

Network meta-analysis on the effect of desensitizing toothpastes on dentine hypersensitivity

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ABSTRACT

Objectives: This network meta-analysis compares different desensitizing toothpastes and placebo in terms of their effects on dentine hypersensitivity (DH) at 2, 4, and 8 weeks.

Materials and methods: A systematic electronic literature search of four databases, and a manual search, were performed to identify randomized controlled trials (RCTs) on different desensitizing toothpastes for the treatment of DH. Pair-wise and network meta-analyses were performed to analyze the desensitization effect at 2, 4, and 8 weeks. The risk of bias was assessed based on the Cochrane guidelines and funnel plots. Statistical heterogeneity, inconsistencies, and ranking probability were also evaluated.

Results: A total of 30 RCTs were included in the network meta-analysis, which included eight desensitizing toothpastes. There was no significant difference in the effect among calcium sodium phosphosilicate-containing (CSPS), potassium-containing (K) and strontium-containing (Sr) toothpastes. In addition, there was no significant difference between fluoride (F) and placebo. The desensitizing toothpaste with the highest probability of being the most effective treatment for DH was nano-hydroxyapatite (n-HA) at 2 and 4 weeks (60% and 67%, respectively), and Ar at 8 weeks (54%).

Conclusions: No significant difference was detected in desensitizing effects among CSPS, K and Sr toothpastes. In addition, there was no significant difference between F and placebo, K and placebo. Furthermore, a significant placebo effect on DH was found in this study. Moreover, n-HA toothpastes may be the best desensitizing toothpastes for treatment of DH, followed by Ar toothpaste.

Clinical significance: Based on the results of present network meta-analysis, n-HA containing toothpastes might be a recommended desensitizing toothpastes considering the treatment of DH.

PROSPERO registration number: CRD42019117710.

1. Introduction

Dentine hypersensitivity (DH) is characterized by short and sharp pain when the exposed dentine of the affected tooth receives external stimulation [1,2]. DH is a common clinical oral health problem with a prevalence of 2% to 57% worldwide [3], and economic development and the aging population may increase the incidence of DH. DH not only affects teeth, but also has an impact on the quality of the patient's life [4,5]. Therefore, effective treatment and control of DH have become an important issue for dentists.

At present, the main mechanism of treating DH is to reduce the fluid flow in dentine tubules or block the nerve response in pulp [5,6]. Based on previous reports, the initial treatment for DH is home use of desensitizing toothpastes [7–9]. Compared with other treatments, desensitizing toothpaste is a convenient, economical, simple, and

noninvasive treatment [10,11]. At this time, numerous desensitizing toothpastes containing potassium, strontium, stannous fluoride, arginine, or nano-hydroxyapatite (n-HA) have been developed for DH [12]. Besides, toothpastes contains bioactive ingredients like Novamin and Biomin, which also give promising results in many clinical trials [13,14].

Previous systematic reviews and meta-analyses have analyzed the efficacy of desensitizing toothpastes against DH [12,15–20]. However, there were some limitations to these systematic reviews. For example, some previous meta-analyses only analyzed the desensitization effect of a specific component of desensitization toothpastes, without analyze all types of desensitization toothpaste. In addition, some previous reports only examined the desensitization effect of desensitization toothpastes at the final follow-up, without considering other follow-up times. Furthermore, the measurement scale of DH and the final follow-up time of

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included studies varied, which may have biased the conclusions. Moreover, these previous systematic reviews and meta-analyses included some studies related to DH periodontal maintenance or outcomes after bleaching, which may also have biased the results. Finally, these previous systematic reviews and meta-analyses did not generate relevance rankings on the desensitization effect for the different desensitizing toothpastes, and patients did not know which desensitizing toothpaste had the best desensitization effect.

Network meta-analysis allows us to synthesize data from both direct and indirect comparisons [21,22]. Clinicians should consider all relevant data when comparing different treatments, and multiple treatment comparisons can be made across studies using a network [23]. In addition, network meta-analysis allows us to estimate the rank probability of each treatment [22]. However, to the best of our knowledge, no network meta-analysis has been performed on the efficacy of different desensitizing toothpastes against DH. Therefore, it is important to conduct a more comprehensive and up-to-date systematic review and network meta-analysis of the efficacy of different desensitizing toothpastes against DH, and to provide relevance rankings for the various desensitizing toothpastes.

Overall, the aim of this network meta-analysis was to provide guidance for selecting an appropriate desensitizing toothpaste in patients with DH using network meta-analysis, which compared different desensitizing toothpastes and placebo treatment at 2, 4, and 8 weeks.

2. Materials and methods

This network meta-analysis was performed based on the international guidelines for conducting and reporting systematic reviews, as applied to pairwise and network meta-analyses [24,25]. Besides, this study was registered in the International Prospective Register of Systematic Review (PROSPERO-CRD42019117710).

2.1. PICOS question

According to the recommendations by the Centre for Evidence-Based Medicine (University of Oxford, Oxford, UK), the participants, interventions, comparisons, outcomes and study designs (PICOS) question was as follows: How do desensitizing toothpastes influence the desensitization effect on DH at 2, 4, and 8 weeks.

Patients: Systemically healthy adult patients with DH.

Intervention and Comparator: Any type of desensitizing toothpaste (potassium, strontium, stannous fluoride, arginine, etc.) and placebo. There were no limits on concentration, frequency, or management method, but follow-up times of 2, 4, or 8 weeks were required.

Outcomes: Desensitization toothpastes and placebo for the treatment of DH were quantitatively assessed using the air-blast test score and the Schiff Cold Air Sensitivity Scale (SCASS (0–3)).

Studies: Only randomized controlled trials (RCTs).

2.2. Inclusion criteria

According to the PICOS model, inclusion and exclusion criteria were established as follows [26]:

- i Clinical studies on adult patients with DH.
- ii DH treated by any type of desensitizing toothpaste (potassium, strontium, stannous fluoride, arginine, etc.).
- iii The follow-up times of studies included 2, 4, or 8 weeks.
- iv Studies with quantitative outcomes that assessed using the air-blast test score and the Schiff Cold Air Sensitivity Scale (SCASS (0–3)).
- v Randomized controlled trials (RCTs)

2.3. Exclusion criteria

- i Animal experiments and *in vitro* studies.

- ii Studies related to DH periodontal maintenance or outcomes after bleaching or restorative treatment.
- iii Studies on other treatments for DH.
- iv The follow-up times of studies did not include 2, 4, or 8 weeks.
- v The outcomes of studies using other types of stimulation or measurement scales to assess.
- vi Prospective, retrospective cohort studies, case studies, unpublished materials, and review papers.

2.4. Information sources and literature search

The MEDLINE, EMBASE, Web of Science, and CENTRAL (Cochrane Library) databases were searched for relevant studies. From inception to December 22, 2018, no search restrictions were applied. The databases were searched for English language studies exploring the effect of different desensitizing toothpastes or placebo on DH, using the following MeSH terms: “Desensitization toothpastes” and “dentine hypersensitivity”. The search strategy was detailed in the Appendix (S1). Regarding “grey” literature, ClinicalTrials.gov, the International Clinical Trials Registry Platform, the ProQuest Dissertation Abstracts and Thesis database, and the System for Information on Gray Literature in Europe Database were also searched. As a supplement to the electronic search, a manual search was conducted to review the reference lists of related papers and review articles.

2.5. Study selection

Randomized controlled trials (RCTs) that compared the effect of different desensitizing toothpastes or placebo on DH were reviewed. Two authors independently screened the study titles and abstracts, identifying studies that met the inclusion criteria for full-text evaluation. In studies with at least three arms, any arm not relevant to our analysis was excluded. If the two authors disagreed during this process, a third author was consulted and an agreement was reached through discussion.

2.6. Data collection process and data items

The information and data required for this study were extracted from the selected studies by two authors. The extracted information and data included: first author of the study, publication year, country, intervention and comparator group, follow-up period, and measurement scale. During this process, if these two authors had different opinions, the discrepancy was resolved by consulting a third author and reached an agreement through discussion.

2.7. Risk of bias within and across studies

The quality and risk of bias of the selected RCTs were assessed using the Cochrane collaboration tool in REVIEW MANAGER (version 5.0 for Windows; the Cochrane Collaboration, Oxford, UK). When all bias indicators were rated as low risk, the risk of RCT bias was deemed low. When one or more bias indicators were rated as uncertain risk, the risk of RCT bias was unclear. All other RCT cases were considered high risk. The possibility of publication bias in the included studies was assessed using funnel plots by STATA (version 14.0; Stata Corp, College Station, TX, USA) [27]. The above steps were performed independently by two authors and any disagreement was resolved by consulting a third author and reaching agreement through discussion.

2.8. Summary measures and synthesis of results

First, a traditional pair-wise meta-analysis was conducted to synthesize studies comparing the same pair of treatments using a random effects model in ADDIS 1.16 (Drugis.org). The results are expressed as mean differences (MDs) with 95% confidence intervals (CIs). The I^2 test

was used to assess heterogeneity across studies and a value $> 50\%$ was considered to indicate moderate to high heterogeneity [28].

Second, a random-effects network within a Bayesian framework model was established using the Markov chain Monte Carlo method in ADDIS 1.16 [29]. The authors networked the translated binary results of the desensitization effect and specified the relationship among the MDs across studies, as in a previous report that combined direct and indirect comparisons of different treatments, to ensure that comparisons of desensitizing toothpastes and placebo regimens were comprehensive [30]. Statistical significance was considered at $P < 0.05$ based on 95% CIs.

The ranking probability of each treatment was also estimated in ADDIS 1.16. The MD of each treatment group compared with arbitrary controls was calculated, and the number of iterations of the Markov chain of the MD ranking of treatments was counted.

2.9. Additional analyses

A variance calculation and a node-splitting analysis were performed using ADDIS 1.16 to evaluate inconsistency within the network meta-analysis. If the difference between random effects variance and inconsistency was large, or the difference between direct and indirect evidence was $P < 0.05$, the results was considered inconsistent. The authors adjusted the included studies to obtain a consistent ideal network based on quantitative estimation.

3. Results

3.1. Study selection

On electronically searching the four databases and manually searching the reference sections of relevant articles, 559 and 36 records were identified, respectively. A total of 150 duplicate articles were excluded. An additional 362 articles were excluded as they did not meet the inclusion criteria after filtering the titles and abstracts. The remaining 83 articles were reviewed the full texts and selected 30 articles that compared the desensitization effect among desensitizing toothpastes and placebo at 2, 4, and 8 weeks after treatment (Fig. 1).

Kappa values for the agreement between reviewers was 0.93 with respect to the screening of titles and abstracts, and 0.96 for the full-text evaluation (corresponding to “almost perfect” inter-rater agreement) [31].

3.2. Study characteristics

Basic characteristics of the final 30 selected studies are summarized in Table 1. Studies were full reports published between 1980 and 2018 that included potassium-containing (K), strontium-containing (Sr), stannous fluoride-containing (SnF₂), potassium- and stannous fluoride-containing (K + SnF₂), calcium sodium phosphosilicate-containing (CSPS), arginine-containing (Ar), nano-hydroxyapatite-containing (n-HA), and fluoride-containing (F) toothpastes [32–61]. The active ingredients in these toothpastes are described in Table 2, which also include the classification of these toothpastes. The follow-up time of these studies ranged from immediately after treatment to 12 weeks. To account for the effect of different follow-up times on the results, and to include as many studies as possible, the authors chose the three most frequently used follow-up times, of 2, 4, and 8 weeks.

The authors established networks for comparison (Fig. 2). In the figure, each node represents a treatment. Connections between nodes denote direct comparisons; node size and the thickness of connections vary according to the number of studies involved in a comparison.

3.3. Risk of bias within studies

The risk of bias assessment showed that only 2 studies had a low

risk, while 8 had a high risk and the remaining 20 had an unclear risk (S2, Fig. 3). And the most common type of bias was allocation concealment.

3.4. Result of individual studies and synthesis of results

Results of the pairwise meta-analysis were provided in the Appendix (S4, S5, S6). Ar was significantly superior to K and F toothpastes and SnF₂ was significantly superior to F toothpastes, at all three follow-up times ($P < 0.05$). n-HA was significantly superior to F toothpastes and placebo at 2 and 4 weeks ($P < 0.05$). CSPS was significantly superior to F toothpastes at 4 weeks, while at 8 weeks K and K + SnF₂ were significantly superior to F toothpaste, and Ar was significantly superior to Sr toothpaste ($P < 0.05$). However, there was no significant difference between F toothpaste and placebo or K toothpaste and placebo at 2 and 4 weeks.

The results of the network meta-analysis were summarized in Table 3. Ar was significantly superior to K, F toothpastes and placebo, and SnF₂ were significantly superior to F toothpaste at all three follow-up times ($P < 0.05$). In addition, n-HA was significantly superior to Sr, K, F toothpastes and placebo, and SnF₂ toothpaste was significantly superior to placebo, at 2 and 4 weeks ($P < 0.05$). Ar was significantly superior to SnF₂ toothpastes, K + SnF₂ was significantly superior to F toothpaste and placebo, and K was significantly superior to F toothpaste at 4 and 8 weeks ($P < 0.05$). Besides, SnF₂ was significantly superior to Sr and K toothpastes at 2 weeks ($P < 0.05$), while at 4 weeks Ar was significantly superior to Sr toothpaste, n-HA was significantly superior to SnF₂ toothpaste, and CSPS was significantly superior to F toothpaste and placebo ($P < 0.05$); at 8 weeks, Sr was significantly superior to F toothpaste ($P < 0.05$).

3.5. Rank probabilities

The desensitizing toothpaste probability rankings were shown in Fig. 5 and Table 4. The rank of each treatment is shown on the histogram, which indicates the probability of being ranked in that position. Lower ranks indicate a better desensitization effect.

According to the network of desensitization effects at 2 weeks, the cumulative probability of being the most efficacious treatment was in the order of n-HA toothpastes (60%) followed by SnF₂, Ar, CSPS, K, Sr, placebo, and F toothpastes. In terms of the desensitization effect at 4 weeks, the cumulative probability of being the most efficacious treatment was in the order of n-HA toothpastes (67%) followed by Ar, K + SnF₂, CSPS, SnF₂, K, Sr, placebo, and F toothpastes. Based on the network of the desensitization effect at 8 weeks, the cumulative probability of being the most efficacious treatment was in the order of Ar toothpastes (54%) followed by K + SnF₂, Sr, K, SnF₂, CSPS, and F toothpastes and placebo.

3.6. Risk of bias across studies

The publication bias was illustrated by funnel-plots (Fig. 4). According to the network meta-analysis, there was no significant asymmetry or evidence of significant bias among the selected studies in terms of the desensitization effect.

3.7. Additional analyses

Results of the inconsistency tests were provided in Appendix (S3). Our results indicate no significant inconsistency between the direct and indirect effect comparisons, excluding arginine-containing (Ar) toothpastes versus fluoride-containing (F) toothpastes at 4 weeks ($P < 0.05$).

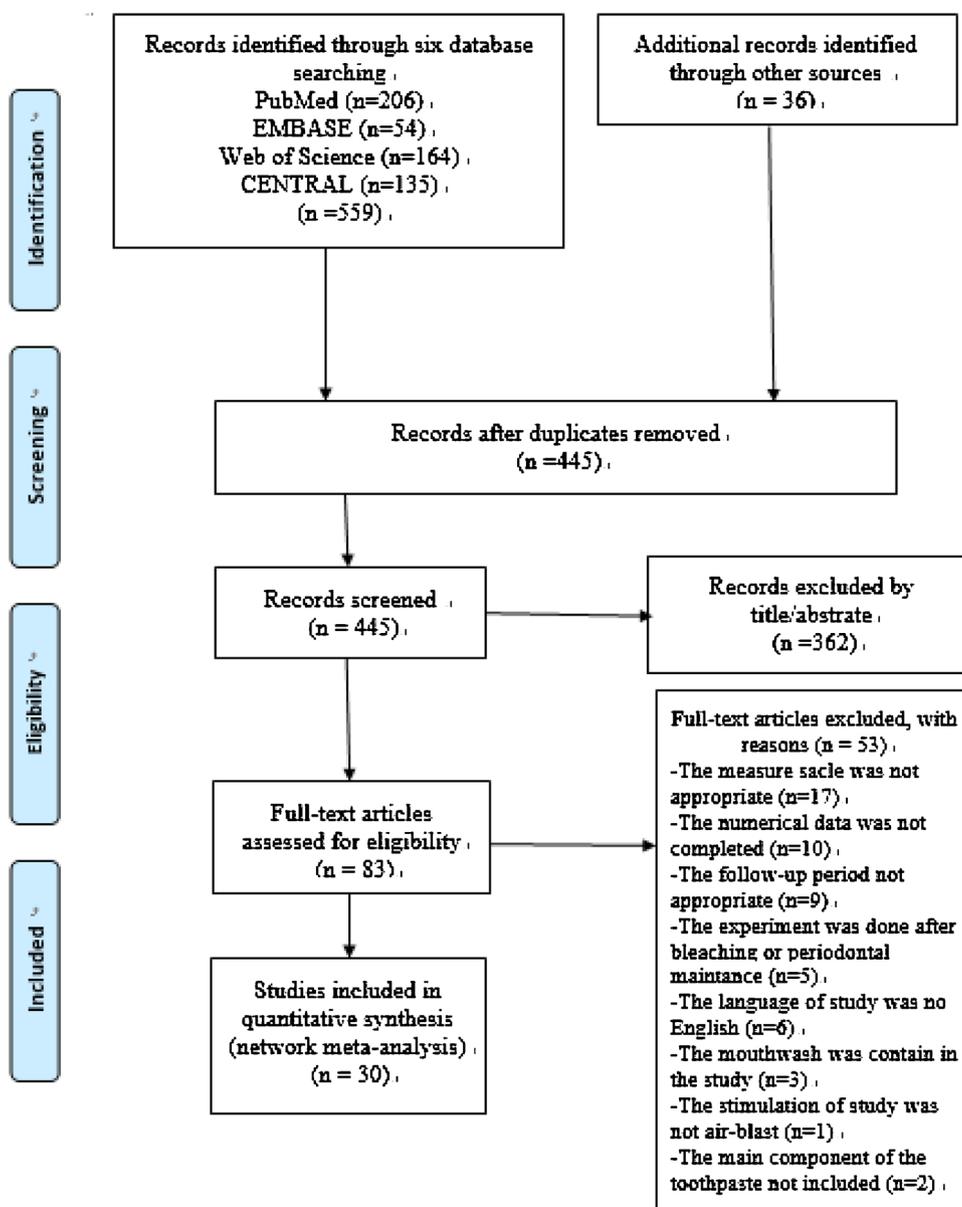


Fig. 1. PRISMA flow program for study selection.

4. Discussion

According to the clinical characteristics of DH, relief of pain and prevention of recurrence are key to treatment. Clinicians should employ a progressive procedure to select the appropriate treatment for DH, and desensitizing toothpaste is often the first step recommended by clinicians for the treatment of DH [62]. There are many types of desensitizing toothpastes on the market, and many studies have shown that desensitizing toothpastes can alleviate the pain associated with DH. However, the best desensitizing toothpaste has not yet been determined. Therefore, it is important to evaluate and compare the efficacy of desensitizing toothpastes.

Some concern has been expressed regarding evaluating the efficacy of desensitizing toothpastes, where the results may be affected by many factors. Using of different methods of external stimulation may also lead to biased results, and previous studies have shown that the quality of evidence for studies of DH treatment based on tactile stimuli is low [18]. Therefore, only studies that using the air-blast test were included in this study. In addition, air-blast test has the advantage of good repeatability [63]. Currently, various measurement scales are used to

assess the degree of pain in DH, such as visual analogue scales (VAS) and SCASS. The use of different measurement scales among studies also decreases the credibility of the results. A previous study indicated that SCASS is the most representative measurement scale to evaluate the degree of pain in DH [18]. Thus, only studies that using SCASS were included in this network meta-analysis. SCASS is also the most commonly used assessment method for DH. In most studies, several follow-up periods for desensitizing toothpaste efficacy are examined, and only the final follow-up time is used for comparison. However, the final follow-up time varies among these studies, which may lead to bias in their conclusions. In addition, previous studies only compared efficacy in terms of one follow-up time, thus, their conclusions were not comprehensive [12,16]. To reduce the influence of the above factors, the authors selected studies with the three most frequently used follow-up times for efficacy comparison, i.e., 2, 4, and 8 weeks. Pain due to DH should be dissociated from pain due to bleaching. Bleaching can lead to pulpitis, which in turn causes pain, contrary to the hydrodynamic theory of DH [64,65]. In addition, sensitivity after periodontal treatment is different from general DH, it can peak over a few days after periodontal treatment and typically decreases after the procedure [66].

Table 1
The characteristics of randomized controlled clinical trials included in the final network meta-analysis (n = 30).

First author of study	Year	Country	Intervention and comparator group	Follow-up period	Pain score type
Tarbet	1980	USA	K/PL	1/2/3/4weeks	SCASS(0-3)
Chesters(1)	1992	USA	K/F	3/8weeks	SCASS(0-3)
Chesters(2)	1992	USA	K/F	3/8weeks	SCASS(0-3)
Nagata	1994	Japan	K/PL	2/4/8/12 weeks	SCASS (0-3)
Schiff	1998	USA	K/F	4/8weeks	SCASS(0-3)
Schiff	2000	USA	K + SnF ₂ /F	4/8 weeks	SCASS(0-3)
Sowinski	2000	USA	K + SnF ₂ /F	4/8 weeks	SCASS(0-3)
Sowinski(1)	2001	USA	K + SnF ₂ /F	4/8 weeks	SCASS(0-3)
Sowinski(2)	2001	USA	K + SnF ₂ /K	4/8 weeks	SCASS(0-3)
Schiff	2005	USA	SnF ₂ /F	4/8 weeks	SCASS(0-3)
Ayad	2009	Canada	Ar/K	3days/2/4/8weeks	SCASS(0-3)
Docimo(a)	2009	Italy	Ar/K	2/4/8weeks	SCASS(0-3)
Docimo(b)	2009	Italy	Ar/K	1/2/4/8weeks	SCASS(0-3)
Ghassemi	2009	Canada	CSPS/F	4/8 weeks	SCASS(0-3)
Day	2010	UK	SnF ₂ /F	2/4 weeks	SCASS(0-3)
Que(1)	2010	China	Ar/F	2/4/8 weeks	SCASS(0-3)
Que(2)	2010	China	Ar/F	2/4/8 weeks	SCASS(0-3)
Chaknis	2011	USA	SnF ₂ /F	4/8 weeks	SCASS(0-3)
Docimo	2011	Italy	Ar/Sr/F	2/4/8 weeks	SCASS(0-3)
He	2011	USA	SnF ₂ /F	Immediate/3days/2 weeks	SCASS(0-3)
Schiff	2011	USA	Ar/Sr	8/10/16weeks	SCASS(0-3)
Kakar	2012	India	Ar/K	2/4/8 weeks	SCASS(0-3)
Hegde	2013	India	Ar/F	2/4/8 weeks	SCASS(0-3)
Kakar (a)	2013	India	Ar/F	2/4/8weeks	SCASS(0-3)
Kakar (b)	2013	India	K/F	4/8weeks	SCASS(0-3)
Kapferer	2013	Austria	Ar/PL	Immediate/4/12 weeks	SCASS(0-3)
Parkinson	2013	UK	SnF ₂ /F	4/8 weeks	SCASS(0-3)
He (a)	2014	USA	SnF ₂ /F	Immediate/3days/2 weeks	SCASS(0-3)
He (b)	2014	USA	SnF ₂ /F	2/8 weeks	SCASS(0-3)
Vano	2014	Italy	n-HA/F/PL	2/4 weeks	SCASS(0-3)
Parkinson	2015	UK	SnF ₂ /F	4/8 weeks	SCASS(0-3)
Hall	2017	UK	CSPS/Ar/F	1/2/4/6/11 weeks	SCASS(0-3)
Vano	2018	Italy	n-HA/F/PL	2/4 weeks	SCASS(0-3)

K:Potassium-containing toothpaste; Sr: Strontium-containing toothpaste; SnF₂: Stannous fluoride-containing toothpaste; CSPS: Calcium sodium phosphosilicate-containing toothpaste; Ar: Arginine-containing toothpaste; n-HA: Nano-hydroxyapatite-containing toothpaste; F:Fluoride-containing toothpaste; PL:Placebo.

Therefore, in this study, tooth sensitivity after bleaching or periodontal maintenance treatment were excluded to reduce heterogeneity among studies. There is no doubt that individual responses to pain vary and placebo effects may also influence the results [67].

Based on the network meta-analysis, at 2, 4, and 8 weeks, Ar had significantly better desensitization effects on DH than K, F toothpastes and placebo. Our results are consistent with a previous study, supporting a superior therapeutic effect of Ar toothpaste versus K and F toothpastes [68]. Arginine and carbonate will react in saliva and produce deposited to block the dentin tubules. In addition, bicarbonate can produce alkaline conditions that conduce to glycoprotein accumulation [12]. All these may explain that the Ar toothpaste has a superior desensitization effect.

Besides, this network meta-analysis included more studies and more stringent inclusion criteria were applied, thereby improving the credibility of the results. Ar was significantly better than SnF₂ toothpastes at

both 4 and 8 weeks, but not at 2 weeks. In addition, SnF₂ was significantly better than the Sr and K toothpastes at 2 weeks. Stannous fluoride can produce insoluble metal compounds that block the dentin tubules and prevent impulse transmission of pulp nerves, which may explain the results that SnF₂ works faster than Sr toothpastes [12]. These results indicate that the Ar had superior long-term effect compared with SnF₂, while SnF₂ had a rapid desensitization effect.

Our results also indicated that n-HA had significantly better desensitization effects than Sr, K, F toothpastes and placebo, at both 2 and 4 weeks. This result agrees with a previous systematic review, showing that n-HA toothpastes were superior for DH relief compared with other desensitizing agents, placebo, or negative control [18]. Nano-hydroxyapatite is a bioactive substance with similar component and structure to teeth, which can block the dentin tubules to alleviate the symptom of DH [16]. Besides, it also determines the regeneration of mineralized layer, which can enhance the effect of desensitization [59]. All these

Table 2
The active ingredient and classification of included toothpastes.

Desensitizing toothpastes	Active ingredient	Desensitization mechanism	Classification
Potassium-containing toothpaste	Potassium ions	Prevent conduction in the pulp nerve	①
Strontium-containing toothpaste	Strontium ions	Blocking the exposed dentine tubules	②
Stannous fluoride-containing toothpaste	Stannous fluoride	Blocking the exposed dentine tubules and prevent conduction in the pulp nerve	①②
Calcium sodium phosphorsilicate-containing toothpaste	Calcium sodium phosphorsilicate	Blocking the exposed dentine tubules	②
Arginine-containing toothpaste	Arginine ions	Blocking the exposed dentine tubules	②
Nano-hydroxyapatite-containing toothpaste	Nano-hydroxyapatite	Blocking the exposed dentine tubules	②
Fluoride-containing toothpaste	Fluoride ions	Blocking the exposed dentine tubules	②

① Nerve response blocking agents; ② Dentinal tubules occluding agents.

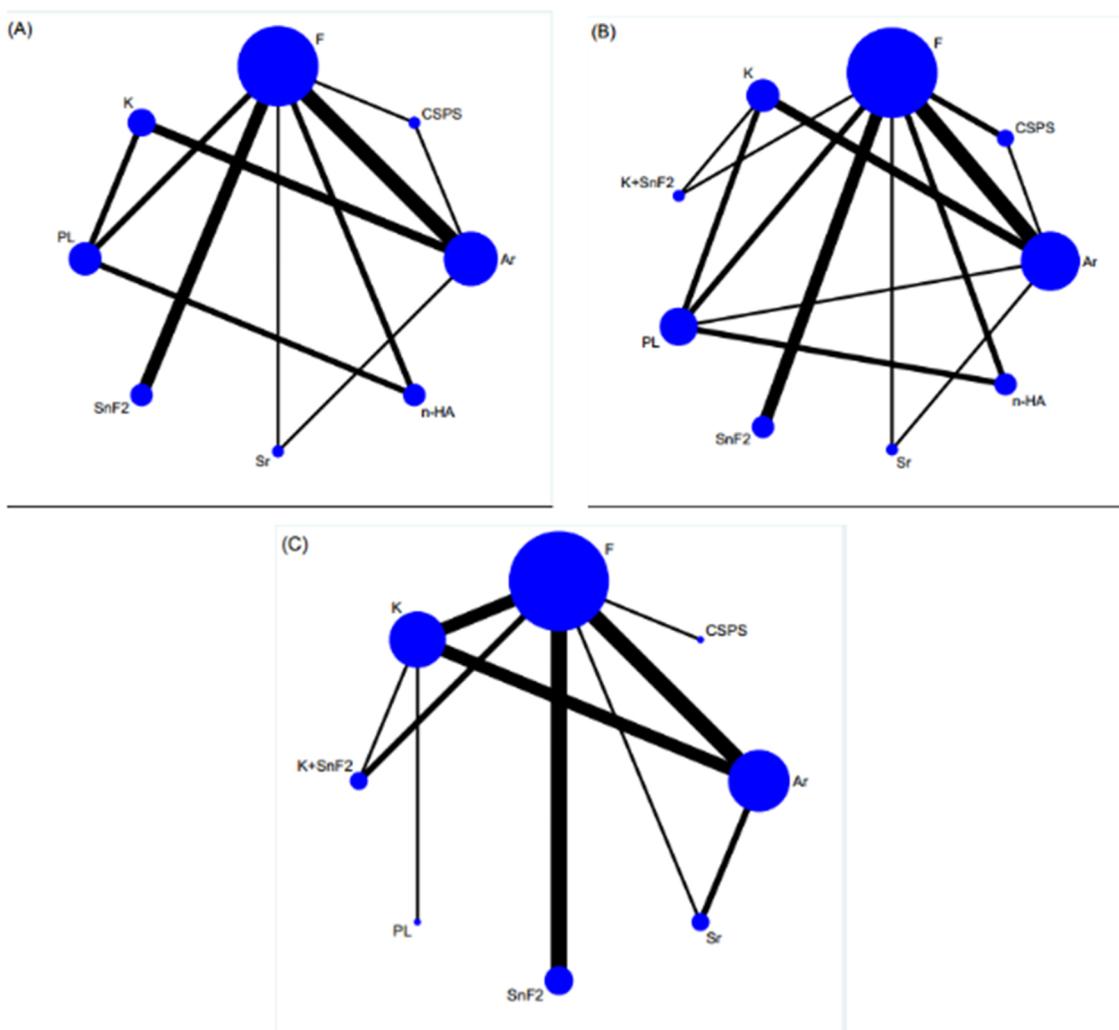


Fig. 2. Network comparing the desensitization effect of desensitizing toothpastes or placebo at 2 weeks (A), 4 weeks (B) and 8 weeks (C). K: Potassium-containing toothpaste; Ar: Arginine-containing toothpaste; SnF₂: Stannous fluoride-containing toothpaste; CSPA: Calcium sodium phosphosilicate-containing toothpaste; Sr: Strontium-containing toothpaste; n-HA: Nano-hydroxyapatite-containing toothpaste; F: Fluoride-containing toothpaste; PL: Placebo; K + SnF₂: Potassium- and Stannous fluoride-containing toothpaste.

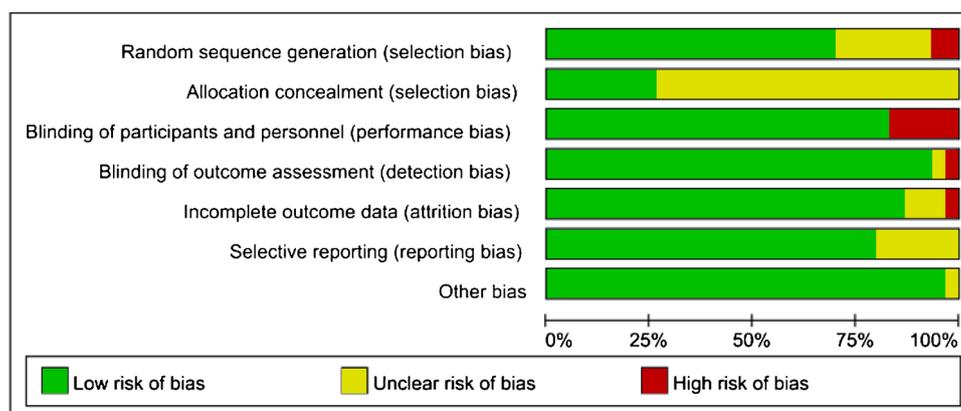


Fig. 3. The risk of bias graph of all the final included RCTs.

may explain that the n-HA toothpaste has the best desensitization effect. Furthermore, our study has shown that n-HA is the most effective desensitizing toothpaste both at 2 and 4 weeks. Regarding the 8-week efficacy, more trials are required.

Based on our results, there was no significant difference in the desensitization effect among CSPA, K, and Sr toothpastes. Previous studies

have shown that K and Sr toothpastes had significantly desensitization effects in DH [16,19]. Potassium ions block the action potential produced by the pulp nerve, which reduce the symptom of DH. And the dentin can absorb strontium ions and react with it to form strontium carbonate, which blocks the dentin tubules [68]. In addition, a previous meta-analysis indicated that CSPA was more effective than the negative

Table 3
Two weeks (A), 4 weeks (B) and 8 weeks (C) desensitization effect based on network meta-analysis.

(A) 2 weeks								
Ar	0.04(-0.66,0.75)	0.67(0.34,1.00)	0.42(0.01,0.83)	0.57(0.08,1.06)	-0.38(-0.88,0.11)	0.52(-0.18,1.20)	-0.49(-1.08,0.11)	
-0.04(-0.75,0.66)	CSPS	0.64(-0.07,1.34)	0.38(-0.42,1.18)	0.53(-0.29,1.34)	-0.42(-1.23,0.37)	0.48(-0.49,1.44)	-0.53(-1.42,0.34)	
-0.67(-1.00,-0.34)	-0.64(-1.34,0.07)	F	-0.25(-0.72,0.22)	-0.10(-0.57,0.34)	-1.06(-1.44,-0.68)	-0.16(-0.85,0.53)	-1.16(-1.71,-0.63)	
-0.42(-0.83,-0.01)	-0.38(-1.18,0.42)	0.25(-0.22,0.72)	K	0.15(-0.34,0.64)	-0.81(-1.43,-0.20)	0.10(-0.69,0.88)	-0.91(-1.55,-0.27)	
-0.57(-1.06,-0.08)	-0.53(-1.34,0.29)	0.10(-0.34,0.57)	-0.15(-0.64,0.34)	PL	-0.96(-1.56,-0.35)	-0.05(-0.86,0.76)	-1.06(-1.60,-0.52)	
0.38(-0.01,0.88)	0.42(-0.37,1.23)	1.06(0.68,1.44)	0.81(0.20,1.43)	0.96(0.35,1.56)	SnF ₂	0.90(0.12,1.69)	-0.10(-0.77,0.57)	
-0.52(-1.20,0.18)	-0.48(-1.44,0.49)	0.16(-0.53,0.85)	-0.10(-0.88,0.69)	0.05(-0.76,0.86)	-0.90(-1.69,-0.12)	Sr	-1.00(-1.88,-0.13)	
0.49(-0.11,1.08)	0.53(-0.34,1.42)	1.16(0.63,1.71)	0.91(0.27,1.55)	1.06(0.52,1.60)	0.10(-0.57,0.77)	1.00(0.13,1.88)	n-HA	
(B) 4 weeks								
Ar	0.21(-0.22,0.65)	0.98(0.73,1.23)	0.56(0.26,0.87)	0.12(-0.38,0.65)	0.88(0.53,1.24)	0.43(0.05,0.82)	0.64(0.10,1.17)	-0.16(-0.62,0.29)
-0.21(-0.65,0.22)	CSPS	0.77(0.37,1.18)	0.35(-0.16,0.87)	-0.09(-0.69,0.56)	0.67(0.16,1.19)	0.22(-0.28,0.73)	0.43(-0.24,1.09)	-0.38(-0.95,0.20)
-0.98(-1.23,-0.73)	-0.77(-1.18,-0.37)	F	-0.42(-0.77,-0.07)	-0.86(-1.35,-0.33)	-0.10(-0.44,0.24)	-0.55(-0.85,-0.24)	-0.34(-0.89,0.19)	-1.15(-1.56,-0.73)
-0.56(-0.87,-0.26)	-0.35(-0.87,0.16)	0.42(0.07,0.77)	K	-0.44(-0.92,0.05)	0.32(-0.04,0.68)	-0.13(-0.59,0.32)	0.08(-0.53,0.67)	-0.72(-1.22,-0.24)
-0.12(-0.65,0.38)	0.09(-0.56,0.69)	0.86(0.33,1.35)	0.44(-0.05,0.92)	K+ SnF ₂	0.76(0.20,1.30)	0.31(-0.30,0.88)	0.52(-0.20,1.22)	-0.28(-0.94,0.33)
-0.88(-1.24,-0.53)	-0.67(-1.19,-0.16)	0.10(-0.24,0.44)	-0.32(-0.68,0.04)	-0.76(-1.30,-0.20)	PL	-0.45(-0.91,0)	-0.24(-0.86,0.37)	-1.05(-1.47,-0.64)
-0.43(-0.82,-0.05)	-0.22(-0.73,0.28)	0.55(0.24,0.85)	0.13(-0.32,0.59)	-0.31(-0.88,0.30)	0.45(0.00,0.91)	SnF ₂	0.21(-0.40,0.81)	-0.59(-1.10,-0.08)
-0.64(-1.17,-0.10)	-0.43(-1.09,0.24)	0.34(-0.19,0.89)	-0.08(-0.67,0.53)	-0.52(-1.22,0.20)	0.24(-0.37,0.86)	-0.21(-0.81,0.40)	Sr	-0.80(-1.47,-0.13)
0.16(-0.29,0.62)	0.38(-0.20,0.95)	1.15(0.73,1.56)	0.72(0.24,1.22)	0.28(-0.33,0.94)	1.05(0.64,1.47)	0.59(0.08,1.10)	0.80(0.13,1.47)	n-HA
(C) 8 weeks								
Ar	0.95(-0.21,2.10)	1.54(1.14,1.95)	0.77(0.33,1.19)	0.09(-0.65,0.82)	1.63(0.40,2.83)	0.76(0.13,1.40)	0.58(-0.14,1.31)	
-0.95(-2.10,0.21)	CSPS	0.59(-0.49,1.66)	-0.18(-1.35,0.99)	-0.87(-2.12,0.39)	0.68(-0.97,2.27)	-0.19(-1.39,0.99)	-0.38(-1.70,0.96)	
-1.54(-1.95,-1.14)	-0.59(-1.66,0.49)	F	-0.77(-1.20,-0.35)	-1.45(-2.11,-0.82)	0.09(-1.15,1.27)	-0.78(-1.27,-0.30)	-0.96(-1.72,-0.19)	
-0.77(-1.19,-0.33)	0.18(-0.99,1.35)	0.77(0.35,1.20)	K	-0.69(-1.37,0)	0.86(-0.29,1.98)	-0.01(-0.66,0.63)	-0.19(-0.99,0.63)	
-0.09(-0.82,0.65)	0.87(-0.39,2.12)	1.45(0.82,2.11)	0.69(0.1,1.37)	K+ SnF ₂	1.55(0.20,2.85)	0.67(-0.14,1.49)	0.50(-0.48,1.49)	
-1.63(-2.83,-0.40)	-0.68(-2.27,0.97)	-0.09(-1.27,1.15)	-0.86(-1.98,0.29)	-1.55(-2.85,-0.20)	PL	-0.87(-2.17,0.45)	-1.05(-2.43,0.35)	
-0.76(-1.40,-0.13)	0.19(-0.99,1.39)	0.78(0.30,1.27)	0.01(-0.63,0.66)	-0.67(-1.49,0.14)	0.87(-0.45,2.17)	SnF ₂	-0.18(-1.10,0.72)	
-0.58(-1.31,0.14)	0.38(-0.96,1.70)	0.96(0.19,1.72)	0.19(-0.63,0.99)	-0.50(-1.49,0.48)	1.05(-0.35,2.43)	0.18(-0.72,1.10)	Sr	

K:Potassium-containing toothpaste; Sr: Strontium-containing toothpaste; SnF₂: Stannous fluoride-containing toothpaste; CSPS: Calcium sodium phosphosilicate-containing toothpaste; Ar: Arginine-containing toothpaste; n-HA: Nano-hydroxyapatite-containing toothpaste; F:Fluoride-containing toothpaste; PL:Placebo.
Grey values signify Multiple-treatment comparisons for 2, 4, and 8 weeks desensitization effect based on network.

Table 4
Rank probabilities of each treatment in terms of 2 weeks (A), 4 weeks (B) and 8 weeks (C) desensitization effect based on network meta-analysis.

(A) 2 weeks									
Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9
Ar	0.00	0.00	0.00	0.04	0.42	0.48	0.06	0.00	0.00
CSPS	0.02	0.03	0.06	0.12	0.31	0.29	0.10	0.06	0.06
F	0.43	0.38	0.15	0.04	0.00	0.00	0.00	0.00	0.00
K	0.06	0.13	0.30	0.39	0.10	0.01	0.00	0.00	0.00
PL	0.23	0.28	0.29	0.15	0.03	0.01	0.00	0.00	0.00
SnF ₂	0.00	0.00	0.00	0.00	0.03	0.10	0.52	0.34	0.00
Sr	0.26	0.17	0.19	0.24	0.09	0.04	0.01	0.00	0.00
n-HA	0.00	0.00	0.00	0.01	0.02	0.07	0.30	0.60	0.00
(B) 4 weeks									
Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9
Ar	0.00	0.00	0.00	0.00	0.00	0.06	0.30	0.49	0.15
CSPS	0.00	0.00	0.02	0.06	0.14	0.39	0.25	0.10	0.05
F	0.66	0.30	0.04	0.00	0.00	0.00	0.00	0.00	0.00
K	0.00	0.03	0.30	0.42	0.20	0.05	0.01	0.00	0.00
K + SnF ₂	0.00	0.00	0.01	0.03	0.09	0.24	0.29	0.20	0.13
PL	0.26	0.52	0.19	0.03	0.01	0.00	0.00	0.00	0.00
SnF ₂	0.00	0.01	0.10	0.25	0.42	0.17	0.04	0.01	0.00
Sr	0.08	0.13	0.34	0.21	0.13	0.06	0.02	0.01	0.00
n-HA	0.00	0.00	0.00	0.00	0.01	0.03	0.09	0.19	0.67
(C) 8 weeks									
Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9
Ar	0.00	0.00	0.00	0.00	0.01	0.06	0.40	0.54	0.00
CSPS	0.08	0.14	0.31	0.14	0.13	0.12	0.05	0.03	0.00
F	0.38	0.54	0.08	0.00	0.00	0.00	0.00	0.00	0.00
K	0.00	0.01	0.19	0.35	0.31	0.13	0.01	0.00	0.00
K + SnF ₂	0.00	0.00	0.00	0.01	0.04	0.15	0.40	0.39	0.00
PL	0.54	0.25	0.12	0.04	0.03	0.02	0.01	0.00	0.00
SnF ₂	0.00	0.03	0.19	0.29	0.28	0.17	0.03	0.00	0.00
Sr	0.00	0.03	0.11	0.16	0.20	0.34	0.11	0.03	0.00

K:Potassium-containing toothpaste; Sr: Strontium-containing toothpaste; SnF₂: Stannous fluoride-containing toothpaste; CSPS: Calcium sodium phosphosilicate-containing toothpaste; Ar: Arginine-containing toothpaste; n-HA: Nano-hydroxyapatite-containing toothpaste; F:Fluoride-containing toothpaste; PL:Placebo.

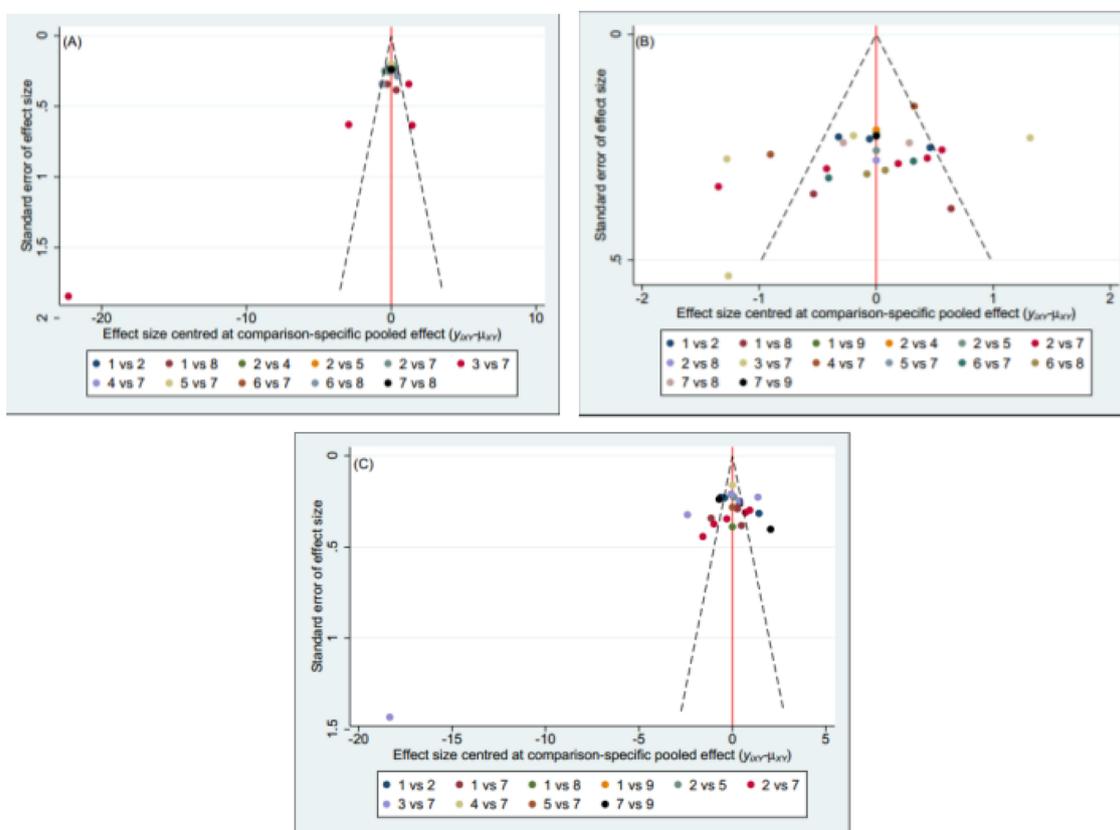


Fig. 4. Comparison-adjusted funnel plots for assessing publication bias and comparing the desensitization effect of desensitizing toothpastes or placebo at 2 weeks (A), 4 weeks (B) and 8 weeks (C). 1:(K) Potassium-containing toothpaste; 2:(Ar) Arginine-containing toothpaste; 3:(SnF₂) Stannous fluoride-containing toothpaste; 4: (CSPS) Calcium sodium phosphosilicate-containing toothpaste; 5:(Sr) Strontium-containing toothpaste; 6:(n-HA) Nano-hydroxyapatite-containing toothpaste; 7:(F) Fluoride-containing toothpaste; 8:(PL) Placebo; 9:(K + SnF₂): Potassium- and Stannous fluoride-containing toothpaste.

control at alleviating DH, similar to our results [20]. CSPS is a bioactive glass that can react with the components in saliva to produce hydroxycarbonate apatite (HCA), which blocks the dentin tubules [20].

F toothpastes are mainly used to prevent dental caries and have minimal desensitization effects [69,70]. Some studies use F toothpastes as the control group to evaluate the efficacy of desensitizing toothpastes [16,19]. Our results showed that F toothpastes have no significant desensitization effects. The reason of this result may be that the concentration of fluoride toothpaste in these studies is relatively low, which does not reflect its desensitization effect. In addition, a placebo effect was also observed in this study that similar to previous studies, indicating that a placebo group must be established in future experiments [71]. The main reason for the placebo effect is that the pain symptom of DH is a subjective feeling. Based on our results, one thing should be noted that the relative effects of various desensitizing toothpastes were not completely consistent at three different follow-up times, which also suggests that the effects of desensitizing toothpastes should be considered to vary by follow-up times and thus should not be generalized.

The studies that included in this network meta-analysis were similar and it makes sense to synthesize the information. However, there were individual differences in the study subjects, and it is difficult to apply similar treatments with respect to the dosage of desensitizing toothpastes. In addition, it is important to note that the studies included in this network meta-analysis were sponsored by companies, and some of the study authors were employees of the companies, which could bias the results.

DH is a subjective symptom and the degree of pain is mainly based on patient self-reports. Other factors may also influence the response of patients to treatment [72]. However, the scale currently used to measure DH only represents the patient's pain in response to stimulation

and does not include other oral or physical conditions that may influence the outcomes [73]. Therefore, a more comprehensive scale is required to evaluate the degree of pain of patients with DH.

To the best of our knowledge, this is the first network meta-analysis comparing the efficacy of desensitizing toothpastes and placebo against DH at 2, 4, and 8 weeks. However, there were several limitations to this study. First, the sample sizes of the included studies were insufficient to draw definitive conclusions with respect to certain of the desensitizing toothpastes. Second, our study was limited to articles published in English and those available in four major literature databases, which may have resulted in selection bias. Third, the effects of patient compliance during treatment were not mentioned in most of the included studies, which may have influenced the results. Fourth, there were differences in the concentrations of desensitizing toothpastes among the included studies, which may have affected the outcomes. Therefore, further high-quality, well-designed RCTs with larger sample sizes are required.

5. Conclusions

Based on our network meta-analysis, there was no significant difference in the desensitization effect among CSPS, K, and Sr containing toothpastes. In addition, there was no significant difference between F containing toothpastes and placebo, K containing toothpastes and placebo. Furthermore, a significant placebo effect on DH was found in this study, which support the importance of including a placebo group in future studies. Moreover, n-HA containing toothpastes may be the best desensitizing toothpaste for the treatment of DH, followed by Ar toothpastes. Therefore, n-HA containing toothpastes might be a recommended desensitizing toothpastes considering the treatment of DH.

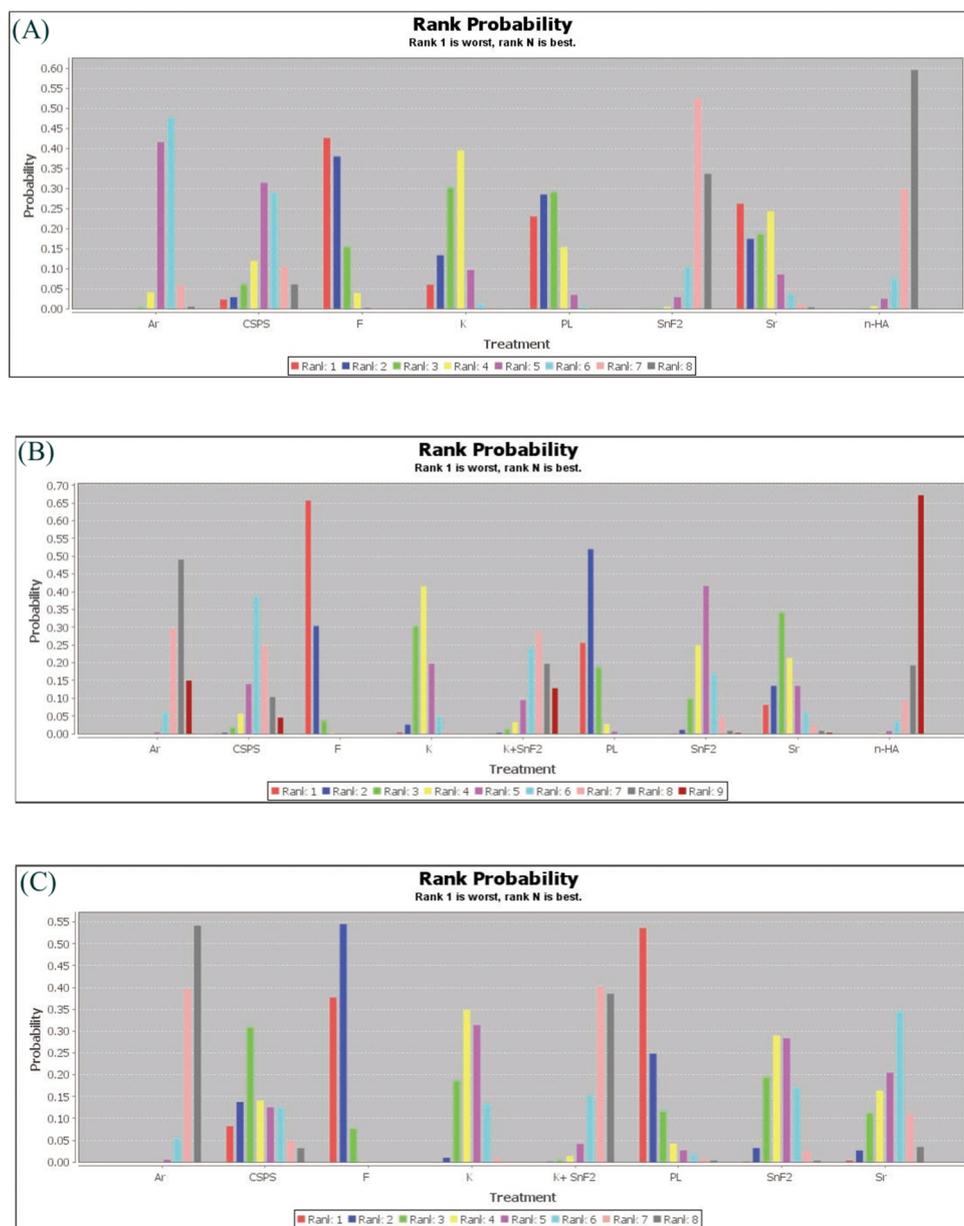


Fig. 5. Ranking probability of each treatment effect on DH at 2 weeks (A), 4 weeks (B) and 8 weeks (C). K: Potassium-containing toothpaste; Ar: Arginine-containing toothpaste; SnF₂: Stannous fluoride-containing toothpaste; CSPA: Calcium sodium phosphosilicate-containing toothpaste; Sr: Strontium-containing toothpaste; n-HA: Nano-hydroxyapatite-containing toothpaste; F: Fluoride-containing toothpaste; PL: Placebo; K + SnF₂: Potassium- and Stannous fluoride-containing toothpaste.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jdent.2019.07.008>.

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