

Effects of chemotherapeutic vs regular toothpastes on dental plaque and gingival inflammation in orthodontic patients with fixed appliances: a systematic review and meta-analysis

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ABSTRACT

Objectives: To analyze, appraise, and synthesize papers in which authors have compared the effects of chemotherapeutic toothpaste (CTP) and regular toothpaste (RTP) on plaque scores (PSs), gingival scores (GSs), and bleeding scores (BSs) in orthodontic patients wearing fixed appliances (FAs).

Materials and Methods: PubMed-MEDLINE, Cochrane-CENTRAL, and Embase databases were searched with predefined search terms until April 2024 for controlled or randomized controlled clinical trials aligning with the aim. In the eligible papers, risk of bias was evaluated, data of interest were extracted, and a descriptive analysis was performed. If possible, meta-analyses and subanalyses on specific factors were conducted. The quality of evidence and strength of the recommendation were rated.

Results: In our search and selection, we obtained five papers describing eight comparisons. Potential risk of bias was assessed as some concerns to high, and heterogeneity was considered substantial. Descriptive analysis revealed no significant difference in PS and BS, with an improvement in GS favoring CTP. Meta-analyses of the end scores showed CTP significantly reduced PS (standardized mean difference [SMD] = -0.26 ; 95% confidence interval [CI] = $-0.52, -0.01$; $P = .04$). However, no significant effects were observed on GS and BS. These findings were supported by the subanalyses on CTP with chlorhexidine (CHX; PS: mean difference [MD] = -5.12 ; 95% CI = $-10.08, -0.15$; $P = .04$). The quality of evidence was graded as very low, and strength of the recommendation was judged as very weak.

Conclusions: For orthodontic patients with FAs, very weak certainty exists in recommending CTP (eg, with CHX) over RTP for use with toothbrushing. CTP may have a very small effect on PS and a small effect on GS. (*Angle Orthod.* 0000;00:000–000.)

KEY WORDS: Dental plaque; Gingival inflammation; Toothpaste; Orthodontic patients with fixed appliances; Systematic review

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INTRODUCTION

Gingivitis is characterized by inflammation of the gums and affects over 50% of the global population.^{1,2} It is primarily attributed to dental plaque accumulation.^{3,4} Typical symptoms are transudation of gingival fluid, redness of the gingival margins, swelling and texture loss of free gingiva, and bleeding on probing.⁴ If untreated, long-standing reversible gingivitis is highly likely to damage the underlying connective tissue and alveolar bone, developing into irreversible periodontitis,^{3,4} which can eventually lead to tooth loss.^{3,5} Undoubtedly, tooth loss adversely influences people's lives in many ways: poor digestion, inadequate nutrition, unclear speech, a toothless smile, adjacent tooth movement, and low quality of life.⁵ Gingivitis should, therefore, be prevented and reversed by reducing dental plaque and maintaining oral hygiene.

However, achieving and maintaining good oral health can be more challenging for patients undergoing orthodontic treatment, especially those with fixed appliances (FAs). FAs can increase the risk of developing gingivitis by stimulating the accumulation of plaque and the colonization of important periodontopathic and superinfecting bacteria in subgingival microflora.^{6,7} For gingivitis control, such patients thus require more efficient daily oral hygiene products. Although mechanical products, such as toothbrushes and interdental brushes, have been proven effective in removing dental plaque and are highly recommended by dental care professionals,⁸ they still have several limitations for these patients. Toothbrushes, for example, can leave plaque in the sensitive region around brackets, and in the space between FAs and gingival margins.⁹

Toothpaste (TP) is commonly used as a supplement to toothbrushing.¹⁰ Although it provides no additional effect on mechanical plaque removal,¹¹ it can have a weak inhibitory effect on plaque regrowth.¹⁰ Fluoride TP, the cornerstone of caries prevention, has been the standard intervention for decades.¹² In addition, chemotherapeutic TP (CTP), which contains chemically active agents like triclosan (Tcs), stannous fluoride (SnF₂), and chlorhexidine (CHX), has been marketed for other oral health benefits.^{13,14} Clinically, CTP could provide more effects on plaque regrowth inhibition than regular fluoride TP.¹⁵ Authors of an umbrella review summarizing evidence from systematic reviews (SRs) in the general population also concluded that CTP containing Tcs or SnF₂ offered substantial benefits for gingival health over regular TP (RTP) with or without fluoride.¹⁶ However, evidence for CTP effects on orthodontic patients with FAs remains limited. Although authors of several clinical

Table 1. Search Terms Used for PubMed-MEDLINE^a

The following strategy was used in the search:
{<intervention> AND <subject>}
("dentifrices" [MeSH Terms] OR "toothpastes" [MeSH Terms] OR
(toothpaste OR dentifrice))
AND
("orthodontics" [MeSH Terms] OR Orthodontic*)^b

^a The search strategy was customized according to the database being searched.

^b The asterisk was used as a truncation symbol.

trials have compared the effects of various CTPs and RTPs on dental plaque and gingival health in this specific population,^{17–19} no one has synthesized these findings into a SR. Closing this gap is critical to improving oral hygiene and ensuring the long-term benefits of orthodontic treatment for these patients.

In this SR, we analyzed, evaluated, and synthesized scientific papers in which authors compared the effects of CTP with RTP on plaque scores (PSs), gingival scores (GSs), and bleeding scores (BSs) in orthodontic patients with FAs. PS, GS, and BS refer to the indices used to evaluate plaque, gingival appearance, and bleeding, respectively.

MATERIALS AND METHODS

This SR was prepared and reported according to the Cochrane Handbook for Systematic Reviews of Interventions²⁰ and the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.²¹ The present study was registered at ACTA ETC (Ethical Committee) under 2022-20175 and at PROSPERO (International Prospective Register of Systematic Reviews) under CRD42022347840²² with the protocol as a priori.

Focused Question

The PICOS strategy²³ was used: In orthodontic patients wearing FAs (P), what are the effects of CTP (I) and RTP (C) on dental plaque and gingivitis parameters (O) based on controlled clinical trials (CCTs) and randomized controlled clinical trials (RCTs; S)?

Search Strategy

The National Library of Medicine, Washington, DC (PubMed-MEDLINE), the Cochrane Central Register of Controlled Trials (Cochrane-CENTRAL), and Embase were searched by two independent reviewers (YL and CV) using predefined search terms up to April 2024. Additionally, the reference lists of the eligible studies were hand-searched to identify any other potentially relevant studies. No restrictions on language or publication

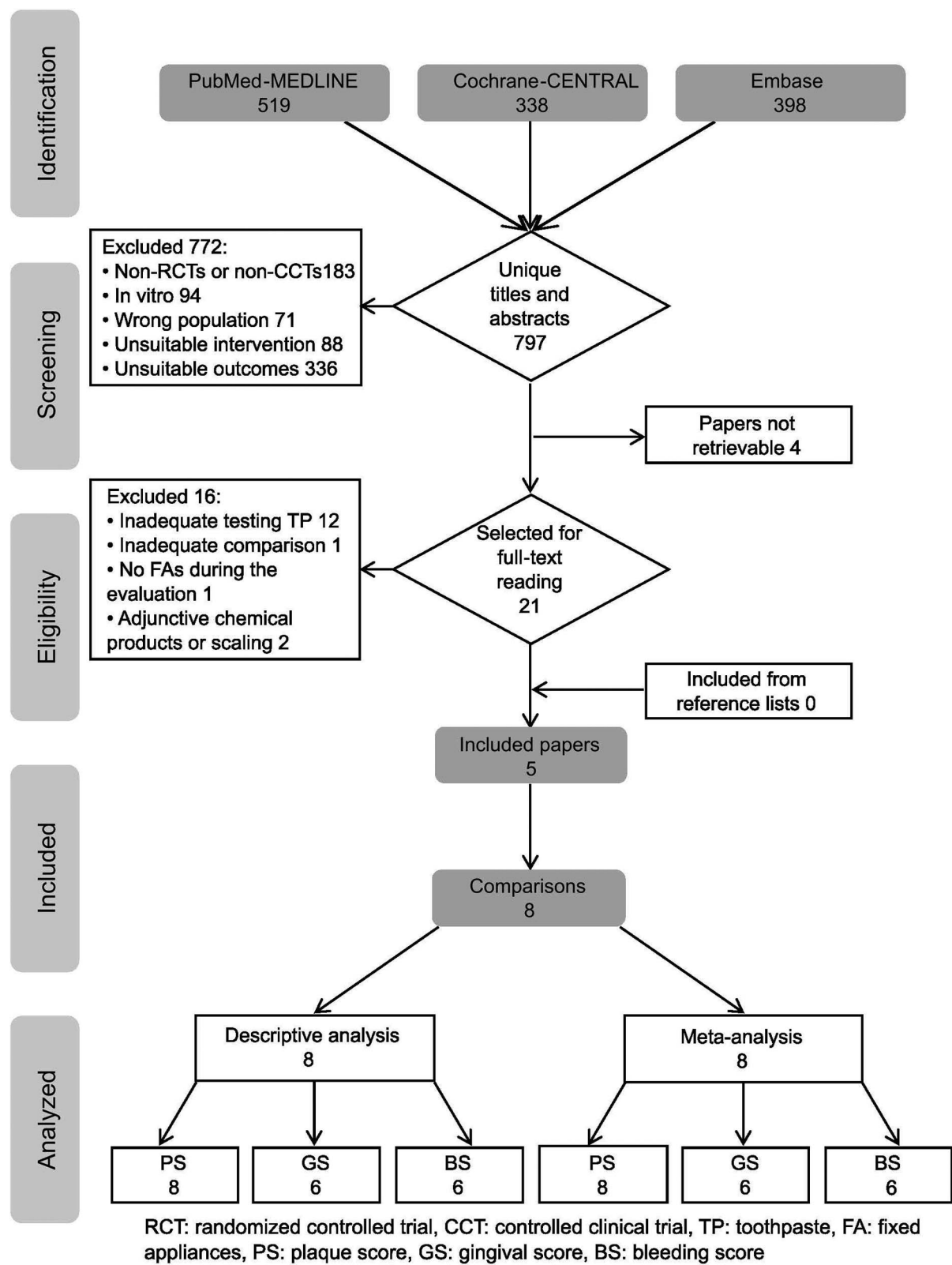


Figure 1. Search and selection results.

Table 2. Overview of the Studies Processed for Data Extraction^a

Study No.	Author	Year	Study Design	Intervention Duration	Risk of Bias ^b	Included Participants, Baseline (End)	Age Range (Mean)	Gender (%)
I	Herrera et al.	2018	RCT, triple-blinded, parallel	3 mo	High	63 (50◇)	12–25 (15.1◇)	M 25◇ (39.7%◇); F 38◇ (60.3%◇)
II	Hoffman et al.	2015	RCT, double-blinded, parallel	6 mo	High	48 (44)	12–25 (15.5◇)	M 32◇ (66.7%◇); F 16◇ (33.3%◇)
III	Oltramari-Navarro et al.	2009	RCT, double-blinded, parallel	12 wk	High	81 (?)	13–35 (?)	M ?; F ?
IV	Olympio et al.	2006	RCT, single-blinded, parallel	24 wk	Some concerns	85 (83◇)	13–32 (?)	M ?; F ?
V	Øgaard et al.	1980	RCT, double-blinded, cross-over	3 wk	High	21 (21)	? (?)	M ?; F ?

^a ? indicates unknown; ◇, calculated by the authors of this review based on the presented data in the selected paper; RCT, randomized controlled clinical trial; TP, toothpaste; TB, toothbrush; CPC, cetylpyridinium chloride; NaF, sodium fluoride; NovaMin, calcium sodium phosphosilicate bioactive glass; F, fluoride; CHX, chlorhexidine; SnF₂, stannous fluoride; brand?, the brand was not specified in the original text.

^b See Supplemental Appendix 2.

date were made. Table 1 indicates the search term details.

Screening and Selection

First, the same two reviewers independently screened the titles and abstracts with the Rayyan application.²⁴ Papers relevant to the focused question or lacking sufficient information went to the next stage. Second, the same two reviewers carefully read the full texts. Papers meeting the inclusion criteria were collected for data extraction and further analyses. If the full text or sufficient information of a paper was unavailable, repeated attempts were made to contact the first or

corresponding authors. Disagreements between the two reviewers were resolved through discussion or, if unresolved, by the judgment of the third reviewer (DES).

Inclusion Criteria

- CCTs or RCTs
- Publications on trials conducted in human beings:
 - Orthodontic patients with FAs
 - Toothbrushing performed by participants
 - In good general health, without systemic diseases
- Comparison: CTP vs RTP (with or without fluoride)
- Parameters of interest: PS, GS, and BS

Table 2. Extended

Comparison of TPs (Brand)	TP Regimen	TBs (Brand)	Other Oral Hygiene Tools (Brand)	Authors Original Conclusion
Test TP: 0.05% CPC, 0.33% NaF, allantoin and aloe vera (VITIS Orthodontic, Dentaïd, Cerdanyola, Spain). Control TP: Without CPC, NaF, allantoin and aloe vera (brand?)	2×/d	Standard TBs (VITIS Orthodontic, Dentaïd, Cerdanyola, Spain)	1. Mouthwash with the same formulation as test/control TP, rinsing with 15 mL during 30 s 2×/d after brushing. 2. Dental floss (VITIS no-wax, Dentaïd, Cerdanyola, Spain) Oral hygiene instructions were reinforced every month.	Use of CPC-based TP and mouthrinse in orthodontic patients had limited effect in reducing plaque accumulation and gingival inflammation.
Test TP: 5% NovaMin and 5000 ppm NaF (ReNew, Sultan Healthcare, Englewood, NJ). Control TP: 0.15% F (Crest, Procter & Gamble, Cincinnati, OH)	?	?	Oral hygiene instructions were reinforced every month.	No difference between a F-containing TP vs a TP containing NovaMin in ability to improve plaque levels and gingival health in orthodontic patients.
Test TP A: 0.50% CHX and 1100 ppm NaF (FGM, Joinville, Santa Catarina, Brazil). Test TP B: 0.75% CHX and 1100 ppm NaF (FGM, Joinville, Santa Catarina, Brazil). Control TP: 1100 ppm NaF (Sorriso Fresh Crystal Mint, Kolynos do Brasil Ltda, Osasco, São Paulo, Brazil)	3×/d for 2 min with TP covering the head of TBs	?	1. Dental floss (brand?). 2. No polishing and scaling during the study period. 3. No other oral hygiene products. 4. Oral hygiene instructions were reinforced every 15 d.	Use of dentifrices with lower concentration of CHX has effectiveness in controlling gingivitis and bleeding in orthodontic patients.
Test TP A: 0.95% CHX and 1100 ppm NaF (FGM, Joinville, Brazil). Test TP B: 0.95% CHX (FGM, Joinville, Brazil). Control TP: 1100 ppm NaF (Sorriso Fresh Crystal Mint, Kolynos do Brasil Ltda, Osasco, Brazil)	3×/d for 2 min with an amount of TP covered the head of TBs	?	1. Dental floss (brand?). 2. No polishing and scaling during the study period. 3. No other oral hygiene products. 4. Oral hygiene instructions were reinforced every 15 d.	Demonstrated the effectiveness of dentifrices containing CHX and F as an adjuvant treatment for gingivitis in orthodontic patients.
Test TP: ?ppm 0.4% SnF ₂ and 1.0% stannous pyrophosphate (brand?) Control TP: Without F or tin (brand?)	2×/d for at least 1 min with the horizontal scrub technique	Soft, multitufted TBs (brand?)	No F rinsing, dental floss, or toothpicks	Plaque-inhibiting effect of SnF ₂ can be maintained in dentifrices for orthodontic patients.

Exclusion Criteria

- Participants with periodontitis
- Professional tooth cleaning conducted during the trial period
- Absence of FAs during the evaluation phase
- Full texts not accessible

Methodological Quality Assessment

To assess the potential risk of bias, the same two independent reviewers used the revised version of the Risk of Bias tool RoB 2.²⁰ Any disagreement regarding the methodological quality assessment between the

two reviewers was settled using the same approach as previously described.

Data Extraction

To extract information from the included papers, the same two independent reviewers used a specially designed form. Its content included authors, publication year, study design, intervention duration, participant characteristics, TP comparisons, toothbrushes, other oral hygiene tools, and original conclusions. The reviewers also collected data on PS, GS, and BS at baseline, end stage, and between the two stages (difference) for all time points. For incomplete

data, the first or corresponding authors were contacted by e-mail. Disagreements over data extraction between the two reviewers were resolved as previously outlined.

Data Analysis

A descriptive analysis was conducted, and meta-analysis was performed only when at least two comparisons were available. This principle was also applied for subanalyses on the same evaluation index or chemically active agent of CTP.

Review Manager software (RevMan 5.3)²⁵ was used for meta-analyses. Standardized mean differences (SMDs), as interpreted by Cohen,²⁶ were used for different indices and mean differences (MDs) for the same index.²⁰ SMD, MD, and their appropriate 95% confidence intervals (CIs) were calculated using a fixed- or random-effects model as necessary. A fixed-effect model was used for fewer than four comparisons and a random-effects model for four or more.^{20,27} For papers with multiple intervention groups, the control group size was divided by the number of comparisons. The same resolution strategy as before was applied to settle disagreements on data analysis between the reviewers.

Heterogeneity Assessment

Clinical and methodological heterogeneity was assessed based on study design, intervention duration, industry funding, participant characteristics, active ingredients in CTP, TP regimen, adjuvant oral hygiene products and procedures, and FA types. Statistical heterogeneity was examined using the χ^2 test and I^2 statistic.²⁰

Grading the Body of Evidence

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) procedure was used to rate the quality of evidence and strength of the recommendation.²⁸ In the GRADE table, it was determined a priori that at least two studies were required for a subcategory of interest. Based on factors including study methodology (risk of bias), result consistency and precision, evidence directness, and publication bias, the quality of evidence was categorized as high, moderate, low, or very low.²⁸ Disagreements on grading were handled according to the previously described approach.

RESULTS

Search and Selection Results

The search yielded 797 unique publications, and five studies (I,¹⁷ II,¹⁸ III,¹⁹ IV,²⁹ and V³⁰) presenting eight

comparisons were recruited. Details of the search and selection are shown in Figure 1 and Supplemental Appendix S1.

Assessment of Methodological and Clinical Heterogeneity

The included studies displayed substantial methodological and clinical heterogeneity. Table 2 details study design, intervention duration, participant characteristics, chemotherapeutic ingredients in CTP, TP usage regimen, toothbrushes, adjuvant oral hygiene tools, and practices.

Regarding funding and conflict of interest, authors of Study V³⁰ did not disclose any details. Authors of studies I¹⁷ and II¹⁸ reported no conflict of interest. Study I¹⁷ and IV²⁹ were supported by dental manufacturers; authors of Study II¹⁸ acknowledged financial support from the Southern Association of Orthodontists (SAO); and authors of Study III¹⁹ had no significant financial or professional interest in industry.

The FAs varied among the included studies. In Study II,¹⁸ FAs were placed on all anterior teeth of both arches. In Study V,³⁰ anterior teeth were bonded with brackets directly, and posterior teeth were banded conventionally. Authors of the remaining studies did not provide detailed FA information.

Methodological Quality Assessment

Table 2 presents the relevant results, with details in Supplemental Appendix S2. Except for Study IV²⁹ judged as some concerns, the other four studies (I,¹⁷ II,¹⁸ III,¹⁹ and V³⁰) were classified as high risk of bias.

Study Outcome Results

In three tables (Supplemental Appendices S3 through S5), we report the results on PS, GS, and BS extracted from the included papers. Data were collected for baseline, end stage, and difference when feasible. Despite multiple requests, no additional data were obtained.

Descriptive Analysis

Table 3 shows that most comparisons indicated no significant difference for PS (88%), a significant difference favoring CTP for GS (67%), and no significant difference for BS (67%).

Meta-Analysis

Meta-analyses were performed after the longest follow-up, with subanalyses by the same evaluation index or chemotherapeutic ingredient in CTP (Table 4). Since authors of Study V³⁰ presented only end-stage data,

Table 3. Descriptive Summary of Statistical Significance Levels Between CTP and RTP for PS, GS, and BS^a

Study No.	CTP	PS	GS	BS	RTP
III	0.50% CHX + NaF	0	0	+	NaF
	0.75% CHX + NaF	0	+	+	NaF
IV	0.95% CHX	0	+	0	NaF
	0.95% CHX + NaF	0	+	0	NaF
V ^b	SnF ₂	+	□	0	Without F or tin
	SnF ₂	0	□	0	Without F or tin
I	CPC + NaF + aloe vera + allantoin	0	+	□	Without CPC, NaF, allantoin and aloe vera
II	5% NovaMin + NaF	0	0	□	F
Summary	–	0 = 87.5%	+ = 66.67%	0 = 66.67%	–

^a + indicates intervention is significantly better than control (intervention had lower scores); 0, no significant difference; □, not studied; PS, plaque score; GS, gingival score; BS, bleeding score; CTP, chemotherapeutic toothpaste; RTP, regular toothpaste; NaF, sodium fluoride; F, fluoride; CHX, chlorhexidine; SnF₂, stannous fluoride; CPC, cetylpyridinium chloride; and NovaMin, calcium sodium phosphosilicate bioactive glass.

^b Paper V has two analyses of the same comparison since PSs and BSs were assessed differently: plaque index by Löe and bleeding index by Ainamo and Bay were used for teeth where the fixed appliances were >1.5 mm from the gingival margin; bracket/band plaque index and bleeding index by Ainamo and Bay were used for posterior teeth with the appliances close to the gingival margin.

meta-analyses for end scores were especially conducted (Table 4). Comprehensive summaries of meta-analyses for other phases and all forest plots are available in Supplemental Appendices S6 through S8.

In the overall meta-analyses and subanalyses of the same evaluation index, no significant difference was found between CTP and RTP at baseline (Table 4). Regarding the end and difference scores, CTP were significantly favored by four of five meta-analyses for PS, two of five for GS, and one of two for BS ($P \leq .05$). When Study V³⁰ was included, a significant difference was found favoring CTP for PS in the overall meta-analysis (SMD = -0.29 ; 95% CI = $-0.51, -0.07$; $P = .009$) and no statistical difference between CTP and RTP for BS in the overall meta-analysis and subanalysis (Table 4).

In the subanalyses of TP with CHX (CHX-TP), no significant difference was observed at baseline (Table 4). CHX-TP significantly outperformed RTP in controlling PS for end scores (MD = -5.12 ; 95% CI = $-10.08, -0.15$; $P = .04$) and difference scores (MD = -8.29 ; 95% CI = $-14.26, -2.31$; $P = .007$), and in reducing GS (MD = -0.14 ; 95% CI = $-0.22, -0.05$; $P = .003$) and BS (MD = -0.48 ; 95% CI = $-0.76, -0.19$; $P = .001$) for difference scores. In the subanalyses of TP with SnF₂ (SnF₂-TP), no significant difference was found on PS and BS for end scores.

Statistical Heterogeneity

In the overall meta-analyses excluding Study V,³⁰ four of nine demonstrated moderate to substantial heterogeneity (Table 4). In subanalyses based on the same evaluation index and chemotherapeutic

ingredient, most revealed unimportant heterogeneity (Table 4).

Evidence Profile

Table 5 summarizes several factors for rating the quality of evidence and grading the strength of the recommendation. The CHX-TP subanalysis, which included two studies (III¹⁹ and IV²⁹), was accepted as a subcategory of interest. Overall, the magnitude of the effect varied from none to small, and the quality of evidence was rated as very low. Consequently, a very weak recommendation was made that, in orthodontic patients wearing FAs, toothbrushing with CTP may slightly outperform RTP for maintaining dental hygiene.

DISCUSSION

CTP is assumed beneficial for reducing plaque¹⁵ and, therefore, to maintain good oral health, which is crucial to helping orthodontic patients with FAs achieve optimal treatment outcomes. However, despite clinical trials that supported the use of CTP for this special group, no reliable summary or recommendation has been established. In this SR, therefore, we aimed to summarize and analyze the effects of CTP vs RTP on plaque and gingivitis parameters in orthodontic patients wearing FAs. Reviewing five papers with eight comparisons, effects were found that ranged from none to small. As the quality of evidence was rated as very low, a very weak recommendation can be made: Toothbrushing with CTP may slightly outperform RTP for maintaining dental hygiene in these patients.

Table 4. Summary of Forest Plots of All Studies Comparing CTP with RTP Concerning the Plaque, Gingival, and Bleeding Scores After the Longest Follow-Up^a

Parameters	Meta-Analysis Type	Evaluation Index	Measurement Moment	No. Including Comparisons
PS	Overall	TMQH, OPI	Baseline	# 6 (I, II, III, IV)
			End	# 6 (I, II, III, IV)
		TMQH, OPI, PI, BPPI	Difference	# 3 (I, III)
			End ^b	# 8 (I, II, III, IV, V)
	Subanalysis (evaluation index)	TMQH (0–5)	Baseline	# 2 (I, II)
			End	# 2 (I, II)
		OPI (0–100)	Baseline	# 4 (III, IV)
			End	# 4 (III, IV)
	Subanalysis (CHX-TP)	OPI (0–100)	Difference	# 2 (III)
			Baseline	# 4 (III, IV)
GS	Overall	MGI, GI	Baseline	# 6 (I, II, III, IV)
			End	# 6 (I, II, III, IV)
			Difference	# 3 (I, III)
			End	# 2 (I, II)
	Subanalysis (evaluation index)	MGI (0–4)	Baseline	# 2 (I, II)
			End	# 2 (I, II)
		GI (0–3)	Baseline	# 4 (III, IV)
			End	# 4 (III, IV)
	Subanalysis (CHX-TP)	GI (0–3)	Difference	# 2 (III)
			Baseline	# 4 (III, IV)
BS	Overall	BI	Baseline	# 4 (III, IV)
			End	# 4 (III, IV)
			Difference	# 2 (III)
			End ^b	# 6 (III, IV, V)
	Subanalysis (evaluation index)	BI (0–1)	End ^b	# 4 (IV, V)
			Baseline	# 4 (III, IV)
	Subanalysis (CHX-TP)	BI	End	# 4 (III, IV)
			Difference	# 2 (III)
	Subanalysis (SnF ₂ -TP)	BI	End ^b	# 2 (V)

^a Standardized mean difference/mean difference and other data are presented for the baseline, end, and difference using a fixed- or random-effects model. CTP indicates chemotherapeutic toothpaste; RTP, regular toothpaste; PS, plaque score; GS, gingival score; BS, bleeding score; CI, confidence interval; TMQH, Turesky (1970) modification of the Quigley and Hein (1962) plaque index; OPI, Heintze et al. (1998) orthoplaque index; PI, Löe (1967) plaque index; BPPI, bracket/band plaque index; BI, Ainamo and Bay (1975) bleeding index; MGI, Lobene et al. (1986) modification of the Löe and Silness (1963) gingival index; GI, Löe and Silness (1963) gingival index; CHX-TP, toothpaste with chlorhexidine; SnF₂-TP, toothpaste with stannous fluoride; and NA, not applicable.

^b Meta-analysis including Study V.

^c Data calculated as mean difference.

^d SMD effect was interpreted by Cohen.

^e $P \leq .05$.

^f I^2 is interpreted as follows: 0% to 40%, unimportant heterogeneity; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity.

^g $P \leq .1$.

CHX-TP

CHX, a widely used antiseptic in dentistry, is considered a gold-standard antiplaque ingredient due to its immediate antibacterial effects and enduring bacteriostatic effects on the oral flora.³¹ Authors of two SRs indicated that CHX mouthwash (CHX-MW) reduced PS, GS, and BS more effectively than placebo or control mouthwash (MW) in gingivitis patients.^{32,33} Another

SR showed that CHX-TP used with a toothbrush supported plaque control and gingivitis inhibition better than placebo or regular TP/gel.³⁴ However, authors of those SRs excluded orthodontic patients wearing FAs. In a more recent SR, Hussain et al.³⁵ focused on CHX use on periodontal health in FA patients and found that, in the short-term (1–3 months), CHX-MW was also associated with lower GS, PS, and BS, while CHX-TP,

Table 4. Extended

Model	SMD	SMD Effect ^d	Test Overall		Test for Heterogeneity		See Supplemental Appendix
			95% CI	P Value	I ² Value (%) ^f	P Value	
Random	−0.05	None	−0.29, 0.20	.71	0%	.42	S6.3.1
Random	−0.26	Small	−0.52, −0.01	.04^e	0%	.84	S6.3.2
Fixed	−0.39	Small	−0.75, −0.03	.03^e	13%	.31	S6.3.3
Random	−0.29	Small	−0.51, −0.07	.009^e	0%	.91	S6.4.1
Fixed	−0.12 ^c	NA	−0.48, 0.24	.51	0%	.41	S6.3.4
Fixed	−0.12 ^c	NA	−0.51, 0.27	.54	0%	.42	S6.3.5
Random	0.40 ^c	NA	−4.37, 5.18	.87	33%	.22	S6.3.6
Random	−5.12 ^c	NA	−10.08, −0.15	.04^e	0%	.73	S6.3.7
Fixed	−8.29 ^c	NA	−14.26, −2.31	.007^e	0%	.98	S6.3.8
Random	0.40 ^c	NA	−4.37, 5.18	.87	33%	.22	S6.3.6
Random	−5.12 ^c	NA	−10.08, −0.15	.04^e	0%	.73	S6.3.7
Fixed	−8.29 ^c	NA	−14.26, −2.31	.007^e	0%	.98	S6.3.8
Fixed	−0.39	Small	−0.82, 0.04	.08	0%	.55	S6.4.2
Random	0.15	None	−0.25, 0.55	.45	61%	.03^g	S7.3.1
Random	−0.26	Small	−0.64, 0.12	.18	54%	.06^g	S7.3.2
Fixed	−0.46	Small	−0.82, −0.09	.01^e	46%	.16	S7.3.3
Fixed	−0.12 ^c	NA	−0.26, 0.03	.11	0%	.43	S7.3.4
Fixed	−0.16 ^c	NA	−0.34, 0.01	.06	0%	.59	S7.3.5
Random	0.11 ^c	NA	−0.01, 0.23	.06	42%	.16	S7.3.6
Random	−0.05 ^c	NA	−0.18, 0.09	.51	70%	.02^g	S7.3.7
Fixed	−0.14 ^c	NA	−0.22, −0.05	.003^e	0%	.58	S7.3.8
Random	0.11 ^c	NA	−0.01, 0.23	.06	42%	.16	S7.3.6
Random	−0.05 ^c	NA	−0.18, 0.09	.51	70%	.02^g	S7.3.7
Fixed	−0.14 ^c	NA	−0.22, −0.05	.003^e	0%	.58	S7.3.8
Random	0.40	Small	−0.07, 0.87	.10	50%	.11	S8.3.1
Random	−0.19	None	−0.51, 0.14	.26	0%	.69	S8.3.2
Fixed	−0.48 ^c	NA	−0.76, −0.19	.001^e	0%	.81	S8.3.3
Random	−0.10	None	−0.36, 0.16	.45	0%	.82	S8.4.1
Random	−0.02 ^c	NA	−0.04, 0.00	.12	0%	.80	S8.4.2
Random	0.40	Small	−0.07, 0.87	.10	50%	.11	S8.3.1
Random	−0.19	None	−0.51, 0.14	.26	0%	.69	S8.3.2
Fixed	−0.48 ^c	NA	−0.76, −0.19	.001^e	0%	.81	S8.3.3
Fixed	0.01 ^c	NA	−0.08, 0.10	.82	0%	1.00	S8.4.3

which was analyzed in two included studies,^{19,29} resulted only in lower PS for the end stage. Based on the same two studies,^{19,29} in this SR, we conducted a subanalysis specifically on CHX-TP (0.50–0.95% concentrations). Although the subanalysis combined data from 3 months²⁹ and 12 months,¹⁹ the findings agreed with the short-term results of the SR by Hussain et al.³⁵ regarding CHX-TP in fixed orthodontic patients.

Prolonged CHX use can cause side effects that include staining, increased calculus, and impaired taste.^{34,36} Authors of the two included studies also recorded data on calculus and staining. They indicated no significant difference for calculus between CHX-TP and RTP. Low-dose CHX showed no significant staining difference, while 0.95% CHX-TP caused significantly more extrinsic staining in orthodontic patients with FAs. Due to the etching process associated with FAs,

Table 5. Summary of Findings on Body of the Estimated Evidence Profile, Appraisal of Certainty, and Strength of the Recommendation Regarding the Efficacy of Chemotherapeutic Toothpaste as Compared With Regular Toothpaste^a

Determinants of the Quality	PS		GS		BS	
	Overall	Subanalysis	Overall	Subanalysis	Overall	Subanalysis
		CHX		CHX		CHX
Study design	RCT	RCT	RCT	RCT	RCT	RCT
No. studies (Table 3, Figure 1)	5	2	4	2	3	2
No. comparisons (Table 3, Figure 1)	8	4	6	4	6	4
No. meta-analyses (Table 3, Figure 1)	8	4	6	4	6	4
Risk of bias (Supplemental Appendix 2)	Moderate to high	Moderate to high	Moderate to high	Moderate to high	Moderate to high	Moderate to high
Consistency	Inconsistent	Rather consistent	Inconsistent	Inconsistent	Inconsistent	Rather consistent
Directness	Direct	Direct	Direct	Direct	Direct	Direct
Precision	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise
Reporting bias	Possible	Possible	Possible	Possible	Possible	Possible
Magnitude of the effect	Very small	Very small	Small	Very small	None	Very small
Quality of a body of evidence	Very low	Low	Very low	Very low	Very low	Low
Strength of the recommendation	Very weak	Very weak	Very weak	Very weak	Very weak	Very weak
Overall recommendation	Very weak certainty for the recommendation that toothpaste with chemically active ingredients may be considered for an added very small effect on PSs and small effect on GSs over regular (fluoride) toothpaste in orthodontic patients with fixed appliances.					

^a RCT, randomized controlled clinical trial; PS, plaque score; GS, gingival score; BS, bleeding score; and CHX, chlorhexidine.

orthodontic patients tend to experience more staining.³⁷ Dental care professionals, therefore, need to balance the advantages and disadvantages of using TP containing different CHX concentrations for FA patients and consider adjunctive antidiscoloration products which can prevent staining without compromising the plaque and gingivitis inhibiting properties of CHX.³⁶ However, this combined approach has not been studied in RCTs.

SnF₂-TP

SnF₂ is another well-recognized antimicrobial ingredient in TP.^{38,39} Authors of two SRs, who excluded orthodontic patients, found SnF₂-TP more effective than RTP for plaque and gingivitis reduction.^{38,39} However, the subanalysis of SnF₂-TP in the current SR, which involved orthodontic patients wearing FAs, found SnF₂-TP did not significantly reduce PS and BS. The subanalysis included only one paper Study V,³⁰ in which authors provided two comparisons of SnF₂-TP vs RTP without fluoride or tin on anterior and posterior teeth during orthodontic treatment; only one of these showed a benefit of SnF₂-TP for PS (Table 3). Authors of another nonincluded study, which evaluated SnF₂-TP on six maxillary anterior teeth before bonding and after debonding, reached a different conclusion. They randomized orthodontic patients into two groups: one using SnF₂/amine fluoride TP and MW and one using NaF TP and MW.⁴⁰ The conclusion was that plaque and gingivitis reduction was slightly more effective in the SnF₂ group than the NaF group.⁴⁰ The inconsistent findings between the included Study V³⁰ and the nonincluded study⁴⁰ may have been due to differences in measurement location (anterior and posterior teeth) and to differences in timing relative to orthodontic treatment (before bonding, during treatment, and after

debonding). FAs, such as brackets and bands, can facilitate plaque accumulation and alter plaque composition, significantly increasing PS, GS, and BS.^{6,7,41} Another potential explanation may have been the intervention difference: Authors of the nonincluded study combined TP and MW,⁴⁰ while the authors of Study V focused only on TP.³⁰ The additional use of SnF₂/amine fluoride MW was more effective than the control MW in reducing PS in patients undergoing periodontal supportive therapy without FA.⁴²

Evaluation Period

According to the guidelines for earning the American Dental Association (ADA) seal of acceptance for chemotherapeutic products for control of gingivitis, at least 6 months are required for studies in which authors assess the safety and efficacy of chemotherapeutic products.⁴³ In this SR, only two of the five included studies representing three comparisons (II¹⁸ and IV²⁹) met this criterion. However, since most people can develop gingivitis in 3 weeks,⁴⁴ intermediate-length trials (2 weeks to 2 months) are also considered to evaluate the plaque- and gingivitis-inhibiting effects of therapeutic products.⁴⁵ As the shortest clinical trial in this SR lasted 3 weeks,³⁰ the included papers were sufficient to assess effect of CTP concerning plaque control and gingivitis inhibition.

Heterogeneity

The included studies showed substantial clinical heterogeneity in TP usage regimen with toothbrushing: three times per day in two studies,^{19,29} twice per day in two others,^{17,30} and unspecified in one.¹⁸ The general recommendation for individuals without FAs is to brush twice daily.⁴⁶ However, for fixed orthodontic patients,

the American Association of Orthodontists advises brushing after every meal, which amounts to three times daily. As the use of TP during toothbrushing does not contribute to the mechanical removal of dental plaque¹¹ and as a strong inverse relationship between brushing frequency and biofilm amount is established,⁴⁷ these variations in brushing times could have influenced the outcomes of the included studies and, consequently, the current findings. The unspecified regimen may also introduce additional uncertainty. These factors were considered in the assessment of heterogeneity and overall grading.

Regarding BS, data were provided by authors of only two included studies, III¹⁹ and IV.²⁹ Although both used the Ainamo and Bay index,⁴⁸ they reported results differently: While authors of Study III¹⁹ presented scores above one, authors of Study IV²⁹ described percentages up to one. Due to this discrepancy, SMD was chosen as the summary statistic for BS in meta-analyses at both baseline and end stage. As only authors of Study III¹⁹ offered difference scores, MD was calculated for the corresponding meta-analysis.

The heterogeneity of the included papers was also examined statistically using the χ^2 test and I^2 statistic. Four of the nine overall meta-analyses showed moderate to substantial heterogeneity ($I^2 = 46\text{--}61\%$, Table 4).²⁰ Most of this heterogeneity was identified in the meta-analyses concerning gingival index (GI), which also contributed to most of the heterogeneity in the subanalyses. One possible clarification for this is that GI is a clinical parameter that assesses and quantifies the severity of gingivitis based on visual signs such as color, consistency, contour, and bleeding on probing.⁴⁹ This makes it difficult to score consistently, resulting in low interexaminer reliability.⁵⁰ Another potential explanation could have been due to different CHX concentrations: the two comparisons involving lower CHX concentrations (0.50–0.75%) in Study III¹⁹ may have contributed more to heterogeneity than those with higher CHX concentration (0.95%) in Study IV.²⁹ This was supported by an earlier SR in which authors indicated the dose-dependent effectiveness of CHX-MW in plaque inhibition.³²

Limitations

This SR had two main limitations:

- First, although, in this SR, we did not consider removable orthodontic appliances, we reviewed studies with different FAs. Participants in Study II¹⁸ had FAs on the anterior teeth, while all the teeth of those in Study V³⁰ were directly bonded or conventionally banded. Since banded posterior teeth are associated with a higher risk of gingivitis,⁴¹ the type of FAs could affect

results of the included studies and, thus, the overall findings of this SR.

- Second, three of the five included papers lacked data on difference scores, thereby complicating the corresponding meta-analysis. Additionally, meta-analyses were based on a limited number of chemotherapeutic agents. Although the quality of evidence and the strength of the recommendation also relied on descriptive analysis, these factors collectively degraded them.

Clinical Implications and Recommendations for Further Research

The findings of this SR have important clinical implications for managing plaque and gingival health in orthodontic patients with FAs. The evidence suggesting that toothbrushing with CTP may slightly outperform RTP for maintaining dental hygiene supports recommending CTP as part of routine oral care for this patient group. Additionally, the alignment of the subanalysis findings with those of the previous SR underscores the reliability of CHX-based interventions. Incorporating these insights into clinical guidelines can help standardize oral health care, improve orthodontic treatment outcomes, and ensure long-term oral health benefits for orthodontic patients with FAs posttreatment.

Given the current SR findings and the evidence on CTP use in the general population,¹⁶ further studies are needed to evaluate the effects of the CHX-TP and SnF₂-TP available on the market. To determine the long-term efficacy of CTP in reducing plaque and gingival inflammation in patients wearing FAs, ADA guidelines dictate that clinical trials lasting at least 6 months are necessary.⁴³ Additionally, it would be beneficial to focus on orthodontic patients using removable devices, especially clear aligners (in view of their rising popularity).⁵¹ Lastly, the CONSORT statement and Template for Intervention Description and Replication checklist can provide valuable guidance on better reporting of RCTs and interventions.^{52,53}

CONCLUSIONS

- Regarding improving oral health, very weak certainty exists in recommending CTP (such as those with CHX) over RTP with toothbrushing for fixed orthodontic patients.
- As the effect of CTP is very small for PS, small for GS, and none for BS, it is probably of little clinical significance.

SUPPLEMENTAL DATA

Appendices S1 through S8 are available online.

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