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Review article

Effect of desensitizing toothpastes on dentine hypersensitivity: A systematic review and meta-analysis

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ABSTRACT

Objectives: To evaluate the desensitizing effect of toothpastes that contain ingredients that act against dentine hypersensitivity (DH) and to compare this effect with negative controls.

Sources: Five databases were searched to identify relevant articles published up to November 27, 2017.

Study selection: Randomized controlled trials (RCTs) comparing desensitizing toothpastes with a toothpastes without desensitizing component in adult patients that suffer from DH were included. The risk of bias was assessed according to the Cochrane guidelines, and the quality of the evidence was evaluated using the GRADE tool. Inverse variance random-effects meta-analyses of standardized mean differences (SMD) and 95% confidence intervals (CIs) were calculated using RevMan 5.3 software.

Data: 53 RCTs with 4796 patients were finally included in the meta-analysis. The toothpastes that contain active desensitization ingredients showed a better desensitizing effect on DH than the negative control, except the strontium- and amorphous calcium phosphate-containing toothpastes. The amorphous calcium phosphate–containing toothpaste had very low-quality evidence, the strontium, potassium and strontium, and potassium and stannous fluoride–containing toothpastes had low-quality evidence, and the other five toothpastes had moderate quality evidence.

Conclusions: Our result support the premise that toothpastes containing potassium, stannous fluoride, potassium and strontium, potassium and stannous fluoride, calcium sodium phosphosilicate, arginine, and nano-hydroxyapatite relieve the symptoms of DH, but does not advise the use of toothpastes that contain strontium and amorphous calcium phosphate. Furthermore, high-quality studies are needed to confirm our results. (PROSPERO CRD42018085639)

1. Introduction

Dentine hypersensitivity (DH) means that the tooth sensitive to external stimuli such as cold, heat, acids, sweet compounds, and other chemicals, friction, and biting hard and other mechanical actions, all of which cause tooth acid, tooth softening, pain, and other symptoms. DH is a rapid-onset sharp pain of short duration. It is not an independent disease, but a common symptom of many dental diseases [1].

DH pain has a negative effect on oral health-related quality of life [2,3]. At present, DH is an important oral health problem, and its prevention and diagnosis have attracted the attention of investigators [4]. There are many causes of DH, including wear, abrasion, and acid etching, which lead to enamel and cementum loss that can lead to dentine tubule exposure [5,6].

The pathogenesis of DH is not clear; currently, there are four theories for its cause: the nerve fiber conduction, dentine fiber conduction, dentine tubule lymphatic conduction, and hydrodynamic theories, the most widely accepted of which is the hydrodynamic theory. In the case of external temperature or mechanical stimulation, the fluid in the small tubules of the dentine can be rapidly shifted, which activates the nerve terminals in the interface of the pulp and dentine, thus causing pain [7–9].

At present, there are many methods for treating DH, such as sodium fluoride protective varnish, Gluma desensitizing agent, resin desensitization agent, laser desensitization, and desensitizing toothpaste [10,11]. Of these therapies, desensitizing toothpaste is convenient, noninvasive, and inexpensive [12,13].

On the market, there are two main types of sensitivity-resistant toothpaste: potassium-containing toothpaste, which has a depolarizing effect on nerve conduction, and toothpastes containing such compounds as strontium chloride, stannous fluoride, calcium sodium phosphosilicate, and arginine, which block the exposed dentine tubules and interrupt the external stimulation to achieve a desensitizing effect [14,15]. Considerable clinical research evidence supports the

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effectiveness of these toothpastes in the treatment of DH, but some investigators think that the quality of the findings is insufficient to reach a convincing conclusion [10,11,16].

Some systematic reviews using meta-analysis have questioned the efficacy of toothpastes containing potassium, strontium, stannous fluoride, arginine, or sodium calcium phosphosilicate for DH [17–20], but these studies only focused on the desensitization effect of a specific component of the toothpaste, and only used a few samples. Only one systematic review with meta-analysis questioned the efficacy of a wide variety of desensitizing toothpastes *versus* a negative control group for DH [21]. However, the conclusion of that study is inconsistent with previous studies and contains a limited number of samples. A more comprehensive and updated systematic analysis of desensitizing toothpastes is needed.

Therefore, we designed experiments to analyze all the up-to-date literature on desensitizing toothpastes to determine whether there is sufficient evidence to support their effect relative to negative controls on DH as measured by air-blast test scores.

2. Materials and methods

This systematic review and meta-analysis was conducted according to the recommendations and principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [22], registered in PROSPERO (CRD42018085639). Corresponding author did the systematic review for this article.

2.1. Search strategy

The first author searched for relevant studies in the five databases PubMed, EMBASE, Web of Science, CENTRAL (Cochrane Library), and the Chinese Biomedical Literature Database without any limitations from their inception up to November 27, 2017. The search strategy was to find all the English- and Chinese-language articles concerning the clinical efficacy of desensitizing toothpaste on DH.

We used the following combined text and MeSH terms: “toothpastes” and “dentine hypersensitivity”. For better readability, the complete search strategy is provided in the appendix. The first author supplemented the manual search by reviewing the reference lists of the related papers and review articles.

2.2. Study selection and data extraction

We regarded studies as eligible for inclusion if they were randomized, controlled clinical trials that had intervention and negative control groups in adults and evaluated the effect of desensitizing toothpaste on DH. The articles were chosen according to the selection criteria of PICO. (1) Patient: adult DH sufferers; those with post-operative interventions (bleaching, periodontal treatment, and restorative treatment) were excluded. (2) Intervention: desensitizing toothpaste; there were no limits on concentration, frequency, intervention period, or management method. (3) Comparator: negative control; such as a vehicle containing the same formula as the intervention, but without an active desensitization component. (4) Outcomes: air-blast test score [VAS (visual analogue scale) and SCASS (Schiff cold air sensitivity scale)]. (5) Studies: randomized controlled trials (RCTs); animal experiments, *in vitro* studies, unpublished materials, and review papers were excluded.

Two authors independently filtered the study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text assessment. Any disagreement between these authors was resolved by consulting a third colleague to reach an agreement. Studies selected for detailed analysis and data extraction were analyzed by two investigators in agreement, and disagreements were resolved by a third investigator.

From the studies included in the final analysis, we extracted the following data: study name (along with that of the first author), publication year, country, number of participants, details of intervention and control groups, follow-up period and check-time points, assessment methods, and the values of air-blast test scores in both the intervention and control groups. We extracted data from the final evaluation when a study had more than one follow-up period [23].

2.3. Risk of bias and assessment of the quality of evidence

Two independent reviewers assessed the quality of the individual studies, based on the Cochrane collaboration tool for assessing the risk of bias as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (e.g., similarity of groups at baseline). Differences were resolved through discussion and, if necessary, consultation with a third auditor. We estimated that a study had a low risk of bias when all areas were at low risk, that it was at moderate risk of bias when one or more areas were at risk of uncertain bias or non-bias, and that it was at high risk of bias when one or more areas were at high risk [24]. We assessed the quality of evidence for the main outcomes of selected studies by Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). This technique is used to determine the overall strength of each meta-analysis.

2.4. Statistical analyses

We assessed the effect of desensitizing toothpaste treatment in DH assessed by the air-blast test score at the final follow-up. Only when adequate similarity was found, between the participants' demographics, intervention, control, evaluation methods, and final follow-up was meta-analysis performed. We chose the standardized mean difference (SMD) with 95% confidence interval (CI) to evaluate differences in the effects of desensitizing toothpastes on DH [25]. In order to combine data from different scales, it has been suggested to divide the mean difference [26]. The standard deviation of each study was used to calculate SMDs that could be compared across studies. We used the I^2 test to evaluate the heterogeneity of the size of the study, and a value > 50% was considered to indicate moderate to high heterogeneity [27]. All the SMDs and 95% CIs were calculated on the basis of the random effects model. The possibility of publication bias was assessed from funnel-plots. Data were analyzed using RevMan 5.3 software (Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Study selection

After searching five databases and manually searching the relevant bibliographies, 809 articles were selected, from which 247 were removed due to duplication. After filtering the titles and abstracts, 414 articles did not meet the inclusion criteria and were removed. We reviewed the full texts of the remaining 148 articles, after which 95 were excluded according to the predetermined criteria (Fig. 1). In the final quantitative analysis, we included 53 randomized, controlled clinical trials.

3.2. Study characteristics

There were 4796 participants in the final 53 randomized controlled clinical trials, of which 2396 were intervention groups and 2400 were negative control groups (details in Table 1). The final included articles were published betwen 1994 and 2017. The countries where these studies were conducted were as follows: the USA (n = 16) [14,28–42], China (n = 9) [43–51], the UK (n = 9) [52–60], India (n = 8) [61–68], Italy (n = 3) [69–71], Canada (n = 2) [72,73], Japan (n = 1) [74],

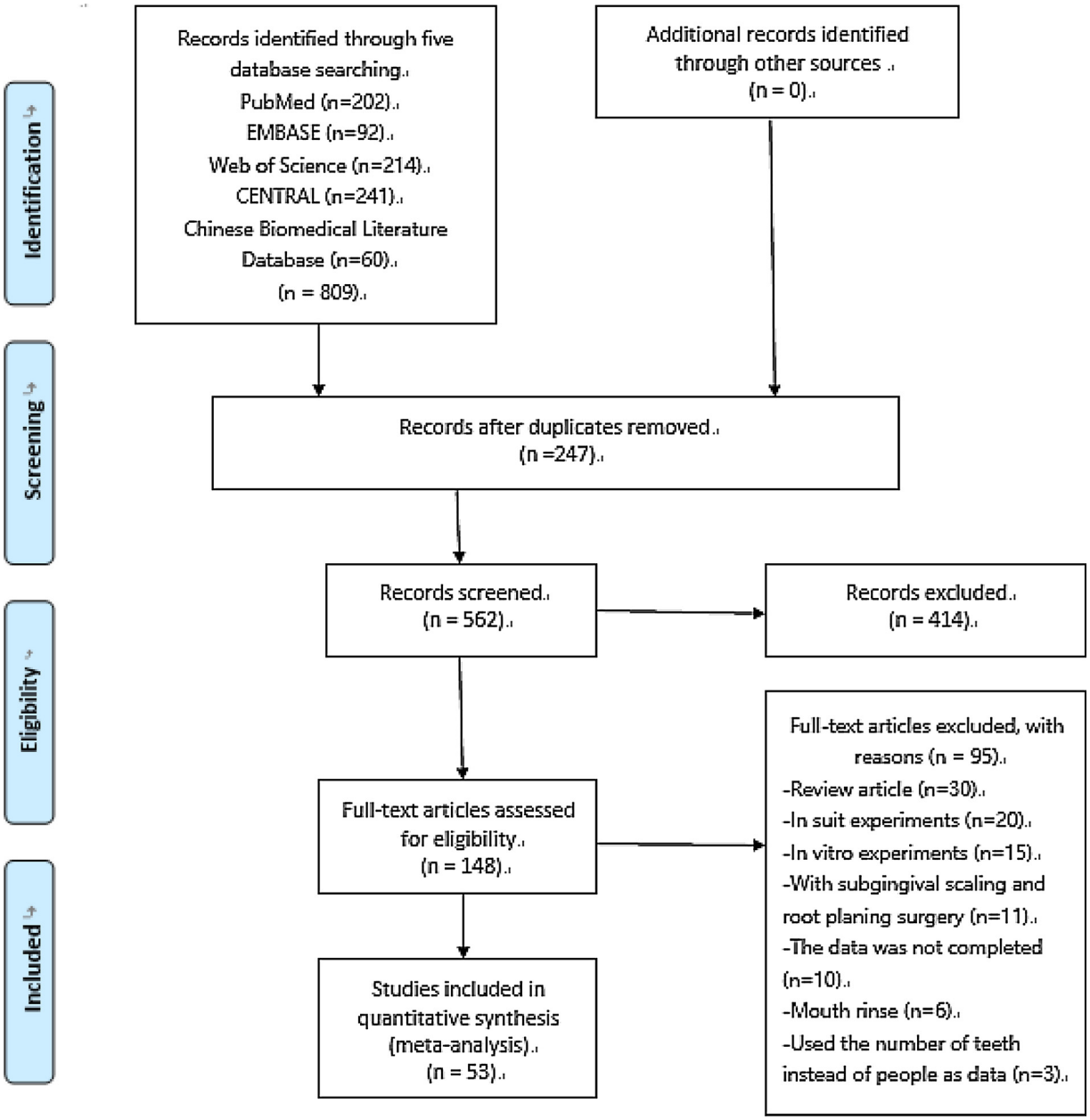

Fig. 1. Flow diagram of identification of relevant trials.

Thailand (n = 1) [75], Croatia (n = 1) [76], Austria *(n = 1)* [77], Dominica (n = 1) [78], and Brazil *(n = 1)* [79]. Their follow-up times ranged from 3 days to 12 weeks. Among the 53 studies, 18 reported the effects of potassium-containing, 13 of arginine-containing, 9 of stannous fluoride-containing, 7 of strontium-containing, 6 of calcium sodium phosphosilicate-containing, 3 of potassium- and strontium-containing or potassium and stannous fluoride-containing, 2 of nano-hydroxyapatite-containing and amorphous calcium phosphate-containing toothpastes. DH was quantified using different scales (VAS [0–10], VAS [0–100], SCASS [0–3]), SCASS [0–3] being the most commonly used.

3.3. Risk of bias assessment and evidence grading

The assessment of risk of bias revealed that 3 studies had a low risk, 6 had a high risk, and the remaining 44 had a moderate risk (Fig. 2). The quality of evidence of the included studies showed amorphous calcium phosphate-containing toothpaste to have a very low quality; strontium, potassium and strontium, and potassium and stannous fluoride-containing toothpastes to have a low quality, and the other five toothpastes to have a moderate quality (Table 2 and Fig. 3).

3.4. Result of individual studies and synthesis of results

The results showed that all the toothpastes containing active desensitization ingredients, except for those containing strontium and amorphous calcium phosphate, had a better desensitizing effect on DH than negative controls (Fig. 4).

4. Discussion

The literature shows that DH has a profound effect on the quality of life of patients [2,3]. Currently, many desensitizing toothpastes are available on the market to relieve this condition. Most of these products either work on the basis of blockage of the exposed dentine tubules or the desensitization of the pulp nerve. However, some researchers have

Table 1
The characteristics of randomized controlled clinical trials included in the final analysis (n = 53).

First author of study	Year	Country	Intervention	Final follow-up period	Pain score type
Potassium-containing toothpaste					
Nagata et al. [74]	1994	Japan	5% potassium nitrate	12 weeks	VRS (0–3)
Schiff et al. [28]	1994	USA	5% potassium nitrate	12weeks	SCASS(0–3)
Silverman et al. [29]	1996	USA	5% potassium nitrate	8weeks	VAS(0–100)
Gillam et al. [52]	1996	UK	3.75% potassium chloride	6weeks	VAS(0–10)
West et al. [53]	1997	UK	5% potassium nitrate	6weeks	VAS(0–10)
Schiff et al. [30]	1998	USA	5% potassium nitrate	8weeks	SCASS(0–3)
Wara et al. [75]	2005	Thailand	5% potassium nitrate	12weeks	VAS(0–10)
Salian et al. [61]	2010	India	5% potassium nitrate	4weeks	VAS(0–10)
Jiang et al. [50]	2010	China	5.53% potassium citrate	4weeks	VAS(0–100)
Zhang et al. [43]	2010	China	3.8% potassium chloride	8weeks	VAS(0–10)
Pradeep et al. [62]	2010	India	5% potassium nitrate	6weeks	VAS(0–10)
Zhuang et al. [45]	2011	China	5% potassium nitrate	4weeks	VAS(0–100)
Liang et al. [44]	2011	China	5.53% potassium citrate	8weeks	VAS(0–100)
Pradeep et al. [63]	2012	India	5% potassium nitrate	6weeks	VAS(0–10)
Elias et al. [31]	2013	USA	5% potassium nitrate	8weeks	SCASS(0–3)
Kakar et al. [64]	2013	India	5% potassium nitrate	8weeks	SCASS(0–3)
Katanec et al. [76]	2016	Croatia	5% potassium nitrate	4weeks	VAS(0–10)
Kumari et al. [68]	2016	India	5% potassium nitrate	12weeks	VAS(0–10)
Strontium-containing toothpaste					
Pearce et al. [54]	1994	UK	8% strontium acetate	12 weeks	VAS(0–100)
Silverman et al. [29]	1996	USA	10% strontium chloride	8 weeks	VAS(0–100)
Gillam et al. [52]	1996	UK	8% strontium acetate	6 weeks	VAS(0–10)
West et al. [53]	1997	UK	8% strontium acetate	6 weeks	VAS(0–10)
Mason et al. [55]	2010	UK	8% strontium acetate	3 days	SCASS(0–3)
Li et al. [32]	2011	USA	8% strontium acetate	7 days	SCASS(0–3)
Docimo et al. [69]	2011	Italy	8% strontium acetate	8 weeks	SCASS(0–3)
Stannous fluoride-containing toothpaste					
Schiff et al. [14]	2005	USA	0.454% stannous fluoride	8 weeks	SCASS(0–3)
Schiff et al. [33]	2006	USA	0.454% stannous fluoride	8 weeks	SCASS(0–3)
Day et al. [56]	2010	UK	0.454% stannous fluoride	4 weeks	VRS(0–3)
Chaknis et al. [34]	2011	USA	0.454% stannous fluoride	8 weeks	SCASS(0–3)
He et al. [35]	2011	USA	0.454% stannous fluoride	2 weeks	SCASS(0–3)
Parkinson et al. [57]	2013	UK	0.454% stannous fluoride	8 weeks	SCASS(0–3)
He & Sharma et al. [36]	2014	USA	0.454% stannous fluoride	8 weeks	SCASS(0–3)
He & Miner et al. [37]	2014	USA	0.454% stannous fluoride	2 weeks	SCASS(0–3)
Parkinson et al. [58]	2015	UK	0.454% stannous fluoride	8 weeks	SCASS(0–3)
Potassium & Strontium-containing toothpaste					
Liu et al. [49]	2012	China	5% potassium nitrate + 2% strontium chloride	3 days	SCASS(0–3)
Antoniazzi et al. [79]	2014	Brazil	5% potassium oxalate + 10% strontium chloride	30 days	VAS(0–100)
Zhang et al. [51]	2017	China	potassium phosphate + strontium chloride	8 weeks	SCASS(0–3)
Potassium & Stannous fluoride-containing toothpaste					
Sowinski et al. [38]	2000	USA	5% potassium nitrate + 0.454% stannous fluoride	8 weeks	SCASS(0–3)
Schiff et al. [39]	2000	USA	5% potassium nitrate + 0.454% stannous fluoride	8 weeks	SCASS(0–3)
Sowinski et al. [40]	2001	USA	5% potassium nitrate + 0.59% stannous fluoride	8 weeks	SCASS(0–3)
Calcium sodium phosphosilicate-containing toothpaste					
Du et al. [46]	2008	China	5% calcium sodium phosphosilicate	6 weeks	VAS(0–10)
Salian et al. [61]	2010	India	5% calcium sodium phosphosilicate	4 weeks	VAS(0–10)
Litkowski et al. [41]	2010	USA	7.5% calcium sodium phosphosilicate	8 weeks	VAS(0–100)
Pradeep et al. [62]	2010	India	5% calcium sodium phosphosilicate	6 weeks	VAS(0–10)
Pradeep et al. [63]	2012	India	5% calcium sodium phosphosilicate	6 weeks	VAS(0–10)
Hall et al. [59]	2017	UK	5% calcium sodium phosphosilicate	11 weeks	SCASS(0–3)
Arginine-containing toothpaste					
Ayad et al. [73]	2009	Canada	8% arginine + calcium carbonate	3 days	SCASS(0–3)
Nathoo et al. [42]	2009	USA	8% arginine + calcium carbonate	3 days	SCASS(0–3)
Fu et al. [47]	2010	China	8% arginine + calcium carbonate	3 days	SCASS(0–3)
Que et al. [48]	2010	China	8% arginine + calcium carbonate	8 weeks	SCASS(0–3)
Docimo et al. [69]	2011	Italy	8% arginine + calcium carbonate	8 weeks	SCASS(0–3)
Li et al. [32]	2011	USA	8% arginine + calcium carbonate	7 days	SCASS(0–3)
Kakar et al. [65]	2012	India	8% arginine + calcium carbonate	8 weeks	SCASS(0–3)
Hegde et al. [66]	2013	India	8% arginine + calcium carbonate	8 weeks	SCASS(0–3)
Elias et al. [31]	2013	USA	8% arginine + calcium carbonate	8 weeks	SCASS(0–3)
Collins et al. [78]	2013	Domonica	8% arginine + calcium carbonate	immediately	SCASS(0–3)
Kapferer et al. [77]	2013	Austria	8% arginine + calcium carbonate	12 weeks	SCASS(0–3)
Kakar & Kohli et al. [67]	2013	India	8% arginine + calcium carbonate	8 weeks	SCASS(0–3)
Hall et al. [59]	2017	UK	8% arginine + calcium carbonate	11 weeks	SCASS(0–3)
Nano-hydroxyapatite-containing toothpaste					
Vano et al. [70]	2014	Italy	15% nano-hydroxyapatite	4 weeks	SCASS(0–3)
Vano et al. [71]	2017	Italy	2% nano-hydroxyapatite	4 weeks	SCASS(0–3)
Amorphous calcium phosphate-containing toothpaste					

(*continued on next page*)

Table 1 (*continued*)

First author of study	Year	Country	Intervention	Final follow-up period	Pain score type
Yates et al. [60]	1998	UK	amorphous calcium phosphate	12 weeks	VAS(0–10)
Ghassemi et al. [72]	2009	Canada	amorphous calcium phosphate	8 weeks	SCASS(0–3)

questioned the evidence for their efficacy over the years [11,80].

A number of problems are associated with evaluating the quality of these desensitizing toothpastes, such as the subjectivity of pain, because the experience of pain varies from person to person. In the face of the same stimulus, one person may feel pain and another may not. Placebo effects also produce false positives or false negatives for desensitizing toothpastes. And different evaluation methods have been adopted, such as cold air, water, thermal or tactile stimuli, and subjective evaluation [53,81,82]. In this study, we chose the air-blast test to reduce the effects of the above factors. In addition is the question of whether these study populations really represent the individual situation of a general DH patient. Therefore, it is very important to select participants according to the experimental requirements.

In the clinical control trials of DH, the choice of an appropriate negative control was a troublesome problem. We acknowledge that it may be too strict to consider only placebo as the control when trying to collect enough study data. Our basic principle was to determine whether the active ingredient in the desensitizing toothpaste relieves DH, which is the basis for the manufacturer's claim of efficacy. Therefore, we includes some valid negative controls in this study, such as the use of commercial low-fluoride, anti-caries toothpaste without the major active desensitization component, which may provide a better test of whether toothpaste containing the active ingredient alleviates DH.

Based on the results of this meta-analysis, potassium-, stannous fluoride–, potassium and strontium–, potassium and stannous fluoride–, calcium sodium phosphosilicate–, arginine-, and nano-hydroxyapatite-containing desensitizing toothpastes are more effective than negative control group in relieving DH, but there was no significant difference in the desensitizing effect on DH between the intervention group that was treated with strontium- or amorphous calcium phosphate–containing desensitizing toothpaste and the negative control group.

Desensitizing toothpastes that contain potassium prevent conduction in the pulp nerve, rather than by blocking the dentine tubules. [83] Previous studies have shown that potassium has a soothing effect on DH, and the Food and Drug Administration of the USA has also confirmed that potassium nitrate is a safe and effective treatment for DH [21,84,85]. Our results also concluded that potassium-containing desensitizing toothpastes relieve DH.

In theory, toothpastes containing strontium works by blocking the exposed dentine tubules and strontium acetate and fluoride especially have good compatibility [86]. However, the research results and our results do not support evidence of a desensitizing function of toothpaste containing strontium alone [21,80], but that toothpaste containing a potassium and strontium mixture does desensitize DH. Based on the results for potassium or strontium toothpaste alone, we speculate that the reason for the desensitizing effect of the potassium and strontium mixture was from the potassium component.

Stannous fluoride-containing toothpaste generates a variety of soluble mineral ions that form an insoluble precipitate, which blocks the open dentine tubules to prevent the entry of stimuli and have a desensitizing effect on DH [87]. From our meta-analysis, we suggest that using toothpaste containing stannous fluoride or stannous fluoride and potassium can relieve the symptoms of DH.

Toothpaste containing calcium sodium phosphosilicate, through its decomposition into calcium and phosphorous ions, and their reaction with saliva components to form a protective layer of hydroxyapatite, physically occludes the exposed dentine tubules, contributing to DH desensitization [19]. In addition, calcium sodium phosphosilicate attracts strongly with the collagen in dentine [88,89]. Nano-hydroxyapatite is a bioactive substance with components and structures resembling teeth [90,91]. Toothpaste containing nano-hydroxyapatite also blocks open dentine tubules to relieve DH [92]. *In vitro* studies have shown that the use of toothpaste containing amorphous calcium phosphate can cause precipitation on the surface of the dentine and in the tubules [93]. Therefore, such toothpaste can also blocked open dentine tubules to relieve DH. Our results shows that both calcium sodium phosphosilicate- and nano-hydroxyapatite-containing toothpastes can relieve DH, but amorphous calcium phosphate-containing toothpaste cannot. In the subgroup analysis of amorphous calcium phosphate-containing toothpaste, the sample size is small in that only have two randomized controlled trials were found, so we reserve our opinion on the results, and hope to have more research on this subject to reach a more accurate conclusion in the future.

Early studies showed that a combination of arginine and calcium carbonate are deposited on the surface of exposed dentine and physically block and close the open tubules to produce desensitization of DH [94]. Our results also support the conclusion that arginine-containing toothpaste can relieve the symptoms of DH.

In studies evaluating the effects of desensitizing toothpastes on DH, air-blast, thermal, tactile, and subjective evaluations have been used. The differences in the evaluation methods may lead to differences in the reproducibility of studies, resulting in high heterogeneity [95]. Several studies showed that a placebo group can also provide significant improvement in relief of DH, and any meaningful differences between the experimental and placebo groups may be masked [53]. The cause of this phenomenon may be the use of different evaluation methods;

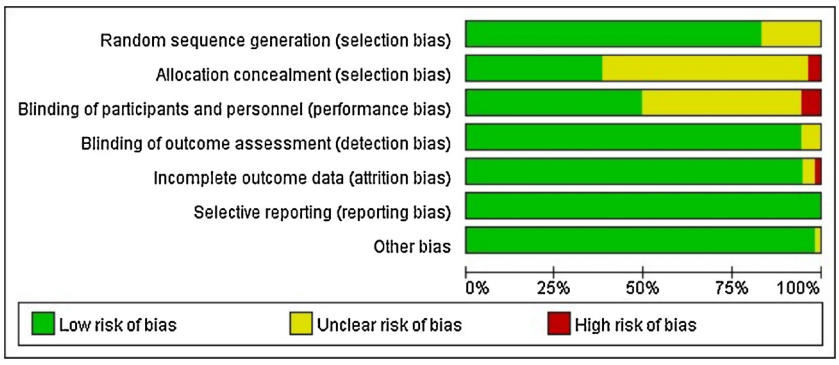

Fig. 2. The risk of bias summary of the final included trials.

Table 2
The GRADE summary of randomized controlled clinical trials included in the final analysis (n = 53).

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	toothpaste	placebo	Absolute (95% CI)		
desensitizing toothpaste − Potassium-containing toothpaste											
18	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	580	577	– SMD **1.27 lower** (1.77 lower to 0.77 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
desensitizing toothpaste − Strontium-containing toothpaste											
7	randomized trials	not serious	serious [b]	not serious	not serious	publication bias strongly suspected [a]	296	299	– SMD **0.35 higher** (0.13 lower to 0.83 higher)	⨁⨁◯◯ LOW	CRITICAL
desensitizing toothpaste − Stannous fluoride-containing toothpaste											
9	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	417	415	– SMD **2.31 lower** (3.39 lower to 1.23 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
desensitizing toothpaste − Potassium & Strontium-containing toothpaste											
3	randomized trials	not serious	not serious	not serious	serious [c]	publication bias strongly suspected [a]	108	112	– SMD **2.42 lower** (4.6 lower to 0.23 lower)	⨁⨁◯◯ LOW	CRITICAL
desensitizing toothpaste − Potassium & Stannous fluoride containing toothpaste											
3	randomized trials	not serious	not serious	not serious	serious [c]	publication bias strongly suspected [a]	116	116	– SMD **2.5 lower** (4.1 lower to 0.91 lower)	⨁⨁◯◯ LOW	CRITICAL
desensitizing toothpaste − Calcium sodium phosphosilicate-containing toothpaste											
6	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	174	174	– SMD **2.01 lower** (3.06 lower to 0.95 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
desensitizing toothpaste − Arginine-containing toothpaste											
13	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	510	515	– SMD **2.52 lower** (3.2 lower to 1.84 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
desensitizing toothpaste − Nano-hydroxyapatite-containing toothpaste											
2	randomized trials	not serious	not serious	not serious	serious [c]	none	70	70	– SMD **2.19 lower** (2.61 lower to 1.76 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
desensitizing toothpaste − Amorphous calcium phosphate-containing toothpaste											
2	randomized trials	not serious	serious [b]	not serious	serious [c]	publication bias strongly suspected [a]	125	122	– SMD **0.54 lower** (1.4 lower to 0.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **SMD:** Standardised mean difference.

Explanations

a. Many studies are funded by companies.

b. The results of each experiment in the group were inconsistent.

c. The sample size of the study is small and the number of participants is small.

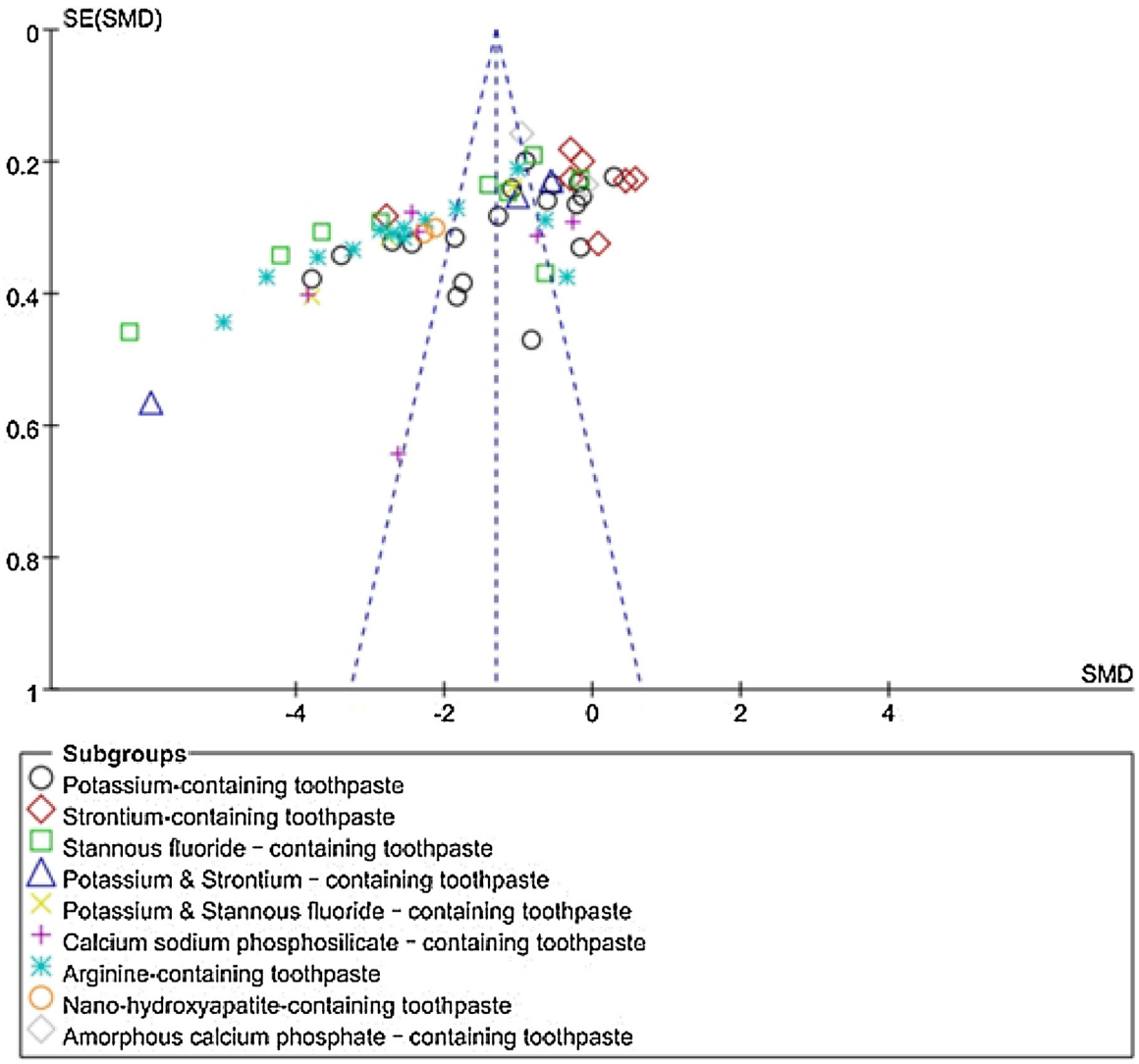

Fig. 3. Funnel-plots of the final included trials.

therefore, the evaluation method for comparisons needs to be standardized. In this study, we chose the air-blast test because it is the most commonly-used method of evaluating DH, and it is reliable [96,97]. In addition, it is closer to the practical situation, because DH patients are exposed to cold stimuli (cold drinks, food, and air) more frequently than to other stimuli.

Because the pain response of DH is an individual and subjective symptom, an objective evaluation method may not be feasible. Currently, a variety of pain assessment scales are used to evaluate the degree of pain of DH, such as the VAS, the VRS, and the SCASS, but there is no “gold standard”. The SCASS is the most frequently used scale; patients respond to the pain induced by stimulation, with a range from 0 to 3. The VRS is also a scale that responds to pain through the patient, with 0 to 3 representing varying degrees of pain. Some researchers prefer to use the VAS, in which the patient marks his or her pain on a straight line 10 or 100 cm long, from pain-free to unbearably painful. Although the VAS method gives more accurate results, it is more complicated to use and has higher error rates, especially in older patients [98]. We used the SMD to combine data from different scales and make comparisons between studies.

The final follow-up time of DH clinical trials depends on whether the short-term or long-term efficacy of the desensitizing toothpastes are assessed. In principle, the duration of DH clinical trials should be sufficient to build up the maximum effect of the desensitizing toothpaste while minimizing the placebo effect. In the 53 randomized controlled clinical trials selected, the final follow-up times were quite different, from immediately to 12 weeks, 8 weeks being the common (nearly half of the total). A previous study also showed that 8 weeks is a suitable duration for most DH clinical trials [99]. However, we should also be aware that when designing DH clinical trials, the duration required to achieve the maximum desensitizing effect may vary for different products [100].

In the 53 studies selected, most were entirely or partly sponsored by companies, and some of the researchers were even employees of these companies. These factors have a major impact on the results and the publication of articles. Several studies have shown that company-sponsored trials are more likely to deliver results that benefit the company, whereas adverse outcomes might not be published [101–103]. This publication bias was evident from our funnel-plots (Fig. 3).

Last, our study has several limitations. First, while the toothpastes containing potassium, stannous fluoride, or argininep rovided > 9 randomized controlled clinical trials, this number for the other desensitizing toothpastes was small ($n < 9$), which may have contributed to the low power of this meta-analysis. Therefore, it was necessary treat the results for these toothpastes with caution. Second, because the search was limited to articles published in Chinese and English, and was limited to the five major literature databases, there may have been

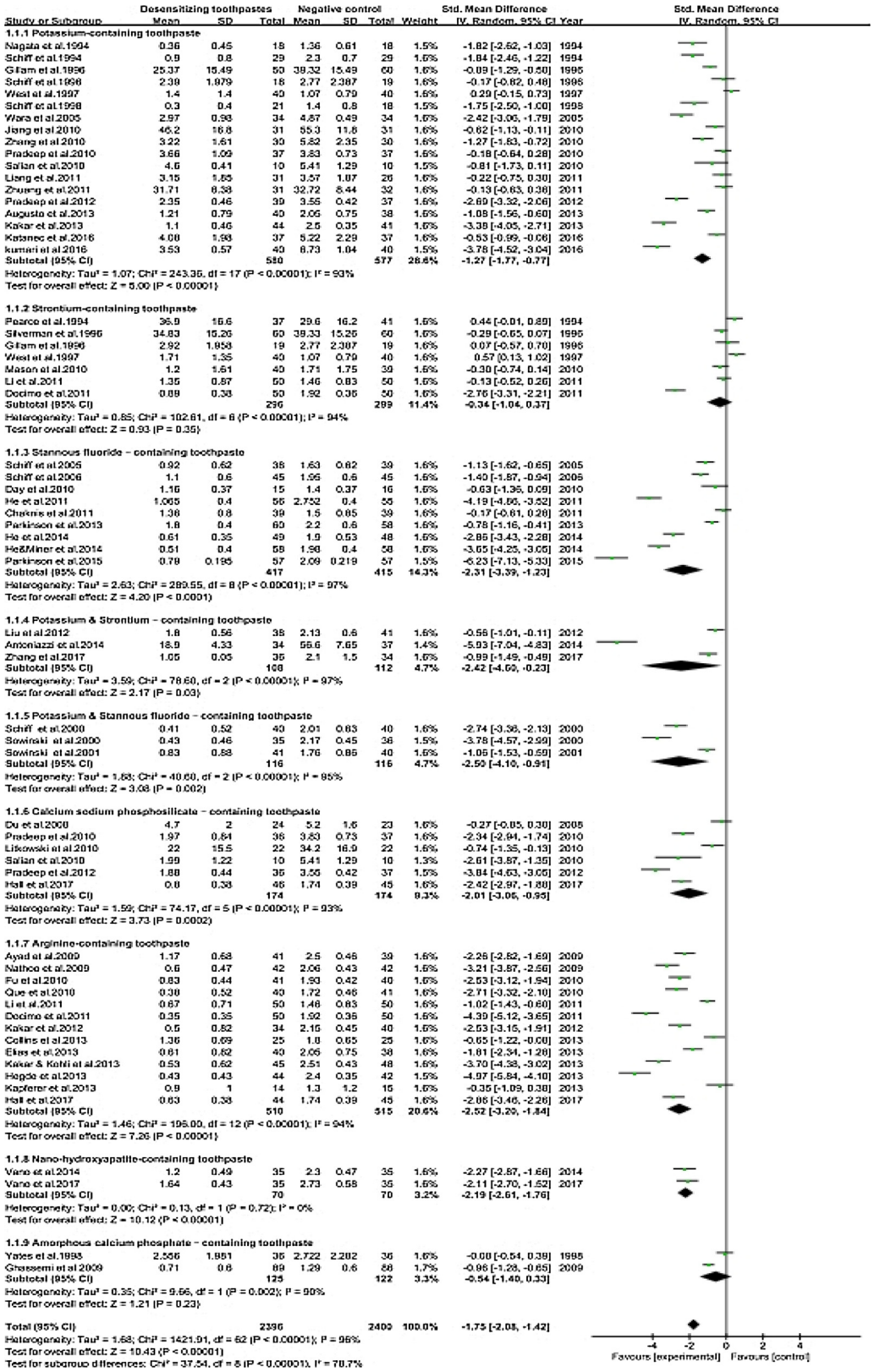

Fig. 4. Forest plot of the effect of desensitizing toothpaste on dentin hypersensitivity.

selection bias. To overcome these problems, additional high-quality, well-designed clinical trials with larger sample sizes are required.

5. Conclusions

Within the limitations of our meta-analysis of 53 randomized, controlled clinical trials, the results indicate that desensitizing toothpastes containing potassium, stannous fluoride, potassium and

strontium, potassium and stannous fluoride, calcium sodium phosphosilicate, arginine, and nano-hydroxyapatite are effective in relieving DH compared to negative controls, but do not suggest that those containing strontium or amorphous calcium phosphate should be used for DH. In future research, more high-quality DH clinical trials with non-company funding should be performed to obtain more accurate conclusions on the effects of desensitizing toothpastes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jdent.2018.05.012.

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