CONCISE REVIEW

International Dental Journal 2020; 70: 418–426

doi: 10.1111/idj.12588

Comparison of new formulas of stannous fluoride toothpastes with other commercially available fluoridated toothpastes: A systematic review and meta-analysis of randomised controlled trials

Danielle Clark-Perry and Liran Levin

[1]*Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada.*

Aim: The aim of this study was to systematically review and analyse the difference in efficacy of stannous fluoride toothpaste formulations in comparison to other fluoridated toothpastes without stannous fluoride. **Materials and methods:** A systematic search of the literature was performed according to PRISMA guidelines. A search strategy was developed to answer the study question and was performed in PubMed-Medline databases. Inclusion criteria were randomised controlled clinical trials comparing stannous fluoride toothpaste formulations with other fluoridated toothpastes not containing stannous fluoride. **Results:** The search in PubMed-Medline databases resulted in 384 articles; 23 articles were downloaded for review, 16 articles were included in the report and six could be used for meta-analysis. All studies were randomised controlled clinical trials that compared clinical outcomes between toothpastes with stannous fluoride combinations and toothpastes with only fluoride. The overall results of the 16 studies favoured the stannous fluoride formulations. However, in a meta-analysis of the randomised controlled clinical trials, it was demonstrated that stannous fluoride toothpaste formulations provided significantly better outcomes based on the Gingival Index (SMD −0.14, 95% CI −0.20, −0.07, P = 0.0001), but not the Modified Gingival Index (SMD −0.30, 95% CI −0.7, 0.09, P = 0.13). **Practical implications:** The antibacterial properties of stannous seem to provide favourable results when formulated with a fluoridated toothpaste. This systematic review highlights the lack of homogenous research available to rigorously compare stannous fluoride toothpaste formulations with other fluoridated toothpastes without stannous fluoride.

Key words: *Plaque, prevention, caries, periodontitis, toothpaste, bacteria, gingivitis*

INTRODUCTION

It is well established that dental plaque (biofilm) is the main causes of the two most prominent dental diseases, caries and periodontal disease[1]. These oral diseases burden the population worldwide, and the association reported between oral health and overall health is continuously growing[2]. Fortunately, it is well understood that if biofilm is removed frequently and effectively, the occurrence of both periodontal disease and caries can be reduced or eliminated[1,3]. As a result, efforts are invested into establishing new methods and improving current methods to make biofilm removal more effective. This includes new toothbrush designs, and new products to assist in oral disease prevention and control.

One of these products is fluoridated toothpastes. Fluoride decreases caries risk and can aid in remineralisation of the enamel. As a result, it is a common and important ingredient found in toothpastes[4]. However, more than just a single formulation of fluoride exists on the market. The fluoride component of toothpastes may be stannous fluoride, amine fluoride with stannous chloride, sodium fluoride, sodium monofluorophosphate, etc.[4]. Different formulations are being developed and researched in an effort to achieve better outcomes for oral health.

Specifically, stannous fluoridated toothpaste combinations ultimately have two effective ingredients. Stannous itself has antibacterial properties, and fluoride has anticavity properties[5]. As a result, stannous fluoride formulations are promoted to help the treatment of gingivitis, erosion, hypersensitivity and oral malodour in addition to the anticaries benefit of the fluoride[5]. In consideration of the additional benefits reported for stannous fluoride formulations, the

purpose of this systematic review and meta-analysis was to investigate the efficacy of stannous fluoridated toothpastes compared with other fluoridated toothpastes without stannous fluoride.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews and Interventions and the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines[6,7]

Focused question

The format used to develop the focused question was based on the PICO (population, intervention, comparison and outcome) structure[6]. Using the PICO format, the following question was used to guide the search strategy: What are the effects of using new formulations of stannous fluoride toothpaste compared with other fluoridated toothpastes without stannous on periodontal and caries parameters in the general population? The *population* was not restricted and included all studies of the general population; the *intervention* was stannous fluoride toothpaste formulations; the *comparison* of interest was other fluoridated toothpastes; and the *outcomes* included any periodontal and caries parameters.

Eligibility criteria

The following inclusion criteria were utilised.

Randomised controlled trials examining patients from the general population published from 2015 until March 2019. This date restriction was chosen due to the rapid development of new toothpaste formulations, and in order to include the recent formulations available for stannous fluoride that were introduced in recent years. Any age, gender and severity of oral health status and medical status were included. Studies comparing stannous fluoride toothpaste formulations with at least one other fluoridated toothpaste without stannous fluoride for daily oral hygiene and reported outcomes related to oral health such as, but not limited to: caries, plaque index, calculus accumulation, gingival index, sensitivity and malodour were included.

The following exclusion criteria were used.

Due to limited resources, an English language restriction was placed. Studies that were not randomised control trials were excluded as well as studies that compared stannous fluoride with non-fluoridated toothpastes.

Search strategy

The National Library of Medicine, Washington DC (MEDLINE-PubMed) was used to search for all appropriate papers to answer the research question. The search was conducted in March 2019 using the following search strategy: (Toothpaste* or dentifrice) AND (stannous) AND (fluoride). The purpose of this search strategy was to ensure that all relevant papers were included in the initial search results.

Screening and selection

Two reviewers (DC and LL) screened the titles and abstracts for papers that met the eligibility criteria. After screening, full-text articles were downloaded and reviewed by both authors.

Assessment of heterogeneity and quality

The following variables were assessed for heterogeneity for each article: study design and methods; length of the study; sample size; commercial funding; drop-out rates; and subject demographics. Each included study was assessed for quality using the Cochrane Risk of Bias Tool, which evaluates studies based on random allocation, random sequence generation, examiner and participant blinding, incomplete outcome data, selective reporting and other biases[6]

Data extraction

Data extraction was done using a data extraction form that included study demographics, length of the study, the intervention, the comparison, indices used, main findings, and whether it was manufacturer funded. If three or more studies assessed the same outcome using the same methods, further numerical data were extracted for meta-analysis.

Data analysis

For qualitative reporting of the included studies, a table was used to communicate the main findings of the included articles. In cases in which meta-analysis was conducted, the random-effects model was chosen and the RevMan 5.3 software was used.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to rank the evidence[8]. The quality of the evidence, strength and direction of the recommendations were rated according to the following aspects: risk of bias; consistency of results; directness of evidence; precision and publication bias; and magnitude of the effect.

RESULTS

Search and selection results

The search in MEDLINE-PubMed resulted in 384 articles. After screening titles and abstracts for applicability, 23 articles were downloaded for review (*Figure 1*). Using the eligibility criteria, a total of 16 studies were included for qualitative analysis[9–24]. Out of the included studies, six could be used for meta-analysis. Reasons for exclusion of full-text studies are provided in *Table 1*[24–31].

Table 1 Reasons for exclusion of full-text studies

Study	Reason for exclusion
Feng, 2016[24]	Comparison included a rinse
Jongsma, 2015[25]	Comparison included a rinse
Mason, 2017[26]	Did not compare stannous fluoride
Milleman, 2016[27]	Did not compare stannous fluoride
Sagel, 2018[28]	Review article
West, 2018[29]	*In situ* study
Zini, 2018[30]	There was not a true control to assess only toothpaste

Study characteristics and heterogeneity

All of the included studies were randomised controlled clinical trials that compared oral health outcomes of a stannous fluoride toothpaste formulation in comparison to another fluoridated non-stannous fluoride toothpaste. The specific characteristics for each study are detailed in *Table 2*. The duration of the studies ranged between 2 and 24 weeks. Much of the heterogeneity amongst the included studies came from the reported outcomes and how they were measured. Studies evaluated different oral health outcomes using different methods. Examples of this included assessing plaque via plaque indices, digital plaque imaging analysis and bacterial community levels, as well as assessing gingival inflammation using gingival indices, bleeding points and pocket depth.

Quality assessment

Most of the included studies had a low or unclear risk of bias based on the application of the Cochrane Risk of Bias tool (*Figure 2*). Only two studies had high risk of bias in the category of participant blinding. These studies were not included in the meta-analysis. Overall, there was an unclear risk of bias labelled for all studies under incomplete outcome data. For the majority of the studies, however, it was unclear or low risk of bias regarding random sequence

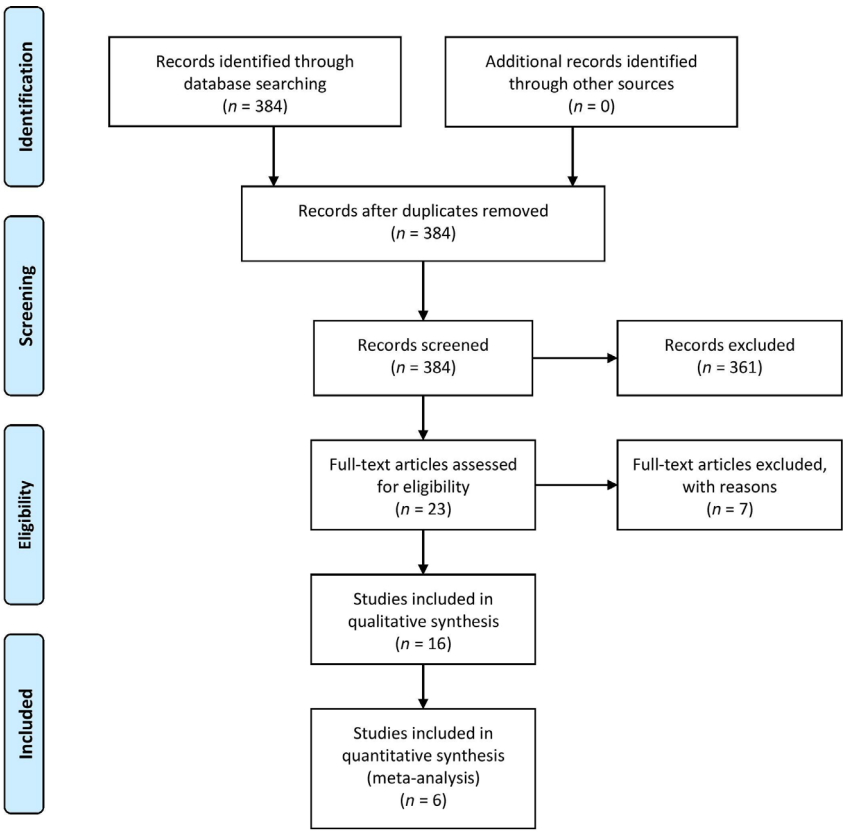

Figure 1. PRISMA flow chart.

Table 2 Characteristics of the included studies

Author, Year	Type of Study	Length of Study	Participants	Intervention/ Comparison	Measured Outcomes	Main Findings of the Study	Manufacturer Funded
Lorenz, 2019[9]	Single centre, RCT, double-blind clinical study	12 weeks	120 (amine fluoride and stannous chloride) 117 (monofluorophosphate)	Amine fluoride and stannous chloride versus monofluorophosphate	PI, GI, mSBI, safety	"...application of amine fluoride/ stannous chloride toothpaste led to a clinically meaningful and more pronounced plaque reduction."	Yes
Singh, 2018[10]	RCT, double-blinded	6 weeks	24 (stannous fluoride and whitening gel) 25 (NaMFP)	Stannous fluoride and whitening gel versus NaMFP	DPIA	"the two-step dentifrice and gel sequence differed significantly ($P < 0.005$) from baseline on daytime plaque coverage, and salivary flow increased significantly ($P = 0.033$) .."	Yes
Parkinson, 2018 31:81–85[11]	Single centre, examiner blind, two treatment arm parallel group RCT	12 weeks	119 (0.454% stannous fluoride) 119 (sodium monofluorophosphate)	0.454% stannous fluoride versus sodium monofluorophosphate	MGI, blood in expectorate, BI	"Statistically significant differences between treatments were observed in favour of the test [stannous fluoride] dentifrice compared with the negative control dentifrice in terms of gingival bleeding ... and gingival inflammation (MGI) ($P < 0.0001$ at weeks 4 and 12 for all)."	Yes
Parkinson, 2015[12]	RCT, examiner-blind, parallel, two treatment group	8 weeks	59 (0.454% stannous fluoride) (59) sodium monofluorophosphate	0.454% stannous fluoride versus sodium monofluorophosphate	Schiff score, tactile threshold, VAS	".. the test dentifrice [stannous fluoride] to be significantly better than the negative control dentifrice in relieving dentin hypersensitivity or all measures ..."	Yes
Hu, 2019[13]	RCT, examiner-blind	24 weeks	49 (0.454% stannous fluoride) 49 (0.76% sodium monofluorophosphate)	0.454% stannous fluoride versus 0.76% sodium monofluorophosphate	GI, PI, GS, Gint, Pint	"the test dentifrice [stannous fluoride) showed statistically significant reductions in all indexes compared with the control dentifrice ($P < 0.001$)"	Yes
Haraszthy, 2019[14]	RCT, single site, double-blind, 2 treatment, parallel design	8 weeks	62 (stannous fluoride) 67 (sodium monofluorophosphate)	O.454% stannous fluoride versus sodium monofluorophosphate	Bacterial reduction	"the stannous fluoride toothpaste provided bacterial reductions in all oral microenvironments 12 h after brushing .."	Yes
Hagenfield, 2019[15]	RCT, double-blind, two centre study	12 weeks	21 (stannous fluoride) 20 (sodium monofluorophosphate)	Amine fluoride/ stannous fluoride versus zinc-substituted carbonated hydroxyapatite	Bacterial community level	"The use of a toothpaste containing anti-adhesive HA did not induce statistically noticeably different changes on microbial composition .."	Yes
Geidel, 2017[16]	RCT, single-blind	24 weeks	25 (herbal toothpaste) 26 (triclosan toothpaste) 25 (stannous fluoride toothpaste)	Herbal toothpaste versus triclosan toothpaste versus stannous fluoride toothpaste	OHI, API, SBI, BOP, PD, AL	"the herbal toothpaste was as a good as the control toothpaste"	Yes
He, 2017; 28 (Spec Iss B): B12–16)[17]	Single centre, RCT, double-blind, parallel group	8 weeks	100 (0.454% stannous fluoride) 100 (0.30% triclosan toothpaste)	0.454% stannous fluoride versus 0.30% triclosan toothpaste	MGI, GBI, number of bleeding sites	"... the stannous fluoride dentifrice group showed statistically significant lower mean MGI and GBI scores than the subjects using the triclosan positive control dentifrice .."	Yes

(continued)

Table 2 continued

Author, Year	Type of Study	Length of Study	Participants	Intervention/ Comparison	Measured Outcomes	Main Findings of the Study	Manufacturer Funded
Gerlach, 2018[18]	3 RCT (1 crossover, 2 parallel)	Variable	Unclear	0.454% stannous fluoride plus hydrogen peroxide versus 0.76% monofluorophosphate	Malodour, plaque, bleeding sites	"Relative to baseline, only the experimental group (0.454% stannous fluoride plus hydrogen peroxide) exhibited significant ($P < 0.05$) improvements at initial and subsequent timepoints in each trial."	Yes
Milleman, 2018[19]	Single centre, randomised, examiner-blind, two treatment arm parallel group study	24 weeks	108 (0.454% stannous fluoride toothpaste) 106 (0.76% sodium monofluorophosphate)	0.454% stannous fluoride toothpaste versus 0.76% sodium monofluorophosphate	Lobene stain index, oral tolerability	"Statistically significantly less anterior tooth staining was observed with up to 24 weeks twice daily brushing with a 0.454% SnF2/5% STP anhydrous dentifrice ..."	Yes
Friesen, 2017[20]	Single centre, RCT, double-blind, parallel group	4 weeks	60 (0.454% stannous fluoride toothpaste sodium) 60 (fluoride/triclosan toothpaste)	0.454% stannous fluoride toothpaste versus sodium fluoride/triclosan toothpaste	RMNPI	"The stabilised stannous fluoride dentifrice provided statistically significant reductions in plaque glycolysis *in vitro* and plaque growth *in vivo* compared with the triclosan dentifrice."	Yes
Parkinson, 2016[21]	3 RCT, examiner-blind, two treatment arm parallel group studies	2 weeks	113–120 subjects	NaF toothpaste versus 0.454% stannous fluoride toothpaste versus 0.76% sodium monofluorophosphate	Schiff sensitivity scale, VAS, tactile stimulus	"While these studies provide evidence for relief of DH with 0.454% stannous fluoride dentifrices after short term use ... the evidence, especially at the earliest time points, is inconclusive and needs further testing."	Yes
Parkinson, 2018 31: 17–23[22]	RCT, single centre, examiner-blinded, two treatment arm parallel group	24 weeks	49 (0.454% stannous fluoride toothpaste) 49 (sodium monofluorophosphate toothpaste)	0.454% stannous fluoride toothpaste versus sodium monofluorophosphate toothpaste	BI, MGI, PI	"Use of a dentifrice containing 0.454% w/w stannous fluoride led to significantly greater control of gingivitis ... and plaque compared with a SMFP dentifrice over a 24-week period."	Yes
Seriwatanachai, 2019[23]	RCT, single centre, double-blind, parallel group	24 weeks	45 (0.454% stannous stabilised zinc phosphate) 45 (0.454% stannous stabilised sodium hexametaphosphate) 45 (0.76% sodium monofluorophosphate)	0.454% stannous stabilised zinc phosphate versus 0.454% stannous stabilised sodium hexametaphosphate versus 0.76% sodium monofluorophosphate	GI, PI, GS, PS, Gint, Pint	"This study reports similar efficacy of a test dentifrice compared with a commercial SnF2 containing dentifrice for plaque control and reduction of gingival inflammation, and provides supporting evidence that the test dentifrice maintains its clinical efficacy with change of formulation."	Yes
He, 2017; 28(Spec Iss B): B21–26[24]	RCT, double-blind, parallel group	8 weeks	41 (0.454% stannous fluoride toothpaste) 39 (NaF toothpaste)	0.454% stannous fluoride toothpaste versus NaF toothpaste	Calculus	"The stannous fluoride toothpaste had 15.1% less adjusted mean calculus at week 6 compared with the control group ($P = 0.05$)"	Yes

AL, attachment level; API, approximal plaque index; BI, bleeding index; BOP, bleeding on probing; DH, Dentinal hypersensitivity; DPIA, digital plaque imaging analysis; GBI, Gingival bleeding index; GI, gingival index; Gint, gingival interproximal index; GS, gingival severity; MGI, modified gingival index; mSBI, modified sulcular bleeding index; OHI, Oral hygiene instruction; PI, plaque index; Pint, plaque interproximal index; PS, plaque score; RCT, randomised controlled trial; RMNPI, Rustogi Modified Navy Plaque Index; SBI, sulcular bleeding index; SMFP, Sodium monofluorophosphate; VAS, visual analogue scale.

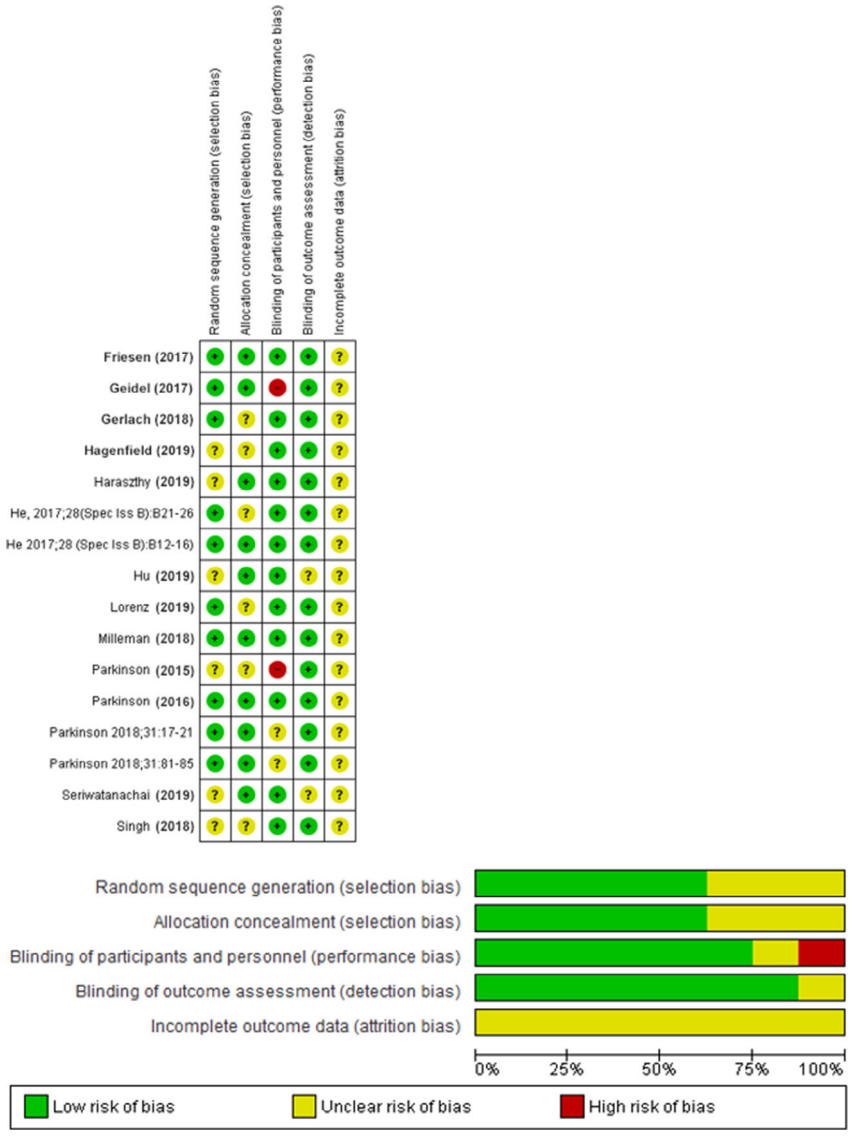

Figure 2. Risk of bias summary.

generation, allocation concealment and blinding of outcome assessment. It is important to note that all studies were manufacturer funded. Because there were no major differences in the quality of the studies, the results of all of the studies were included in *Table 2*.

Study outcome results

Overall, 16 studies compared the use of a stannous fluoride toothpaste formulation with a fluoridated toothpaste without stannous fluoride. Despite the large number of studies, there was great variability in the reporting outcomes and toothpaste formulations.

None of the studies that fulfilled the inclusion criteria were found to assess caries indices as an outcome variable.

A total of six studies assessed plaque using a variety of indices, including: plaque index, digital plaque imaging analysis, bacterial reduction, and the Rustogi Modified Navy Plaque index (RMNPI). All six studies that assessed plaque found that the use of stannous fluoride toothpaste formulations had better outcomes than fluoridated toothpastes without stannous fluoride. However, each study used different indices to reach their conclusions, and thus a meta-analysis was not attempted[9,10,13,18,20,21]. Two studies assessed biofilm based on bacterial reduction and, although Haraszthy et al. found a significant bacterial reduction with the stannous fluoride formulation used in their study, Hagenfield et al. did not find a significant difference in microbial composition between the two fluoride formulations used in their study[14,15]. Other outcomes that were included amongst the 16 studies were sensitivity, calculus accumulation, bleeding and malodour, along with several others. The specific details are outlined in *Table 2*.

There were six studies that were used for meta-analysis[1,11,13,17,22,23]. All six studies included gingival inflammation as an outcome variable. Three studies assessed gingival inflammation using the gingival index (GI), and the other three studies used the modified gingival index (MGI). The outcome for the MGI meta-analysis was that there was no significant difference between stannous fluoride formulations in comparison to other fluoridated toothpastes (SMD −0.30, 95% CI −0.7, 0.09, $P = 0.13$; *Figure 3*). However, based on the GIs, the meta-analysis showed statistically significantly better outcomes for the stannous fluoride formulations (SMD −0.14, 95% CI −0.20, −0.07, $P = 0.0001$; *Figure 4*).

Evidence profile

The GRADE evidence profile is detailed in *Table 3*. All of the included studies for each outcome were randomised controlled trials. Thus, each outcome started at the highest levels of evidence. Reasons for downgrading included: unclear or high risk of bias assessments, publication bias, and magnitude of effect based on clinical significance. Publication bias was present in the outcome comparisons and because the studies were manufacturer-funded. Overall, there is inconsistent evidence supporting the advantage of stannous fluoride toothpaste formulations on gingival inflammation compared with non-stannous fluoride toothpastes.

DISCUSSION

The antibacterial properties of stannous may benefit the oral health of an individual when formulated with fluoride toothpastes. Several studies compare the use of stannous fluoride formulations with other fluoridated non-stannous toothpastes and demonstrate favourable results regarding plaque accumulation, bleeding indices and calculus accumulation along with many other parameters (*Table 2*). Gingival inflammation was also a common outcome assessed amongst the studies; however, only three studies used the GI to assess inflammation, while three studies used the MGI, and several other studies used different indices. Thus, meta-analysis was only attempted on these data, and the results showed that stannous fluoride toothpaste formulations had favourable outcomes when measured via the GI, but there were no statistically significant differences when measured via the MGI.

The GI was developed by Loe and Sillness in 1963, and scored the gingival tissues from 0 to 3, where 0 meant normal, 1 meant mild inflammation, 2 meant moderate inflammation, and 3 meant severe inflammation[32,33]. Later, in 1963, changes to the GI led to the MGI where the scoring became more detailed and mild inflammation was expanded to include the extent of inflammation[32,33]. The MGI then was scored as 0 being absent of inflammation, 1 being mild inflammation where not all of the gingiva is involved, 2 mild inflammation in all portions of the gingiva, 3 being moderate inflammation, and 4 being severe inflammation[32,33]. The difference in indices in combination with the different toothpaste formulations may have led to the contradictory outcomes of the present meta-analysis.

Nonetheless, toothpastes are only one part of good oral hygiene. Although toothpastes are beneficial in the prevention of caries, treatment of dentinal hypersensitivity as well as other benefits, other tools are necessary to provide the mechanical removal of the biofilm[34,35]. The most common tools used for this mechanical removal are toothbrushes and interproximal cleaning aids. Manual toothbrushes and power toothbrushes are available to patients, with two recent systematic reviews highlighting that oscillating

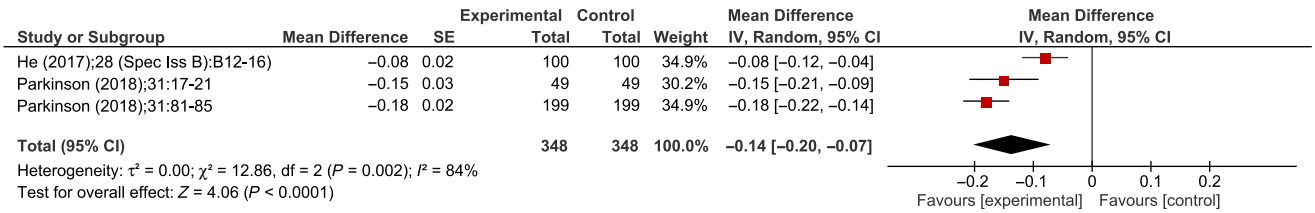

Figure 3. Modified gingival index (MGI) forest plot.

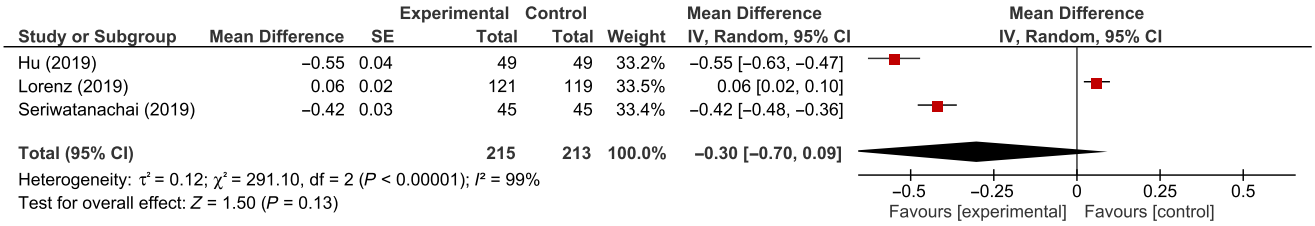

Figure 4. Gingival index (GI) forest plot.

Table 3 GRADE evidence profile for each outcome based on the meta-analysis data

Grade	Gingival inflammation (MGI)	Gingival inflammation (GI)
Study design	RCT	RCT
Studies no.	3	3
Comparisons no.	1	1
Risk of bias	Unclear-low	Unclear-low
Consistency	Inconsistent	Consistent
Directness	Direct	Direct
Precision	Rather precise	Rather precise
Publication bias	Yes	Yes
Level of certainty	Moderate	Moderate
Magnitude of the effect	No difference	Some difference
Direction of the recommendation	There is some inconsistent evidence that stannous fluoride toothpaste formulations positively influence gingival inflammation	

GI, gingival index; MGI, modified gingival index; RCT, randomised controlled trial.

rotating power toothbrushes may be more effective than other power toothbrushes[36,37]. Several interdental cleaning aids also exist, such as floss, wooden toothpicks and interproximal brushes[38]. It is important to recognise that the conclusion from a recent literature review was that floss did not have the best outcomes for interproximal cleaning, while the use of a wooden toothpick with intense oral hygiene instructions provided better outcomes[38]. Because poor oral hygiene is an important primary risk factor for most common dental diseases, taking the time to modify this risk factor with patients is critical[39]. Frequently repeated oral hygiene instructions are key in prescribing the correct oral hygiene tools to the patient, which include a minimum of a toothbrush, toothpaste and interdental cleaning aid.

It is noteworthy that the exact formulations of stannous fluoride toothpastes are not detailed in published manuscripts and, thus, it is difficult to group different stannous fluoride formulations. The available stannous fluoride toothpastes that were included in this study vary in formulation and in product usage, which adds heterogeneity to both the meta-analysis and entire results section. Furthermore, for this review, Medline-PubMed was the only database used, and it is possible that some trials were not included. It is noteworthy though that although the search does not appear complicated or sophisticated, the few text words that were used were chosen over a more complex search strategy with MESH terms to ensure all articles in the database containing those words were included[40]. It was assumed that the broad nature of the terms used in this specific search would allow for a comprehensive search in Medline-PubMed. Another important note is the difference between statistical significance and clinical relevance. Although results in the literature may be statistically significant and based on well-conducted studies, it is crucial that clinicians understand that statistical significance does not always correspond with clinical significance and interpret the results critically prior to using them to inform practice decision-making.

CONCLUSION

There is some evidence to suggest that stannous fluoride toothpaste formulations may have more favourable oral health outcomes than toothpastes without stannous fluoride. However, there are insufficient homogenous studies to allow for a larger meta-analysis to be conducted and for stronger conclusions to be drawn.

Conflicts of interest

The authors deny any conflicts of interest related to this study.

Disclosure

Dr Liran Levin has received sponsorship for lectures from Colgate, Sunstar, P&G, Adin Implants, and Dentsply Sirona. Mrs Danielle Clark-Perry has received sponsorship for lectures from Sunstar and P&G.

REFERENCES

1. Hasan A, Palmer RM. A clinical guide to periodontology: pathology of periodontal disease. *Br Dent J* 2014 216: 457–461.
2. The Challenge of Oral Disease – A call for global action. *The Oral Health Atlas*, 2nd edn. Geneva: FDI World Dental Federation; 2015: 13.
3. Kwon T, Levin L. Cause-related therapy: a review and suggested guidelines. *Quintessence Int* 2014 45(7): 585–591.
4. Harris NO. García-Godoy F, Nathe CN. *Primary Preventive Dentistry*, 8th edn. Boston (Mass.): Pearson; 2014.
5. He T, Farrell S. The case for stabilized stannous fluoride dentifrice: an advanced formulation designed for patient preference. *J Clin Dent* 2017 28(4 Spec No B): B1–5.
6. Higgins JPT, Green S. (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available from http://handbook.cochrane.org.
7. Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009 2009(339): b2535.
8. GRADE Working Group, Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group. Available from http://www.gradeworkinggroup.org/index.htm.
9. Lorenz K, Hoffmann T, Heumann C *et al.* Effect of toothpaste containing amine fluoride and stannous chloride on the reduction of dental plaque and gingival inflammation. A randomized controlled 12-week home-use study. *Int J Dent Hyg* 2019 17 (3): 237–243.

10. Singh M, Papas A, Gerlach RW. Safety and effectiveness of a two-step dentifrice/gel sequence with medication-associated hyposalivation: A randomized controlled trial in a vulnerable population. *Am J Dent* 2018 31(Sp Is A): 24A–28A.
11. Parkinson CR, Amini P, Jose A *et al*. A 12-week randomized clinical study investigating the anti-gingivitis efficacy of a 0.454% w/w stannous fluoride dentifrice. *Am J Dent* 2018 31 (2): 81–85.
12. Parkinson CR, Jeffery P, Milleman JL *et al*. Confirmation of efficacy in providing relief from the pain of dentin hypersensitivity of an anhydrous dentifrice containing 0.454% with or without stannous fluoride in an 8-week randomized clinical trial. *Am J Dent* 2015 28(4): 190–196.
13. Hu D, Li X, Liu H *et al*. Evaluation of a stabilized stannous fluoride dentifrice on dental plaque and gingivitis in a randomized controlled trial with 6-month follow-up. *J Am Dent Assoc*. 2019 150(4S): S32–S37.
14. Haraszthy VI, Raylae CC, Sreenivasan PK. Antimicrobial effects of a stannous fluoride toothpaste in distinct oral microenvironments. *J Am Dent Assoc* 2019 150(4S): S14–S24.
15. Hagenfeld D, Prior K, Harks I *et al*. No differences in microbiome changes between anti-adhesive and antibacterial ingredients in toothpastes during periodontal therapy. *J Periodontal Res* 2019 54(4): 435–443.
16. Geidel Alexander, Krüger Monika, Schrödl Wieland *et al*. Control of plaque and gingivitis by an herbal toothpaste - a randomised controlled study. *Oral Health Preventive Dent* 2017 2017(15): 407–413.
17. He T, Eusebio R, Goyal CR *et al*. Assessment of the effects of a novel stabilized stannous fluoride dentifrice on gingivitis in a two-month positive-controlled clinical study. *J Clin Dent* 2017 28(4 Spec No B): B12–16.
18. Gerlach RW, Sagel PA. Initial evidence of two-step dentifrice/gel sequence effects on health: outcomes from three randomized controlled trials. *Am J Dent* 2018 31(Sp Is A): 7A–12A.
19. Milleman KR, Patil A, Ling MR *et al*. An exploratory study to investigate stain build-up with long term use of a stannous fluoride dentifrice. *Am J Dent* 2018 31(2): 71–75.
20. Friesen LR, Goyal CR, Qaqish JG *et al*. Comparative antiplaque effect of two antimicrobial dentifrices: laboratory and clinical evaluations. *J Clin Dent* 2017 28(4 Spec No B): B6–11.
21. Parkinson CR, Hughes N, Hall C *et al*. Three randomized clinical trials to assess the short-term efficacy of anhydrous 0.454% w/w stannous fluoride dentifrices for the relief of dentin hypersensitivity. *Am J Dent* 2016 29(1): 25–32.
22. Parkinson C, Amini P, Wu J *et al*. A 24-week randomized clinical study investigating the anti-gingivitis efficacy of a 0.454% w/w stannous fluoride dentifrice. *Am J Dent* 2018 31(1): 17–23.
23. Seriwatanachai D, Triratana T, Kraivaphan P *et al*. Effect of stannous fluoride and zinc phosphate dentifrice on dental plaque and gingivitis: a randomized clinical trial with 6-month follow-up. *J Am Dent Assoc* 2019 150(4S): S25–S31.
24. He T, Eusebio R, Goyal CR *et al*. Assessment of the effects of a novel stabilized stannous fluoride dentifrice on gingivitis in a two-month positive-controlled clinical study. *J Clin Dent* 2017 28(4 Spec No B): B12–16.
25. Feng X, He T, Cao M *et al*. A randomized clinical trial to assess anti-plaque effects of an oral hygiene regimen with a stannous-containing sodium fluoride dentifrice, advanced manual toothbrush, and CPC rinse. *Am J Dent* 2016 29(2): 120–124.
26. Jongsma MA, van der Mei HC, Atema-Smit J *et al*. In vivo biofilm formation on stainless steel bonded retainers during different oral health-care regimens. *Int J Oral Sci* 2015 7(1): 42–48.
27. Mason S, Karwal R, Bosma ML. Two randomized clinical studies to confirm differential plaque removal by sodium bicarbonate dentifrices in a single timed brushing model. *J Clin Dent* 2017 28(3): 44–48.
28. Milleman JL, Milleman KR, Santos SL *et al*. Subjective assessment of enamelon(R) preventive treatment gel in a self-reported dry-mouth population. *Compend Contin Educ Dent* 2016 37 (8): e5–8
29. Sagel PA, Gerlach RW. Clinical evidence on a unique two-step stannous fluoride dentifrice and whitening gel sequence. *Am J Dent* 2018 31(Sp Is A): 4A–6A.
30. West N, He T, Hellin N *et al*. Erosion protection efficacy of a 0.454% stannous fluoride dentifrice versus an arginine-containing dentifrice. *Am J Dent* 2018 31(2): 63–66.
31. Zini A, Timm H, Barker ML *et al*. A randomized controlled clinical trial to evaluate the efficacy of an oscillating-rotating electric toothbrush, a stannous fluoride dentifrice, and floss on gingivitis. *J Clin Dent* 2018 29(2): 64–68.
32. Rebelo MAB, de Queiroz AC. Gingival Indices: State of Art, Gingival Diseases - Their Aetiology, Prevention and Treatment, Dr. Fotinos Panagakos (Ed.); 2011. ISBN: 978-953-307-3767, InTech.
33. Löe H. The gingival index, the plaque index and the retention index systems. *J Periodontol* 1967 38(6): 610–616.
34. Whelton HP, Spencer AJ, Do LG *et al*. Fluoride revolution and dental caries: evolution of policies for global use. *J Dent Res* 2019 98(8): 837–846.
35. Clark D, Levin L. Non-surgical management of tooth hypersensitivity. *Int Dent J*. 2016 66(5): 249–256.
36. Deacon SA, Glenny AM, Deery C *et al*. Different powered toothbrushes for plaque control and gingival health. *Cochrane Database Syst Rev*. 2010 (12): CD004971. https://doi.org/10.1002/14651858.CD004971.pub2
37. Clark D, Levin L. Systematic review and meta-analysis of randomized controlled studies comparing oscillating-rotating and other power toothbrushes. *JADA* 2020 151(4): 265–275.e6.
38. Richards D. The effectiveness of interproximal oral hygiene aids. *Evid Based Dent* 2018 19(4): 107–108.
39. Clark D, Levin L. Editorial: modifying risk factors - the next step. *Oral Health Prev Dent* 2018 16(1): 5.
40. Jenuwine ES, Floyd JA. Comparison of Medical Subject Headings and text-word searches in MEDLINE to retrieve studies on sleep in healthy individuals. *J Med Libr Assoc* 2004 92(3): 349–353.

Correspondence to:
Liran Levin,
Faculty of Medicine & Dentistry,
School of Dentistry,
University of Alberta,
5-468 Edmonton Clinic Health Academy, 11405 - 87 Avenue NW, 5th Floor,
Edmonton, AB T6G 1C9, Canada.
Email: liran@ualberta.ca