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Systematic Review

Efficacy of adjunctive anti-plaque chemical agents: a systematic review and network meta-analyses of the Turesky modification of the Quigley and Hein plaque index

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Abstract

Aim: The aim of this systematic review and network meta-analysis (NMA) was to compare the efficacy of different anti-plaque chemical agents, in 6-month, home-use, randomized clinical trials (RCTs), in terms of plaque index (PlI) changes.

Material and Methods: RCTs assessing PlI were identified, screened, and evaluated for inclusion. Relevant information was extracted, and quality and risk of bias were assessed. Mean differences between baseline-end were calculated to obtain weighted mean differences and 95% confidence intervals. NMA protocols were applied to assess direct and indirect comparisons among products using Turesky PlI.

Results: Eighty-three papers were included: 49 examined dentifrices, 32 mouthrinses and 2 both. The NMA analysed 51 studies including data from 4242 and 4180 subjects for dentifrices and mouthrinses respectively. For dentifrices, triclosan-copolymer and chlorhexidine showed the greatest effect, with significant differences when compared with stannous fluoride. For mouthrinses, essential oils and chlorhexidine showed the greatest effect, with significant differences when compared with delmopinol, alexidine and cetylpyridinium chloride.

Conclusion: Within the limitations of this study (including the severe imbalance in the amount of evidence), dentifrices containing triclosan-copolymer or chlorhexidine and mouthrinses containing essential oils or chlorhexidine showed the greatest effect on PlI scores as assessed with NMA.

Key words: antiseptic; gingivitis; network meta-analyses; plaque index; systematic review

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Conflict of interest and source of funding statement

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Gingivitis and periodontitis are highly prevalent diseases (Albandar 2002, Sheiham & Netuveli 2002, Petersen & Ogawa 2012) and their prevention depends on supragingival biofilm control (Chapple et al. 2015). However, as mechanical biofilm removal is not always as good as desired (van der Weijden & Hioe 2005), chemical oral hygiene products have been developed and marketed to improve the efficacy of self-performed biofilm control.

There is general consensus supported by established guidelines that plaque inhibitory and antiplaque activities of a given formulation must be proven in long-term (at least 6 months), home-use, randomized clinical trials (RCTs) (Council on Dental Therapeutics 1986). In these studies, the use of the tested formulations should be adjunctive to conventional daily mechanical plaque control measures. A recent systematic review, including only this type of trials, has demonstrated that the use of chemical agents provides statistically significant improvements in gingival, bleeding and plaque indices, when compared to a negative control (Serrano et al. 2015). However, no comparisons among different products were performed, which could have offered a ranking of products based on their efficacy.

Network meta-analysis (NMA), also known as multiple treatment meta-analyses or mixed treatment meta-analysis, uses the evaluation of the network geometry to allow the integration of data from direct (when treatments are compared within a trial) and indirect comparisons (when treatments are compared between trials by combining results with a common comparator treatment) (Cipriani et al. 2009, Hutton et al. 2015). Furthermore, it provides information about the hierarchy of competing interventions in terms of treatment ranking by means of cumulative probability curves (surface under the cumulative ranking, SUCRA) (Salanti & Ioannidis 2011, Hutton et al. 2015). However, in order to produce valid results, it is important that the distribution of effect modifiers (average patient age, gender distribution, disease severity, and a wide range of other plausible features) is similar across studies. This balance increases the plausibility of eliable findings from an indirect comparison through the common comparator. As a consequence, the presence of a similar distribution of effect modifiers across studies (called "the assumption of transitivity") should be taken into account before performing a NMA (Hutton et al. 2015).

Therefore, the main purpose of this study was to perform a NMA aiming to compare the adjunctive efficacy of different chemical agents on plaque index changes, based on the data provided by home-use, 6-month RCTs included in a recently published systematic review (Serrano et al. 2015).

Material and Methods

Protocol development

The initial protocol designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement for reporting of systematic reviews (Liberati et al. 2009, Moher et al. 2009, Hutton et al. 2015) has already been published (Serrano et al. 2015). This protocol was modified according to the PRISMA extension (Appendix S1) statement (Hutton et al. 2015) in order to incorporate the NMA of health care interventions. Briefly, the study was designed to answer the following focused question: in humans with gingivitis (*Patients*), what is the comparative efficacy of chemical *plaque control* formulations used adjunctively to mechanical oral hygiene measures, with or without previous professional prophylaxis (*Intervention*), as compared to subjects using a positive or negative control adjunctive to mechanical oral hygiene (*Comparison*), in terms of changes in plaque, gingival or bleeding indices (*Outcome*), with a minimum follow-up of 6 months. For the present work, only plaque index results were considered, due to the amount of information derived from NMA (Hutton et al. 2015).

Eligibility criteria

The search strategy for the available publications has been documented in a previous paper (Serrano et al. 2015) and is available in Appendix S2. In addition to the listed inclusion and exclusion criteria applied (Appendix S3), transitivity as eligibility criteria was added for the NMA, and determined the exclusion of all papers that did not have a proper placebo control group that could be comparable with the rest of the placebo control formulations employed in the trials, which was necessary for assessing indirect comparisons of active agents through a true comparable placebo control formulation (Catala-Lopez 2013). Trials testing the efficacy of both dentifrices and mouthrinses in the same treatment group were also excluded for the same reason. In addition, when the study population included only young or elderly participants, trials were also excluded (Appendices S4 and S5).

Information sources and search

An electronic search was conducted on PubMed CENTRAL up to and including April 3rd 2016. References of retrieved papers and previously published systematic reviews were hand searched.

Study selection and data collection

Eligibility assessment was performed through title and abstract analysis and full-text analysis. Two reviewers (JS, ME) screened titles and abstracts for possible inclusion in the review, according to the inclusion criteria, as previously described (Serrano et al. 2015). An additional screening was performed to identify all papers reporting plaque indices, even without reporting gingival or bleeding indices.

Data extraction

Data were extracted by two reviewers (JS, ME) under the supervision of a third reviewer (DH). When the differences between (Δ) baseline-end were not reported, they were calculated using the formula: $\Delta Vary = Var2 - Var1$, where, Var1 was the mean value before treatment and Var2 the mean value after treatment. In addition, the variance of ΔVar was estimated with the formula: $SVar^2 = SVar1^2 + SVar2^2 - (2*r*SVar1*SVar2)$, where $SVar^2$ is the variance of the difference, $SVar1^2$ is

the variance of the mean baseline value, and $Svar2^2$ is the variance of the mean end value. A correlation r of 0.5 was assumed as described before (Paraskevas et al. 2008).

Risk of bias in individual studies

Risk of bias was evaluated by assessing the quality of methods of each RCT according to the checklist suggested in the Cochrane reviewers' handbook (Higgins et al. 2011) and the CONSORT statement (Moher et al. 2012). Quality of reporting analysis, as well as an evaluation of specific methods for oral hygiene product studies were performed (Serrano et al. 2015).

Summary measures and synthesis of results

Tables were created to summarize all the previously mentioned items. Outcomes were summarized as mean and standard deviation (SD) or standard error (SE, if SD were not provided), for both baseline and 6-month values. To compare the selected studies, a mean treatment effect (baseline-6 months) was calculated and results were pooled and analysed using weighted mean differences (WMD) and 95% confidence intervals (CI).

Firstly, pairwise meta-analyses (PMA) for each delivery format (mouthrinses or dentifrices) were performed for studies that directly compared different active ingredients *versus* placebo control, using a random effects model. Active ingredients with similar formulations were pooled in clusters, as it was done in the previous systematic review (Serrano et al. 2015). When the same cluster was present more than once in the same study, the different arms of the same study were combined in only one (Higgins & Green 2011). For each pairwise comparison, differences in means with 95% CI were used.

Then, a NMA was conducted to simultaneously compare the different active ingredients and placebo control for each delivery format (mouthrinses and dentifrices). Basically, a NMA is the combination of direct and indirect estimates of relative treatment effects in a single analysis. Apart from the direct within-trial comparisons between two treatments, the NMA incorporates indirect comparisons constructed from two studies that have one treatment in common.

To review the network geometry, a network graph was generated and analysed: each cluster of active ingredient or placebo control was drawn by a node and direct comparisons between them were represented by links between the nodes. The size of the nodes reflects the proportionate numbers of patients randomly assigned to each treatment. The line thickness indicates the number of studies supporting each comparison.

The NMA was based on a multivariate random effects meta-regression (White et al. 2012). The consistency of the results was qualitatively examined by comparing the results obtained via PMA *versus* NMA. It was also examined by fitting both consistency and inconsistency, by design-by-treatment interaction models (Higgins et al. 2012). The surface under the cumulative ranking curve (SUCRA) was used to potentially rank the treatments (Salanti & Ioannidis 2011).

All analyses were done using Stata statistical software (release 13.0, StataCorp, College Station, TX) (White 2015).

Results

Study selection

The flow chart is shown in Fig. S1. From the update of our previous systematic review (Serrano et al. 2015), 89 articles were included. Due to the lack of fulfilment of transitivity criteria, 13 studies were excluded for the present review: those studies performed in young or elderly patients (Lang et al. 1982, Spets-Happonen et al. 1991, Sgan-Cohen et al. 1996, Jayaprakash et al. 2007, Schiffner et al. 2007), lacking a proper placebo control product (Flemmig et al. 1990, Chaves et al. 1994), evaluating the combination of dentifrices and mouthrinses (Harper et al. 1990, Kopczyk et al. 1991, Mengel et al. 1996, Paraskevas et al. 2004, 2005) or having baseline levels of plaque that differ from those of other papers (Triratana et al. 2015). Five new studies that were excluded from the previous review due to the lack of a placebo control group were added (Mankodi et al. 2002, Rosin et al. 2002, Archila et al. 2004, Albert-Kiszely et al. 2007, Boneta et al. 2010). Two additional papers, that were not available for the previous systematic review, were included in this study (Williams et al. 1997, Mankodi et al. 2005b), totalling a number of 83 papers.

Study characteristics

Study setting (country, centres), number of centres, target populations and study duration are described in Table S1. Number of patients, gender distribution, age and smoking habits are depicted in Table S2. The indices assessed and the methods of assessment are found in Table S3. Periodontal status was defined in the inclusion/exclusion criteria of some studies (see Table S4).

Type of interventions

An overview of the interventions is presented in Table S5. According to active agent and delivery format (Appendix S6), dentifrices were divided into 16 categories/clusters (Table S6) and mouthrinses into 10 categories/clusters (Table S7). According to placebo control and delivery format, placebo control dentifrices were divided into three groups [monofluorophosphate (MFP), sodium fluoride (NaF) and others] (Table S8) and placebo control mouthrinses into four groups (0.025% NaF, 5% hydro-alcohol, minus active placebo and others) (Table S9). However, due to similar results among groups, one placebo control group was considered per delivery format.

Studies included one ($n = 56$), two ($n = 18$), three ($n = 8$) or four (Hoffmann et al. 2001) test groups. For each individual study, specific instructions were given to use the assigned evaluated products (Tables S6 and S7), with a wide variety of protocols, most of them including a twice-per-day use, with a defined usage time and amount. Additional elements (Table S5), related to the interventions, demonstrated clear variability among studies: product usage partially supervised ($n = 11$);

specific instructions for the examination days ($n = 31$); professional prophylaxis before baseline assessment ($n = 10$); professional prophylaxis after baseline ($n = 53$).

Risk of bias in individual studies

The evaluation of the risk of bias, according to the Cochrane list (Table S10) and to the independency of the study (Table S11) are summarized in Tables 1 and 4.

Quality of design and reporting in individual studies

In Table S12, items related to registration are shown: ethical committee approval ($n = 27$), informed consent ($n = 52$) or registration of the RCT ($n = 1$). The same Table summarizes aspects related to the statistical analyses and outcome assessment, showing the number of manuscripts reporting sample size and/or power analysis calculation ($n = 24$), the primary statistical test ($n = 79$), an intent-to-treat analysis ($n = 9$), a full-mouth approach ($n = 69$), calibration ($n = 25$), the number of examiners ($n = 57$) and their skills/experience ($n = 20$).

Synthesis of the results (network meta-analyses)

It was not possible to include data from 20 papers in the meta-analyses, due to the lack of relevant information (mean, SD, SE, sample size) or to the duplicity of data (Appendix S5). Sixty-three papers were finally selected for quantitative analysis.

To evaluate the efficacy of the tested products in terms of plaque level changes, the Turesky modification (Turesky et al. 1970) of the Quigley & Hein (Quigley & Hein 1962) plaque index (PlI) was chosen, since it was the most commonly used PlI in the included papers: out of 63, 12 papers were excluded from these analyses due to the use of a different PlI (Mauriello & Bader 1988, Stephen et al. 1990, Svatun et al. 1993a, b, Zimmermann et al. 1993, Schaeken et al. 1996, Beiswanger et al. 1997, Shapira et al. 1999, Hoffmann et al. 2001, Archila et al. 2004, Albert-Kiszely et al. 2007, Sreenivasan et al. 2011).

Dentifrices

The most commonly studied active agent was triclosan/copolymer (tric_cop) (19 trials, 1405 patients) followed by stannous fluoride (SnF) (seven trials, 493 patients), chlorhexidine (CHX) (three trials, 244 patients) and with just one trial essential oils (EEOO) (95 patients), thiocyanate/carbamide peroxide (SCN-/H2O2) (70 patients), zinc citrate (ZnCit) (55 patients), triclosan/zinc citrate (tric_ZnCit) (31 patients), triclosan/pyrophosphate (tric_pyro) (29 patients), aloe vera (28 patients) and sodium metafluoride phosphate with zinc (NaMFP_Zn) (42 patients). A total of 2492 patients were included in dentifrice groups and a placebo control dentifrice was used as the comparing arm in 26 studies (1759 patients) (Table 1). The placebo control dentifrices reported a mean treatment effect after 6 months of use that ranged from −0.35 to 1.42.

The network graph in Fig. 1 represents the evidence comparing placebo control and the nine active agents for changes in PlI. A total of 55 different comparisons were possible. All active products had direct comparisons against placebo control [CHX ($n = 3$); EEOO ($n = 1$); SnF ($n = 5$), ZnCit ($n = 1$), aloe ($n = 1$), tric-ZnCit ($n = 1$), tric-cop ($n = 16$), tric-pyro ($n = 1$), NaMFP_Zn ($n = 1$)], except SCN-/H202. Tric_cop was directly compared with SCN-/H202 ($n = 1$), aloe ($n = 1$), tric_pyro ($n = 1$), tric_ZnCit ($n = 1$) and SnF ($n = 3$). The remaining 40 potential comparisons were not directly tested in RCTs.

Nine independent PMA and one NMA for studies that directly compared different active ingredients *versus* placebo control were performed (Table 2). The results from NMA were similar to those obtained from PMA in terms of WMD, with all active agents showing greater reductions in PlI than placebo control, except for tric_ZnCit and tric_pyro from PMA. No statistically significant differences were found between EEOO, SnF, NaMFP_Zn and ZnCit *versus* placebo in the NMA, while these differences were statistically significant in the PMA. The opposite occurred in the case of CHX, where statistically significant differences were found *versus* placebo control in the NMA, and no significant differences were found in the PMA.

When comparing active ingredients *versus* placebo control, the greatest WMD in the NMA was found for the comparison with aloe [WMD = −0.82; $p = 0.02$; 95% CI (−1.53; 0.12)], followed by CHX [WMD = −0.76; $p = <0.001$, 95% CI (−1.21; −0.32]. The smallest WMD was found for the comparison with tric_ZnCit [WMD = −0.13; $p = 0.65$; 95% CI (−0.70; 0.44) (Table 2).

The NMA model allowed comparisons between active agents, some of which had never been directly tested (Table 3). The largest WMD was found for the comparison between aloe and tric_ZnCit [WMD = 0.69; $p = 0.13$; 95% CI (−0.21; 1.78)], with tric_ZnCit showing the lowest effect. However, no statistically significant differences were found between agents in dentifrices except for the comparison between SnF and CHX [WMD = 0.57, $p = 0.02$, 95% CI (0.08, 1.07)] or tric-cop [(WMD = −0.34, $p = 0.00$, 95% CI (−0.56, −0.12)], favouring tric-cop and CHX in both cases. The network inconsistency was low (Chi-square = 5.25, $p = 0.386$).

The *ranking of treatments* according to SUCRA results from NMA was the following: (1) aloe (79.6), (2) CHX (79.1); (3) ZnCit (70.9); (4) SCN-/H2O2 (63.9); (5) tric-cop (59.4); (6) NaMFP_Zn (56.7); (7) EEOO (56.3); (8) tric_pyro (27.8); (9) SnF (26.0); (9) tric-ZnCit (22.1) and placebo control (8.3) (Fig. S2).

Mouthrinses

The most commonly studied active agent was EEOO (nine trials, 746 patients) followed by cetylpyridinium chloride (CPC) at concentrations higher than 0.05% (CPC_H, six trials, 449 patients), CHX at concentrations equal or higher than 0.10% (CHX_H, 4 trials, 147), delmopinol (two trials, 326 patients), CPC at concentrations equal or lower than 0.05% (CPC_L) (three trials, 298 patients), tric_cop (three trials, 166 patients), alexidine (two trials, 205 patients) and EEOO without alcohol (EEOO_noAlc, one trial, 107 patients). A total of 2440 patients were included in mouthrinse groups. Placebo control was used as the comparison arm in 23 studies (1736

Table 1. Studies on dentifrices: study characteristics, product comparisons, plaque index results and summary of risk of bias

Reference	Product	Group	*N*	6 months-baseline changes PlI		Risk of Bias (# of items ranked as follows:)		
				Mean	SD	Low	High	Unclear
Allen et al. (2002)	NaF toothpaste	Placebo	36	−0.13	0.417	✓	✗✗	??
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	36	0.53	0.550			
	0.3% tric, 2% copolymer, 0.243% NaF, special silica (high-cleaning silica)		38	0.51	0.420			
Bolden et al. (1992)	NaF toothpaste	Placebo	155	0.48	0.516	✓✓	✗✗	??
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	155	0.83	0.541			
Boneta et al. (2010)	SnF/SHMP	SnF	55	0.83	0.555	✓	✗✗	???
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	54	1.41	0.645			
Charles et al. (2001)	MFP	Placebo	100	0.78	0.292	✓	✗✗	???
	Tric_cop	tric_cop	102	1.28	0.291			
Coelho et al. (2000)	vehicle control	Placebo	94	0.21	0.396	✓✓✓	✗	??
	EEOO	EEOO	95	0.71	0.456			
Deasy et al. (1991)	NaF toothpaste	Placebo	63	0.11	0.372		✗✗✗	???
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	58	0.68	0.350			
Denepitiya et al. (1992)	NaF toothpaste	Placebo	75	0.05	0.430	✓	✗✗	???
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	70	0.44	0.436			
Garcia-Godoy et al. (1990)	NaF toothpaste	Placebo	54	0.72	0.376	✓✓	✗	???
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	54	1.78	0.366			
Kanchanakamol et al. (1995)	customary	Placebo	62	0.10	0.44		✗✗	????
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	62	0.63	0.49			
Mallatt et al. (2007)	NaMFP	Placebo	66	0.45	0.459	✓✓✓✓	✗	?
	0.454% SnF, SHMP	SnF	62	0.68	0.374			
Mankodi et al. (1992)	NaF toothpaste	Placebo	149	0.75	0.409	✓✓	✗✗	??
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	145	0.98	0.448			
Mankodi et al. (1997)	NaF toothpaste	Placebo	54	−0.01	0.507		✗	?????
	0.454% Snf	SnF	50	0.60	0.420			
Mankodi et al. (2002)	0.454% SnF, SnCl, sodium gluconate	SnF	54	0.2	0.441	✓✓	✗✗	??
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	55	0.64	0.37			
Mankodi et al. (2011)	NaF toothpaste	Placebo	58	−0.03	0.429		✗	?????
	0.3% tric, 2% copolymer, 0.243% NaF	tric_cop	57	0.60	0.426			
Mankodi et al. (2005a)	MFP	Placebo	66	0.61	0.381	✓✓	✗	???
	0.454% SnF, SHMP	SnF	64	0.59	0.405			
Mateu et al. (2008)	NaF toothpaste	Placebo	48	1.00	0.573		✗✗	????
	0.3% tric, 2% copolymer, 0.243% NaF, 17% silica	tric_cop	46	1.64	0.551			
McClanahan et al. (1997)	NAF toothpaste	Placebo	174	−0.35	0.493	✓✓	✗✗	??
	0.454% SnF, silica	SnF	154	−0.22	0.489			
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	155	−0.33	0.484			
Pradeep et al. (2012a)	no-antiinflamatory properties	Placebo	28	1.42	0.753	✓✓✓✓	✗	?
	Aloe vera	aloe	28	2.13	0.659			
	Tric, polymer, fluoride	tric_cop	28	1.78	0.648			
Pradeep et al. (2012b)	placebo gel	Placebo	30	0.25	0.19	✓✓✓✓		??
	1% CHX	CHX	30	2.04	0.66			
Rathe et al. (2007)	144 ppm F	Placebo	29	−0.16	0.577	✓✓✓✓✓	✗	
	0.05% CHX, 0.8% aluminium lactate, 1400 ppm F	CHX	30	0.17	0.539			

Table 1. (continued)

Reference	Product	Group	*N*	6 months-baseline changes PII		Risk of Bias (# of items ranked as follows:)		
				Mean	SD	Low	High	Unclear
Renvert & Birkhed (1995)	MFP	Placebo	28	−0.07	0.405	✓✓✓	✗✗	?
	0.3% tric, 2% copolymer, SLS	tric_cop	26	0.20	0.338			
	0.3% tric, 5.0% pyro, SLS	tric_pyro	29	0.02	0.286			
	0.2% tric, 0.2% ZnCit, 0.5% SLS	tric_ZnCit	31	−0.05	0.425			
Rosin et al. (2002)	Tric_cop	tric_cop	70	0.08	0.68	✓✓✓✓		??
	RCP (SCN & carbamida peroxide)	SCN-/H2O2	70	0.13	0.650			
Schiff et al. (2006)	NaF toothpaste & flossing	Placebo	40	0.25	0.245		✗✗✗	???
	0.3% tric, 2% copolymer, 0.243% NaF, silica & flossing	tric_cop	37	0.57	0.289			
	0.3% tric, 2% copolymer, 0.243% NaF, silica		37	0.55	0.226			
Triratana et al. (1993)	NaF toothpaste	Placebo	60	0.12	0.436	✓✓	✗✗	??
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	60	0.81	0.432			
Triratana et al. (2002)	NaF liquid toothpaste	Placebo	59	0.55	0.300	✓✓✓	✗	??
	0.3% tric, 2% copolymer, 0.243% NaF, silica	tric_cop	60	1.38	0.259			
Williams et al. (1997)	NaF toothpaste	Placebo	58	0.29	0.455		✗	?????
	0.454% SnF	SnF	54	0.78	0.452			
Williams et al. (1998)	MFP toothpaste	Placebo	44	−0.02	0.483	✓✓	✗✗	??
	2% ZnCit, 0.76% MFP	ZnCit	55	0.68	0.491			
Yates et al. (1993)	No CHX-NaF	Placebo	85	0.68	0.509	✓✓✓	✗	??
	1% CHX	CHX	91	1.03	0.598			
	1% CHX, 1000 ppm NaF		93	0.97	0.584			
Zhong et al. (2015)	1450 ppm NaFMFP_Zn-free	Placebo	44	0.53	0.197		✗✗	????
	1450 ppm NaMFP_Zn	NaMFP_Zn	42	1.03	0.285			

N, number of participants included in the RCT; SD, standard deviation; PII, Turesky plaque index.
SnF, stannous fluoride; CHX, chlorhexidine; EEOO, essential oils; NaF, sodium fluoride; tric, triclosan; cop, copolymer; pyro, pyrophosphate; ZnCit, zinc citrate; LC, low concentration; HD, high concentration; CPC, cetylpyridinium chloride; noAlc, no alcohol; ZnS, zinc sulphate; ZnCl, zinc chloride; SnCl, stannous chloride; MFP, monofluorophosphate; Na, sodium; SLS, sodium lauryl sulphate; pyro, pyrophosphate; F, fluor; Zn, zinc.

patients). See Table 4. The placebo control mouthrinses reported a mean treatment effect after 6 months of use that ranged from −0.16 to 0.78.

The network graph in Fig. 2 represents the evidence comparing placebo control and eight active agents in mouthrinses. A total of 36 comparisons were possible. All active products were directly compared against placebo control [CHX_H ($n = 4$), CPC_H ($n = 6$), CPC_L ($n = 3$), EEOO ($n = 9$), EEOO_noAlc ($n = 1$), alexidine ($n = 2$), delmopinol ($n = 2$) and tric_cop ($n = 3$). The following comparisons between active agents were observed: (a) CPC_L *versus* EEOO ($n = 1$) and *versus* EEOO_noAlc ($n = 1$); (b) CPC_H *versus* EEOO ($n = 1$) and *versus* CHX_H ($n = 1$) and (c) CHX_H *versus* delmopinol ($n = 1$) and *versus* EEOO ($n = 2$). The remaining 22 comparisons have never been directly tested in RCTs.

Eight independent PMA and one NMA for studies that directly compared different active ingredients *versus* placebo control were performed (Table 2). The results from the NMA were similar to those obtained in the PMA in terms of WMD, with all active agents showing greater reductions in PII than placebo control. Statistically significant differences were found in both meta-analyses, except for CPC_L, alexidine and delmopinol *versus* placebo control in the NMA.

When comparing active agents *versus* placebo control, the largest WMDs in the NMA were found with EEOO [WMD = −0.86; $p = <0.001$, 95% CI (−1.05; −0.76)] and EEOO_noAlc [WMD = −0.86; $p < 0.001$; 95% CI (−1.30; −0.42)], followed by CHX_H [(WMD = −0.78; $p < 0.001$; 95%CI (−1.07; −0.49)]. The smallest WMD was found for the comparison with alexidine [WMD = −0.18; $p = 0.40$; 95% CI (−0.60; 0.24)] (Table 2).

Regarding NMA (Table 5), no statistically significant differences were found when comparing CHX with EEOO [WMD = −0.09; $p = 0.58$; 95% CI (−0.39; 0.22)], with EEOO_noAlc [WMD = −0.08; $p = 0.75$; 95% CI (−0.6; 0.44) and with tric_cop (WMD = 0.1; $p = 0.68$; 95% CI (−0.38; 0.58)]. In addition, no statistically significant differences were found when comparing EEOO with EEOO_noAlc. Statistically significant differences were found when comparing CHX, EEOO and EEOO_noAlc *versus* CPC_H, CPC_L, alexidine and delmopinol. The network inconsistency was low (Chi-square = 11.17, $p = 0.344$).

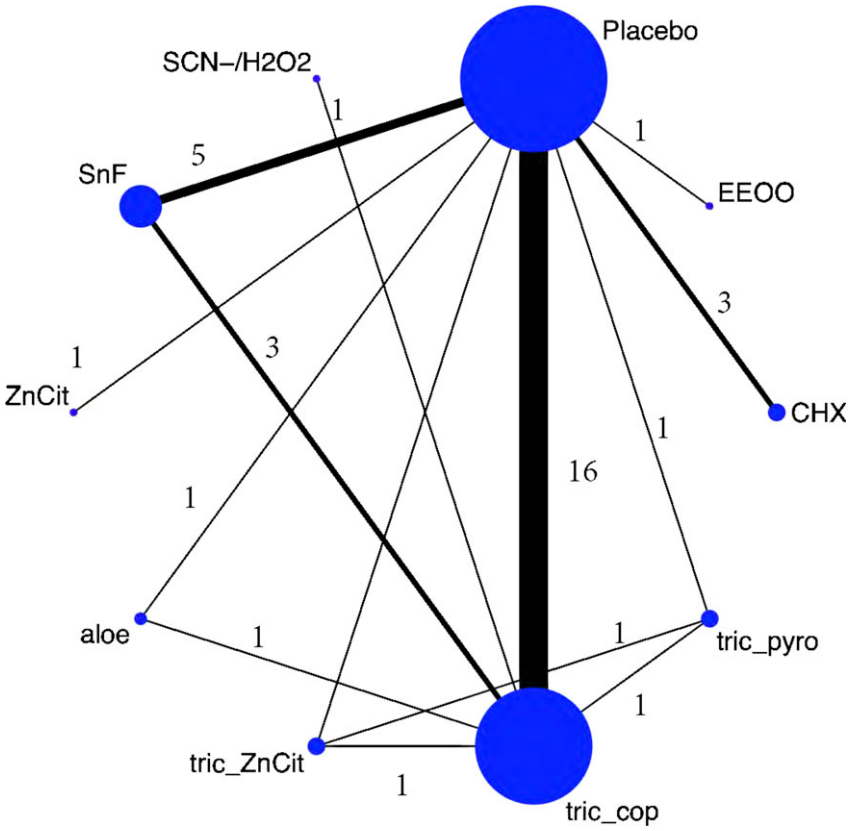

Fig. 1. Dentifrices: network meta-analysis graph (net diagram). Each node represents a category of active agent (cluster). The following active agents were included: CHX, chlorhexidine; EEOO, essential oils; SCN-/H2O2, thiocyanate/carbamide peroxide; SnF, stannous fluoride; ZnCit, zinc citrate; aloe, aloe vera; tric, triclosan; cop, copolymer; pyro, pyrophosphate; NaMFP_Zn, sodium monofluorophosphate with zinc.

The ranking of treatments according to SUCRA was the following: (1) EEOO (87.4); (2) EEOO_noAlc (85.4); (3) CHX_H (78.6); (4) tric_cop (68.5); (5) CPC_H (43.4); (6) CPC_L (29.8); (7) delmo (29.0); (8) alexi (23.4) and (9) placebo control (4.7) (Fig. S3).

Discussion

The beneficial effect of the use of different antiplaque chemical agents was supported by the original systematic review (Serrano et al. 2015). However, some of the agents showed stronger and more consistent evidence of their efficacy than others and further clarification of the most convenient formulations was clearly needed. The present NMA offers additional information and knowledge on which products have more solid scientific evidence because it allows direct (tested in RCTs), indirect (never tested in RCTs) and mixed comparisons among different agents. Therefore, the main objective of this study was to compare the efficacy of different antiseptic agents in controlling plaque levels with the aid of NMA. Although the primary outcome measures of the original systematic review were gingival and/or bleeding

Table 2. Results [weighted mean difference (WMD) and 95% confidence interval (CI)] for comparisons for individual agents *versus* placebo control

Delivery format	Agent	PMA						NMA			
		n	WMD	*p*	lower CI	upper CI	I^2 (heterogeneity)	WMD	*p*	lower CI	upper CI
Dentifrices	CHX	3	−0.81	0.09	−1.74	0.12	98.20%	−0.76	**0.00**	−1.21	−0.32
	EEOO	1	−0.50	**0.00**	−0.62	−0.38		−0.50	0.16	−1.14	0.14
	SnF	5	−0.28	**0.01**	−0.49	−0.07	90.70%	−0.19	0.10	−0.42	0.04
	ZnCit	1	−0.70	**0.00**	−0.89	−0.51		−0.70	0.06	−1.53	0.12
	aloe	1	−0.71	**0.00**	−1.08	−0.34		−0.82	**0.02**	−1.53	−0.12
	tric_ZnCit	1	0.12	0.27	−0.09	0.33		−0.13	0.65	−0.70	0.44
	tric_cop	16	−0.49	**0.00**	−0.60	−0.28	94.20%	−0.53	**0.00**	−0.68	−0.37
	tric_pyro	1	0.05	0.59	−0.13	0.23		−0.20	0.49	−0.78	0.37
	NaMFP_Zn	1	−0.50	**0.00**	−0.40	−0.60		−0.50	0.11	−1.11	0.11
Mouthrinses	CHX_H	4	−0.70	**0.00**	−0.86	−0.54	58.10%	−0.78	**0.00**	−1.07	−0.49
	CPC_H	6	−0.48	**0.00**	−0.68	−0.29	90.90%	−0.41	**0.00**	−0.65	−0.17
	CPC_L	3	−0.23	**0.05**	−0.47	−0.00	95.10%	−0.26	0.07	−0.55	0.02
	EEOO	9	−0.83	**0.00**	−1.05	−0.60	97.00%	−0.86	**0.00**	−1.05	−0.68
	EEOO_noAlc	1	−0.75	**0.00**	−0.83	−0.67		−0.86	**0.00**	−1.30	−0.42
	alexi	2	−0.18	**0.00**	−0.29	−0.06	39.50%	−0.18	0.40	−0.60	0.24
	delmo	2	−0.15	**0.01**	−0.25	−0.05	0%	−0.24	0.27	−0.67	0.19
	tric_cop	3	−0.68	**0.00**	−0.85	−0.51	68.90%	−0.67	**0.00**	−1.05	−0.30

n, number of studies; PMA, pair-wise meta-analysis; NMA, network meta-analysis. *p* values are presented in bold if $p \leq 0.05$.
CHX, chlorhexidine; EEOO, essential oils; SnF, stannous fluoride; ZnCit, zinc citrate; aloe, aloe vera; tric, triclosan; cop, copolymer; pyro, pyrophosphate; CHX, chlorhexidine; H, high concentration; L, low concentration; CPC, cetylpyridinium chloride; EEOO, essential oils; noAlc, no alcohol; alexi, alexidine; delmo, delmopinol; tric, triclosan; cop, copolymer; NaMFP_Zn, sodium monofluorophosphate with zinc.

Table 3. Studies on dentifrices: results [weighted mean difference (WMD) and 95% confidence interval (CI)] of direct, indirect and mixed comparisons among products

Product	*versus*	WMD	*p*	Lower CI	Upper CI
CHX	EEOO	0.26	0.51	−0.51	1.04
	NaMFP_Zn	0.26	0.49	−0.49	1.02
	SCN-/H2O2	0.19	0.56	−0.48	1.02
	SnF	0.57	**0.02**	0.08	1.07
	ZnCit	0.06	0.88	−0.80	0.93
	aloe	−0.06	0.89	−0.89	0.78
	tric_ZnCit	0.63	0.09	−0.09	1.36
	tric_cop	0.24	0.32	−0.23	0.71
	tric_pyro	0.56	0.13	−0.17	1.29
	NaMFP_Zn	0.00	1.00	−0.88	0.88
EEOO	SCN-/H2O2	−0.08	0.85	−0.85	0.70
	SnF	0.31	0.37	−0.37	0.99
	ZnCit	−0.20	0.69	−1.18	0.78
	aloe	−0.32	0.51	−1.27	0.63
	tric_ZnCit	0.37	0.40	−0.49	1.22
	tric_cop	0.03	0.94	−0.68	0.63
	tric_pyro	0.30	0.50	−0.56	1.16
NaMFP_Zn	SCN-/H2O2	−0.08	0.84	−0.83	0.68
	SnF	0.31	0.35	−0.34	0.96
	ZnCit	−0.20	0.68	−1.16	0.76
	aloe	−0.32	0.50	−1.25	0.61
	tric_ZnCit	0−37	0.39	−0.47	1.20
	tric_cop	−0.03	0.93	−0.66	0.60
	tric_pyro	0.30	0.49	−0.54	1.14
SCN-/H2O2	SnF	0.39	0.11	−0.08	0.85
	ZnCit	−0.12	0.78	−0.99	0.74
	aloe	−0.25	0.55	−1.06	0.57
	tric_ZnCit	0.44	0.21	−0.25	1.14
	tric_cop	0.05	0.82	−0.36	0.46
	tric_pyro	0.37	0.30	−0.33	1.08
SnF	ZnCit	−0.51	0.20	−1.28	0.26
	aloe	−0.63	0.09	−1.36	0.10
	tric_ZnCit	0.06	0.85	−0.54	0.66
	tric_cop	−0.34	**0.00**	−0.56	−0.12
	tric_pyro	−0.01	0.97	−0.62	0.59
ZnCit	aloe	−0.12	0.82	−1.14	0.90
	tric_ZnCit	0.57	0.23	−0.37	1.50
	tric_cop	0.17	0.65	−0.58	0.93
	tric_pyro	0.50	0.30	−0.44	1.44
aloe	tric_ZnCit	0.69	0.13	−0.21	1.58
	tric_cop	0.29	0.41	−0.40	0.99
	tric_pyro	0.62	0.18	−0.28	1.52
tric_ZnCit	tric_cop	−0.39	0.17	−0.96	0.17
	tric_pyro	−0.07	0.82	−0.69	0.55
tric_cop	tric_pyro	0.32	0.26	−0.24	0.89

CHX, chlorhexidine; EEOO, essential oils; SCN-/H2O2, thiocyanate/carbamide peroxide; SnF, stannous fluoride; ZnCit, zinc citrate; aloe, aloe vera; tric, triclosan; cop, copolymer; pyro, pyrophosphate; NaMFP_Zn, sodium monofluorophosphate with zinc.
p values are presented in bold if $p \leq 0.05$.

indices, the present paper evaluates the capacity of individual active agents in preventing plaque accumulation assessed by the most commonly used PlI, namely, the Turesky modification of the Quigley & Hein PlI. This index was widely used among the included papers (in contrast to the variety of gingival/bleeding index) and represents an ideal outcome variable to explore the validity of the NMA.

For this NMA to produce valid results, it was necessary to fulfil the transitivity criteria (the distribution of effect modifiers should be similar) (Hutton et al. 2015). This was accomplished by adding specific inclusion criteria related to transitivity and by assessing the specific characteristics of placebo controls. Placebo controls from dentifrices had different delivery format and higher PlI reductions than mouthrinse placebo controls. Therefore, two different NMA were performed for each delivery format.

Dentifrices

In the comparisons versus placebo control, all active agents showed greater reductions in PlI than placebo control, except for tric_ZnCit and tric_pyro in the PMA. These results were similar to the ones assessed by our previous review (Serrano et al. 2015) and to those published in other systematic reviews for SnF (WMDs ranging −0.31 to −0.112) (Gunsolley 2006, Paraskevas & van der Weijden 2006) and tric-cop (WMDs ranging −0.447 to −0.823) (Davies et al. 2004, Hioe & van der Weijden 2005). The efficacy of the CHX formulations was also suggested by our previous study (Serrano et al. 2015). The other tested agents could only be assessed by one trial supporting each product, so further clinical research is requested to clarify and support their real efficacy to reduce plaque levels.

When indirect or mixed comparisons among active agents were performed using NMA, the only clear statistical superiority was observed for CHX and tric_cop *versus* SnF. To the best of our knowledge, CHX and SnF were not previously compared in any systematic review. However, the same clinical and statistically significant differences were found in favour of tric_cop when compared to SnF for plaque index reduction in a recent systematic review (Salzer et al. 2015).

SUCRA values represent a simple transformation of the probability that a treatment would be among the best treatments. It provides a hierarchy of treatments and accounts both for the location and the variance of all relative treatment effects (Salanti & Ioannidis 2011). *Regarding the SUCRA results* from this NMA, although aloe had the best results, only one trial supports its use. CHX had the second best results, with three trials supporting its use. Tric_cop, although placed in the fifth position in the ranking of products, had 16 trials supporting its clinical efficacy. On the other hand, active agents in third and fourth places had only one trial supporting their efficacy. Therefore, ranking results should be interpreted with

Table 4. Studies on mouthrinses: study characteristics, product comparisons, plaque index results and summary of risk of bias

Reference	Product	Group	*N*	6 months-baseline changes PI		Risk of Bias (# of items ranked as follows)		
				Mean	SD	Low	High	Unclear
Allen et al. (1998)	No CPC rinse	Placebo	52	0.15	0.35		✗✗	????
	0.05% CPC	CPC_L	59	0.69	0.33			
Ayad et al. (2011)	0.05% NaF. no alcohol	Placebo	56	−0.16	0.51	✓	✗	????
	0.075% CPC. 0.05% NaF. no alcohol	CPC_H	54	0.89	0.45			
Ayad et al. (1995)	0.025% NaF	Placebo	48	0.29	0.38	✓✓✓	✗	??
	0.03% tric. 0.125% copolymer. 0.025% NaF	tric_cop	47	0.92	0.37			
Bauroth et al. (2003)	5% hydro-alcohol	Placebo	110	0.41	0.42	✓	✗	????
	EEOO	EEOO	108	0.93	0.57			
Charles et al. (2011)	5% hydro-alcohol	Placebo	100	0.78	0.29	✓	✗✗	???
	EEOO	EEOO	101	1.99	0.52			
Charles et al. (2004)	5% hydro-alcohol	Placebo	37	0.14	0.38	✓✓✓	✗✗	?
	0.12% CHX	CHX_H	36	0.93	0.45			
	EEOO	EEOO	34	0.73	0.41			
Claydon et al. (1996)	Minus active placebo	Placebo	147	0.31	0.56	✓✓✓✓✓	✗	
	0.1% delmopinol	delmo	147	0.40	0.56			
	0.2% delmopinol		142	0.49	0.56			
Cortelli et al. (2012)	5% hydro-alcohol	Placebo	133	0.40	0.33	✓✓✓✓	✗	?
	0.05% CPC	CPC_L	131	0.50	0.32			
	EEOO. ZnCl. NaF	EEOO	128	1.01	0.32			
Cortelli et al. (2013)	5% hydro-alcohol	Placebo	109	0.32	0.29	✓✓✓	✗✗	?
	0.05% CPC. no alcohol	CPC_L	108	0.40	0.27			
	EEOO. no alcohol	EEOO_noALc	107	1.07	0.29			
Cortelli et al. (2014)	5% hydro-alcohol	Placebo	117	−0.09	0.29	✓✓✓	✗✗	?
	0.07% CPC	CPC_H	108	0.27	0.28			
	EEOO	EEOO	113	1.12	0.28			
Costa et al. (2013)	Coloured saline-based	Placebo	27	0.181	0.43	✓✓✓✓	✗	?
	0.07% CPC. no alcohol	CPC_H	33	0.691	0.69			
Gordon et al. (1985)	Minus active placebo	Placebo	38	−0.09	0.39		✗✗	????
	EEOO	EEOO	44	0.22	0.37			
Hase et al. (1998)	Minus active placebo	Placebo	33	−0.04	0.63	✓✓	✗	???
	0.2% CHX	CHX_H	30	0.56	0.63			
	0.2% delmopinol. sodium hydroxide	delmo	37	0.20	0.59			
Mankodi et al. (2005b)	Placebo. no alcohol	Placebo	62	0.34	0.40		✗	?????
	0.07% CPC. no alcohol	CPC_H	57	0.76	0.42			
Overholser et al. (1990)	5% hydro-alcohol	Placebo	42	0.71	0.44	✓✓✓	✗	??
	0.12% CHX	CHX_H	41	1.56	0.44			
	EEOO	EEOO	41	1.44	0.45			
Sharma et al. (2002)	5% hydro-alcohol	Placebo	101	0.32	0.35	✓	✗✗✗	??
	EEOO	EEOO	98	1.34	0.49			
Sharma et al. (2004)	5% hydro-alcohol. floss	Placebo	81	0.41	0.35	✓✓✓	✗✗	?
	EEOO. floss	EEOO	79	1.62	0.52			
Spolsky & Forsythe (1977)	No alexidine	Placebo	111	−0.03	0.42	✓✓✓✓	✗	?
	0.035% alexidine	alexi	103	0.10	0.30			
Stookey et al. (2005)	Placebo	Placebo	86	0.14	0.45	✓✓	✗✗	??
	0.12% CHX	CHX_H	40	0.68	0.44			
	0.075% CPC	CPC_H	82	0.52	0.43			
	0.10% CPC		90	0.50	0.43			
Triratana et al. (1995)	Flavoured/coloured water placebo	Placebo	59	0.13	0.59	✓✓	✗✗	??
	0.3% tric. 0.125% copolymer. 0.025% NaF	tric_cop	59	1.01	0.55			
Van Leeuwen et al. (2015)	Minus active placebo	Placebo	25	0.09	0.39	✓✓✓✓✓	✗	
	0.07% CPC	CPC_H	25	0.30	0.38			
Weatherford et al. (1977)	Placebo	Placebo	105	0.03	0.52	✓✓		????
	0.035% alexidine	alexi	102	0.28	0.66			
Worthington et al. (1993)	0.025% NaF	Placebo	57	0.03	0.37	✓✓	✗	???
	0.3% tric. 0.125% copolymer. 0.025% NaF	tric_cop	60	0.59	0.42			

N, number of participants included in the RCT; SD, standard deviation; PII, Turesky plaque index.
SnF, stannous fluoride; CHX, chlorhexidine; EEOO, essential oils; NaF, sodium fluoride; tric, triclosan; cop, copolymer; pyro, pyrophosphate; ZnCit, zinc citrate; LC, low concentration; HD, high concentration; CPC, cetylpyridinium chloride; noAlc, no alcohol; ZnS, zinc sulphate; ZnCl, zinc chloride; SnCl, stannous chloride; MFP, monofluorophosphate; Na, sodium; SLS, sodium lauryl sulphate; pyro, pyrophosphate; F, fluor.

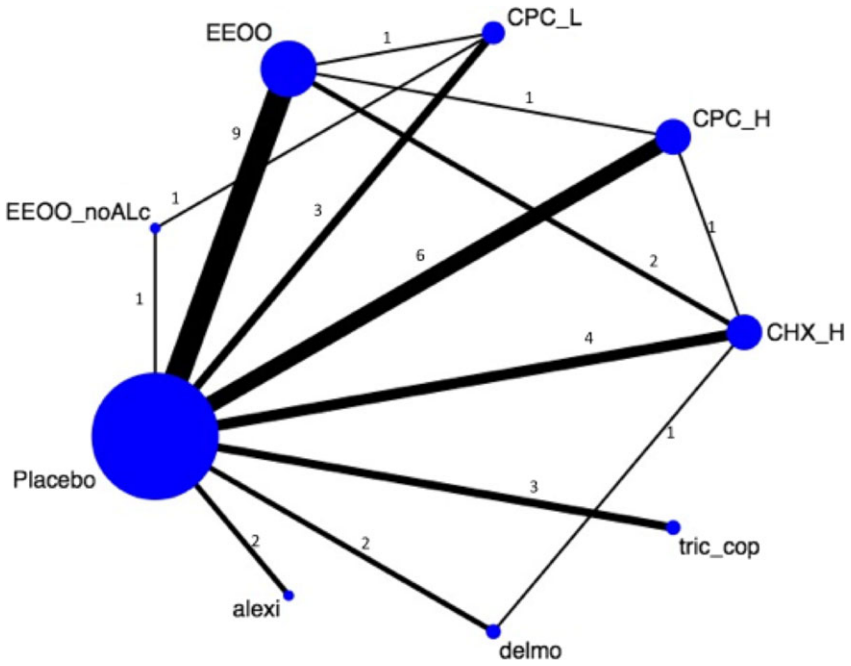

Fig. 2. Mouthrinses: network meta-analysis graph (net diagram). Each node represents a category of active agent (cluster). The following active agents were included: CHX, chlorhexidine; H, high concentration; L, low concentration; CPC, cetylpyridinium chloride; EEOO, essential oils; noAlc, no alcohol; alexi, alexidine; delmo, delmopinol; tric, triclosan; cop, copolymer.

caution, as there are wide differences in the number of trials supporting each active agent.

Mouthrinses

In the comparison versus placebo control, all active agents showed greater reductions in PII than placebo. The largest WMDs in the NMA were found when comparing placebo control with EEOO (WMD = −0.86) and EEOO_noAlc (WMD = −0.86), followed by CHX_H (WMD = −0.78). These NMA results are similar, in terms of WMDs, to those assessed in our previous PMA (Serrano et al. 2015) and to those published by other systematic reviews, in the case of EEOO (WMDs ranging −0.830 to −0.827) (Gunsolley 2006, Stoeken et al. 2007, Serrano et al. 2015), CHX_H (WMDs ranging −1.04 to −0.640) (Gunsolley 2006, Serrano et al. 2015),

When indirect or mixed comparisons among active agents were performed using NMA, no statistically significant differences were found when comparing the efficacy of CHX and EEOO (WMD = −0.09). These results are in disagreement with the ones reported in another systematic review that directly compared these two products, and found that, although the magnitude of the differences was small, CHX rinses showed a statistically significant higher plaque reduction than EEOO (n = 5, WMD: 0.19, p = 0.0009) (van Leeuwen et al. 2011). The variability of the results could be due to their definition of long-term trials (≥4 weeks *versus* 6 months in this study), which determines different study selection.

Attending to the *ranking of products* obtained from SUCRA analysis, EEOO obtained the best results (n = 9). EEOO_noAlc and CHX_H were in second and third place, respectively, with similar results from SUCRA, but with fewer trials supporting their efficacy (one and three respectively). These results could be of importance when recommending a home-use antiplaque product.

The innovative aspect of this study is that this is the first time that NMA is used to assess the clinical efficacy of antiseptic products, where indirect and mixed comparisons were studied and explained. This helps to clarify which product showed the greatest evidence and clinical activity for reducing plaque levels, although the antigingivitis effectiveness should be also studied and ranked in future publications to clarify correlations between plaque and gingivitis indexes, in order to better understand the clinical efficacy of these products from a therapeutic standpoint. However, it is also important to highlight that only RCTs that fulfilled the consensus criteria for the evaluation of oral hygiene products (Council on Dental Therapeutics 1986) were included. The thorough extraction of data from the studies has not only allowed for a comprehensive description of the included trials but for the analyses of 80 direct, indirect and mixed comparisons. According to these analyses, important conclusions were drawn about home-use antiseptic agents that can be prescribed by oral healthcare professionals to improve individual plaque control.

Regarding the risk of bias of individual studies and the evaluation of the quality of the trials and their reporting (Tables S10–S12), it must be pointed out that there were some relevant issues, such as the lack of true randomization of several studies (Deasy et al. 1991, Mankodi et al. 1992, Allen et al. 1998, 2002), lack of information on the blinding of evaluators and/or participants and lack of independency. Most of the studies demonstrated statistically significant differences favouring test groups, suggesting not only a risk of bias associated with the lack of independency but also a high risk of publication bias. Another limitation of this review is the lack of attention to agents with other mechanisms of action, beside antimicrobial effect, such as antiadhesion, "chemical" removal or effects over the biofilm matrix. Very limited information is available today for such agents.

In conclusion and, within the limitations of this study (including the severe imbalance in the amount of evidence), when comparing among products and formulations, CHX and EEOO in mouthrinses, and CHX and tric_cop in dentifrices appear to be the most efficacious active agents for supragingival plaque control. The high variability in the number of studies comparing each active agent and the different

Table 5. Mouthrinses: results [weighted mean difference (WMD) and 95% confidence interval (CI)] of direct, indirect and mixed comparisons among products

Product	*versus*	WMD	*p*	Lower CI	Upper CI
CHX_H	CPC_H	0.37	**0.03**	0.03	0.71
	CPC_L	0.51	**0.01**	0.12	0.91
	EEOO	−0.09	0.58	−0.39	0.22
	EEOO_noAlc	−0.08	0.75	−0.6	0.44
	alexi	0.6	**0.02**	0.08	1.11
	delmo	0.54	**0.02**	0.08	1.00
	tric_cop	0.1	0.68	−0.38	0.58
CPC_H	CPC_L	0.14	0.45	−0.22	0.51
	EEOO	−0.46	**0.00**	−0.73	−0.18
	EEOO_noAlc	−0.46	0.07	−0.95	0.04
	alexi	0.22	0.36	−0.26	0.71
	delmo	0.17	0.5	−0.31	0.65
	tric_cop	−0.27	0.24	−0.72	0.18
CPC_L	EEOO	−0.6	**0.00**	−0.91	−0.29
	EEOO_noAlc	−0.6	**0.01**	−1.01	−0.18
	alexi	0.08	0.75	−0.43	0.59
	delmo	0.03	0.92	−0.48	0.54
	tric_cop	−0.41	0.09	−0.88	0.06
EEOO	EEOO_noAlc	0.001	1	−0.46	0.46
	alexi	0.68	**0.00**	0.22	1.14
	delmo	0.62	**0.01**	0.17	1.08
	tric_cop	0.19	0.38	−0.23	0.61
EEOO_noALc	alexi	0.68	**0.03**	0.07	1.29
	delmo	0.62	**0.05**	0.01	1.23
	tric_cop	0.19	0.53	−0.39	0.77
alexi	delmo	−0.06	0.85	−0.66	0.54
	tric_cop	−0.49	0.09	−1.06	0.07
delmo	tric_cop	−0.44	0.14	−1.01	0.14

CHX, chlorhexidine; H, high concentration; L, low concentration; CPC, cetylpyridinium chloride; EEOO, essential oils; noAlc, no alcohol; alexi, alexidine; delmo, delmopinol; tric, triclosan; cop, copolymer.
p values are presented in bold if $p \leq 0.05$.

risks of bias make it necessary to interpret the data with caution. Severe imbalance in the amount of evidence for each intervention may affect the power and reliability of the overall analysis (Mills et al. 2013).

Implications for future research

With the present systematic review, direct and indirect comparisons have helped to identify the most relevant agents in terms of plaque control levels. The same analysis should be performed for gingival indices, in order to clarify and rank the most efficient agents to prevent and treat gingivitis onset, and to analyse the correlation between plaque and gingivitis, and possible disconnection between plaque reduction ranking and gingivitis effectiveness ranking.

Moreover, it may be necessary to assess the influence of different factors on the results of the NMA, in order to explain heterogeneity. Population characteristics, baseline plaque and gingivitis levels and risk of bias should be also included in the analyses and interpretation of results.

Implications for clinical practice

As it was found on the previous systematic review, the adjunctive use of chemical agents to mechanical plaque control offers advantages in terms of prevention of gingival inflammation development and in plaque levels control.

Even though the number of products analysed and tested was high, specific recommendations can be made based on the results of the present review and network meta-analysis. For mouthrinses, the most efficient agents reducing plaque scores were essential oils and chlorhexidine. For dentifrices, triclosan-copolymer and chorhexidine seemed to be the most efficient.

However, in order to clarify the real efficacy of every agent, not only in reducing plaque levels but also in gingival inflammation, it would be desirable to correlate these results with the ones resulting from the analyses of the gingival indices.

When prescribing an antiseptic product to improve plaque levels, clinicians should take into account, the results of this network meta-analysis, in terms of magnitude of the clinical effect and consistency of the results.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PRISMA Extension for Network Meta-analysis.
Appendix S2. Electronic search strategy.
Appendix S3. Inclusion and exclusion criteria for paper selection.
Appendix S4. Excluded studies after full-text analysis and main reason for exclusion.
Appendix S5. Excluded studies from network meta-analysis with Turesky modification of Quigley and Hein plaque index and main reason for exclusion.
Appendix S6. Commonly used acronyms and abbreviations.
Fig. S1. PRISMA flow diagram of the study (n, number of papers).
Fig. S2. Dentifrices: ranking of products (SUCRA). The following active agents were included: CHX, chlorhexidine; EEOO, essential oils; SCN-/H2O2, thiocyanate/carbamide peroxide; SnF, stannous fluoride; ZnCit, zinc citrate; aloe, aloe vera; tric, triclosan; cop, copolymer; pyro, pyrophosphate; NaMFP_Zn, sodium monofluorophosphate with zinc.
Fig. S3. Mouthrinses: ranking of products (SUCRA). The following active agents were included: CHX, chlorhexidine; H, high concentration; L, low concentration; CPC, cetylpyridinium chloride; EEOO, essential oils; noAlc, no alcohol; alexi, alexidine; delmo, delmopinol; tric, triclosan; cop, copolymer.
Table S1. Study characteristics: affiliation, sample recruitment and study duration.
Table S2. Study characteristics: sample size, gender, age and smoking, for each comparison, categorized by the delivery format (dentifrice [D], dentifrice and rinse [D&R], rinse [R]) and by the main active ingredient.
Table S3. Study characteristics: outcome assessment, with selected indices and sites and teeth assessed.
Table S4. Study characteristics: periodontal status as defined by the inclusion criteria.
Table S5. Interventions: supervision, instructions and other treatments, as reported in the included studies.
Table S6. Interventions (dentifrices): description of the products tested, including main active ingredients and brand name, together with the provided instructions.
Table S7. Interventions (mouth rinses): description of the products tested, including main active ingredients and brand name, together with the provided instructions.
Table S8. Results for the placebo group in trials testing dentifrices.
Table S9. Results for the placebo group in trials testing mouthrinses.
Table S10. Evaluation of the risk of bias in individual studies, as suggested by the Cochrane reviewers' handbook: selection, performance, detection bias and attrition.

Table S11. Evaluation of the risk of bias in individual studies, as suggested by the Cochrane reviewers' handbook: other potential sources of bias.

Table S12. Qualitative and reporting aspects of the included studies with regard to registration, statistics and outcome assessment.

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Clinical Relevance

Scientific rationale for the study: The use of antiseptics as antiplaque or antigingivitis agents has been widely evaluated. However, there is a scarcity of studies reporting on direct comparisons among active agents, and therefore, a network meta-analysis may aid to identify the most efficacious ones.

Principal findings: When ranking active agents, chlorhexidine and essential oils in mouthrinses, and chlorhexidine and triclosan-copolymer in dentifrices, showed the greatest effect on plaque index.

Practical implications: There is consistent evidence showing that the adjunctive use to mechanical plaque control of dentifrices or mouthrinses with specific active agents improve the reduction of plaque levels.