(((((("Tooth Demineralization"[Mesh]) AND "Dental Caries"[Mesh]) AND "Dental Caries/etiology"[Mesh]) AND ("Dental Caries/therapy"[Mesh])) AND "Tooth Demineralization/etiology"[Mesh])).

The initial run of search yielded 2374 articles pertaining to the topic. After search term optimisation, 86(3.62%) articles were short-listed. This was the first level of automatic filtering applied to the search engines using Boolean Logic. The search result was further refined by introducing various filters, like availability of full text, free access and publication history (last 20 years to last 5 years) etc. Each of the filters provided a sharper focus

towards the current trends in research. After reducing the time span to 5 years (January 1, 2010, to January 1, 2015), the total number of studies left was 68(2.84%)(3.62%).

Inclusion Criteria

1. Any treatment option that can treat WSL.
2. Any preventive anti-cariogenic treatment that may also prevent WSL.
3. Minimally invasive treatment options that may be altered to treat WSL.
4. Factors that may lead to WSL or carious lesion.

Exclusion Criteria

1. Treatment of rampant caries and severe early childhood caries.
2. Treatment of root caries.

On the basis of the above criteria, the study rejected 38(1.6%) studies. Of the 30(1.26%) articles identified, 26(87%) pertained to therapeutic agents of dental caries that may be effective in treating or preventing WSL, and 6(20%) covered aetiological factors of caries and WSL. The search was done using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure-2).

Result

Of the studies selected, 11(%) were in vitro studies and 2(%) were in situ. Besides, 6(%) studies were in vivo; 3(%) of which were randomised clinical trials (RCTs), 1(%) was non-RCT, 1(%) cross-sectional and 1(%) animal study. Also, 7(%) were reviews that were included in order to investigate more treatment options. Aetiological factors of the selected studies were noted (Table-1) and so was the case with characteristics, citations, reason for inclusion and summary of results that highlighted the

Table-1: Studies with aetiological factors of White spot lesion.

Author's name & Year	Type of study	White spot lesion/ caries	Etiological factors	Rationale
Moynihan and Kelly 2014 ³²	Systematic review	Yes	Free sugar.	Reducing free sugar intake can significantly reduce the risk of caries
Shimizu, Deeley et al. 2013 ³³	In vitro study	Yes	Gene	Specific gene contributing to caries
Armfield, Spencer et al. 2013 ³⁴	Cross-sectional study (humans)	Yes	Sugar Fluoridated water	Sugar sweetened beverages increase the risk of caries but fluoridated water reduced its effect
Huang, Roloff-Chiang et al. 2013 ³⁵ (repeated)	In vivo study. Clinical trial	Yes	Orthodontic treatment	Demineralized white spot lesion caused due to orthodontic treatment
Hadler-Olsen, Sandvik et al. 2012 ³⁶	In vivo study cross-sectional study	Yes	Orthodontic treatment	Obvious cause of WSL
Maltz, Jardim et al. 2010 ¹³	Review	Yes	Bad oral hygiene, sugar intake, others.	First step of caries is a white spot lesion

Table-2: Characteristics of studies with anti-cariogenic agents and details on results.

Author's name & year	Type of study/ conflict of interest	Therapeutic agent	Treatment/ therapy	Non-invasive treatment options	Rationale	Conclusive remarks
De Luca, Franca et al. 2014 ¹⁹	In vitro /Nil	Varnish (15% propolis-chitosan Formulations)	Preventive. Antimicrobial activity against	Preventive and Non-invasive	Non-invasive treatment option	To confirm clinical efficacy further studies are required. Non-invasive therapy.
Motta, Bussadori et al. 2014 ³⁷	Randomized, clinical trial.	Papacarie [®] is a gel containing papain and chloramine	Chemo-mechanical removal	Minimally invasive	Minimally invasive treatment option	Minimally invasive option
Ammari, Moliterno et al. 2014 ³⁸	Randomized clinical trial	Papacarie [®] and Carisol [™]	Chemo-mechanical removal	Minimally invasive	Minimally invasive treatment option	Minimally invasive but not better than manual excavation
Silva, Castilho et al. 2014 ³⁹	In vitro study	Brazilian plant extracts	Antimicrobial against SM	Preventive option	Preventive. antimicrobial	Extract Ipomoea alba showed strong activity against SM
Pan, Mao et al. 2013 ²⁶	Rat model and in vitro	Genetic mutant of SM it is gcrR deficient.	Replacement of natural flora with mutants.	Mutant bacteria produce less acid	Preventive. Replacement of natural flora	Preventive therapy only at initial stages of research. It may have potential in future
Juric 2013 ¹²	Review	Pit and fissure sealants	As preventive measure and for occlusal caries	Composite resin sealant, Glass-ionomers	Discussed preventive treatment of occlusal caries	Weather to cover pit and fissure caries or remove the caries is controversial. May need more studies
Chen, Zhu et al. 2013 ²⁸	In vivo animal study	Anti-cariogenic DNA vaccine	Vaccine	Immune response induction	Non-invasive and preventive.	Preventive therapy only at initial stages of research. It may have potential in future
Tomczyk, Pleszczynska et al. 2013 ²⁰	In vitro	Drymocalis rupestris extracts anti cariogenic	Bactericidal and bacteriostatic.	Anti-microbial and Inhibits dental plaque	Potential anti-cariogenic agent	Further studies required to check exact constituent responsible
Gagetti, Mastroberardino et al. 2013 ²⁵	Review on In vivo studies	Probiotics	Reduce LB and SM count. Control plaque pH	Preventive	Potential anti-cariogenic agent	More in vivo studies required. Most of the proved its anti-cariogenic activity
Mei, Li et al. 2013 ¹⁵	In vitro study	Silver-diamine-fluoride	Inhibits biofilm formation	Preventive non-invasive	Reduce destruction of collagen and reduce cariogenic bacteria	Established clinical success but this study determined mechanism of action
Huang, Roloff-Chiang et al. 2013 ³⁵	Randomized clinical trial	MI paste (casein phosphopeptide-amorphous calcium phosphate) and fluoride varnish	Mineralization of white spot lesion (WSL) with re-mineralizing agents	Non-invasive treatment	Replenish the lost mineral content of WSL	Study could not find any difference between normal tooth paste and the re-mineralizing paste or varnish. Further studies required to confirm this observational study.
Takeuchi, Kawamura et al. 2012 ¹⁶	In vivo study Follow up was 5 year. Not randomized	Fluoride mouth rinsing in school children	Once a week at school for 5 years compared to children who did FMR for only one year	Preventive non-invasive	Showed less carious teeth in children on FMR for longer time	Group with longer FMR had more pit and fissure sealant treatment compared to other group which is a big confounder in the study
Zhan, Cheng et al. 2012 ¹⁷	Randomizecontrolled clinical trial	Xylitol wipes	Reduction in number of new cases with caries in deciduous teeth	Non-invasive	Effective treatment in deciduous teeth	Preventive in deciduous teeth. Limitations in study and may need further studies.
Eckert, Sullivan et al. 2012 ²¹	Review	Synthetic peptide C16G2, antimicrobial	Selective antimicrobial action against of S. mutans (major cariogenic bacteria)	Non-invasive	Potential in future	Specific antibiotic is better than broad spectrum antibiotic. Further clinical studies with long follow up may be more conclusive.

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Author's name & year	Type of study/ conflict of interest	Therapeutic agent	Treatment/ therapy	Non-invasive treatment options	Rationale	Conclusive remarks
Brighenti, Gaetti-Jardim et al. 2012 ¹⁸	In situ	Extract of Psidium cattleianum leaves	Decreased the total anaerobic bacterial count. Confounders notified.	Potential non-invasive	Potential in future	Further in vivo testing required to remove confounders.
Cheng, Weir et al. 2012 ³¹	In vitro	Novel Composite with tetra calcium phosphate fillers	Anti-bacterial, release of calcium and phosphate ions and good strength	Minimally invasive treatment.	Potential in future	Further studies are required
Uju and Obioma 2011 ²⁴	In situ	Tropical plant materials	Antimicrobial against	Natural alternative to antibiotic	Non-invasive treatment option	Further studies are required to determine the clinical effectiveness
Alavaikko, Jaakkola et al. 2011 ²⁹	In vitro	Nano-emulsions	Effective antimicrobial activity and reduce the surface adhesion.	Non-invasive	Non-invasive potential anti-cariogenic agent	May be effective in prevention and treatment of dental caries.
Sentila, Gandhimathi et al. 2011 ¹⁴	In vitro	Various tooth pastes and mouthwashes.	Anti-bacterial effect against	Non-invasive	Non-invasive antibacterial	Triclosan, chlorhexidine showed good results even at lower concentration. Better alternatives required
Jeon, Rosalen et al. 2011 ²²	Review	Natural anti-cariogenic agents	May act differently	Non-invasive	Non-invasive Naturally occurring	More research is required to bring these to clinics
Lobo, Fonteles et al. 2011 ²³	In vitro	Essential oil of plant origin	Lippia sidoides Cham extract has antibacterial effect	Preventive against early childhood caries	Non-invasive naturally occurring	Further clinical studies are required
(Gordan, Garvan et al. 2010 ²⁷	Case-control	Alkali production by arginine deimi-nase and urease activities of bacteria	Reversal in acidic pH can be achieved by alkali producing bacteria	Non-invasive	It has the potential to treat or prevent WSL	Could not prove it by statistically significant difference of cases and controls. Need further studies
Bonifait and Grenier 2010 ⁴⁰	Review	Cranberries	Inhibition of organic acids and biofilm formation by bacteria	Non-invasive	May prevent WSL	Not systematically reviewed may need more investigation.
Maltz, Jardim et al. 2010 ¹³	Review	Fluoride Dental sealants	Anti-cariogenic preventive	Non-invasive	May prevent WSL	Need more details related to WSL
Branco-de-Almeida, Murata et al. 2011 ⁴¹	In vivo	7-epiclusianone Plant extract	Effective against bacteria and biofilm formation	Non-invasive	May prevent WSL	Need more testing related to its toxicity
Lee, Karthikeyan et al. 2010 ³⁰	In vitro	Cetylpyridinium chloride (already approved by FDA) nano-emulsion	Nano-emulsion proven to target cell membranes of bacteria and other micro-organisms. Prevent bacterial adhesion. More effective than chlorhexidine	Non-invasive	This study has shown possible mechanisms of action which may be used to treat or prevent WSL	Study design and oral environment simulation are the strength of this study. Potential in prevention of WSL

therapeutic agents with potential to treat WSL (Table-2).

Discussion

After combining the results of therapeutic agents used in minimal invasive treatment options, viability of specific agents to be used as definitive treatment option can be analysed.

Aetiological factors related to demineralization and dental caries

Different aetiological factors were found in studies. General causes included free sugar intake, sweetened beverages, orthodontic treatment, bad oral hygiene, diet, tobacco,

stress and alcohol. Specific aetiologies covered in these studies were presence of specific gene, anaerobe bacteria especially streptococcus mutans (SM), frequent reduction in potential of hydrogen (pH), surface adhesive properties of bacteria, biofilm formation and production of organic acid. Most of the studies were related to eradication of cause (Table-2). And a few additional factors were also noted (Table-1). Method and mechanism of these aetiology-specific treatments may help in treating WSL.

Various treatment options

The various options to treat WSL found in literature were further classified under following headings. Their

potential is also explained.

1: Established therapies

There are various options used in clinics that treat caries with minimal invasion. Considering these for treating WSL may have certain issues. Use of Pit and fissure sealants by covering WSL was found to be controversial.^{12,13} Triclosan and chlorhexidine that act against SM needs better alternative to resolve WSL.¹⁴ Fluoride-containing therapies.¹⁵⁻¹⁷ make enamel more resistant to de-mineralisation but does not re-mineralise WSL. Xylitol wipes were only tested for deciduous teeth. These issues may be resolved by combining different treatment options.

2: Antibacterial / anti-cariogenic agents of plant origin

Extracts of various plants have been tested for their anti-cariogenic ability.¹⁸⁻²⁴ In view of these antibacterial agents, Psidium Cattleianum leave extracts (PCLE) showed interesting results. PCLE increased the hardness of enamel but use of surfactant in the study may act as confounder. Hence, further studies are required for testing its use in the treatment of WSL. Most of these agents target the cariogenic bacteria, specifically SM. WSL that are caused by bleaching or by etching does not result from cariogenic bacteria or formation of biofilm. Hence, antibacterial agents of plant origin cannot solely resolve de-mineralisation.

3: Changing the oral habitat

Changing oral habitat by use of probiotics,²⁵ mutants of SM²⁶ or alkali-producing bacteria²⁷ are at initial stages of research. These reduce the cariogenic bacteria and their activity. Mode of action is reversal of acidic pH or reducing bacterial adhesion in oral cavity.²⁵⁻²⁷ Further research is required to establish its use in the treatment of WSL.

4: Vaccination against cariogenic bacteria

DNA vaccine that can be used via nasal cavity against SM is at initial stages of development. This might prevent SM activity but still cannot prevent de-mineralisation of tooth surface resulting due to reasons other than SM.²⁸

5: Nano-emulsion

It acts as disinfectant and reduces surface energy. It protects the surface of enamel.^{29,30} It might be considered a preventive option for WSL, but on the contrary it may hinder the etching or bleaching process. Thus its use may be controversial in certain situations.

6: Novel composite with antibacterial properties as well as re-mineralising

efficiency

Combination of antimicrobial properties and the ability to re-mineralise may be effectively used during orthodontic treatment to prevent WSL. Further research is required in this field to establish its use for bonding or banding during orthodontic treatment.³¹

Conclusion

Most of the treatment options found in literature related to treatment of anti-cariogenic agents fail to provide a complete cure of WSL. The possible treatment option may be further explored. Further research in combining anti-cariogenic agents with a re-mineralising agent may effectively treat or prevent a WSL.

Disclaimer: Non.

Conflict of Interest: None.

Source of Funding: None.

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