Journal of Dentistry 82 (2019) 11–21

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent

Review article

Clinical efficacy of nano-hydroxyapatite in dentin hypersensitivity: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Dentin hypersensitivity
Desensitizing agents
Meta-analysis
Clinical trials

ABSTRACT

Objectives: To evaluate the desensitizing effect of nano-hydroxyapatite (n-HAP) on dentine hypersensitivity (DH).

Sources: Seven electronic databases were searched on April 27, 2018.

Study selection: Randomized clinical trials (RCTs) were included based on the PICO strategy: Participants – Humans with DH; Intervention – n-HAP-containing desensitizing; Comparison –n-HAP-free treatments or placebo/negative control; and Outcomes – relief of DH. The risk of bias was classified by the Cochrane guidelines. Five meta-analyses were performed to evaluate the efficacy of n-HAP with regard to pain assessment stimuli (primary outcome); comparison of n-HAP with other treatments or placebo/negative control, and effectiveness of at-home and in-office n-HAP use (secondary outcomes). The quality of the evidence was evaluated using the GRADE.

Data: Six RCTs with 4 weeks of follow-up were included in the meta-analysis. For the primary outcome, n-HAP showed a better desensitizing effect for evaporative stimuli (SMD -1.09 [-1.24, -0.94], $p < 0.00001$) and tactile stimuli (SMD -0.93 [-1.42, -0.43]) than other treatments ($p = 0.0002$). However, there was no difference between n-HAP and other treatments for the cold stimuli (SMD -0.17 [-0.81, 0.48], $p = 0.61$). In an overall analysis, n-HAP-containing treatment showing the most significant desensitizing effect (SMD -0.93 [-1.19, -0.68], $p < 0.00001$) with a high quality of evidence for pooled results. In the secondary outcomes, n-HAP showed the best effect in the overall analysis ($p < 0.05$) with moderate quality evidence.

Conclusions: The n-HAP-containing treatment showed better clinical performance than other treatments for DH relief. However, long-term follow-up RCTs are required in the future before definitive recommendations can be made.

Clinical significance: Dentin hypersensitivity is a common global condition and its multifactorial etiology has led to the development of several treatments. The n-HAP-containing treatment showed greater DH relief when compared to other desensitizing agents, placebo or negative control.

1. Introduction

Dentin hypersensitivity (DH) has been defined as a “short, sharp pain arising from exposed dentin in response to stimuli typically thermal, evaporative, tactile, osmotic or chemical and which cannot be ascribed to any other form of dental defect or pathology” [1]. This clinical condition can have a negative effect on the individual’s oral health-related quality of life (OHRQoL) [2]. A recent systematic review by Douglas-de-Oliveira et al. [3] indicated that reducing DH is related to improvement in OHRQoL.

Several theories have been proposed in order to explain the biological mechanism of DH [4–6], with the hydrodynamic theory being the most widely accepted [7,8]. Brännström and his co-workers published over 20 years’ worth of studies on both human and animal models supporting this theory, which has remained the most popular explanation to date [9–11]. Their convincing explanation shows that when external stimuli occur, 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 [9]. The ideal DH treatment should thus occlude the dentinal tubules, which would

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https://doi.org/10.1016/j.jdent.2018.12.014
Received 4 October 2018; Received in revised form 20 December 2018; Accepted 27 December 2018

reduce the movement of the intratubular fluids through mechanical principles [12].

Recently, nano-hydroxyapatite (n-HAp)-based desensitizing agents have shown promising clinical improvements in DH [13,14]. However, although this bioactive agent is considered one of the most biocompatible materials, being widely applied in medicine and dentistry as a bone substitute and for tooth remineralization [15], some clinical trials have shown an equivalent result between n-HAP and other desensitizing agents [16–18]. For this reason, there is no consensus in the literature about the effectiveness of n-HAP in the treatment of DH.

Some systematic reviews and meta-analyses have examined the efficacy of toothpastes containing various desensitizing agents for the relief of DH [19–22], but the gold standard agent for DH relief has not yet been determined. Recently, a systematic review with a meta-analysis evaluated the desensitizing effect of toothpastes contain various desensitizing agents (DA), including n-HAP, in comparison with negative controls [23]. However, this meta-analysis investigated only n-HAP-containing toothpastes, excluding the use of in-office treatments. Furthermore, the effect of n-HAP has not been specifically assessed and only two studies evaluating n-HAP were included in this study. Therefore, a more comprehensive and updated systematic analysis of n-HAP-containing desensitizing agents is needed to evaluate their effect in different forms of presentation.

To the best of the authors' knowledge, to date, no systematic review or meta-analysis has been undertaken on this important issue. Thus, the objective of the present study was to evaluate, through a systematic review of the literature and meta-analysis, the clinical efficacy of n-HAP for the relief of DH. The null hypothesis adopted in this study is that there is no significant difference in the reduction of DH treated with n-HAP, other desensitizing agents, placebo or negative control.

2. Materials and methods

2.1. Protocol and registration

The study protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42018085801), and followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [24].

2.2. Search strategy

Seven databases, namely PubMed, Web of Science, CENTRAL (The Cochrane Library), Scopus, LILACS, ClinicalTrials.gov, and OpenGrey were searched on April 27, 2018. The MeSH terms and keywords were selected and detailed search strategies were adapted for each database (Table 1). The search strategy aimed to identify all relevant articles published without language or date restriction. A supplemental manual search was conducted by reviewing the reference lists of the related papers and review articles.

2.3. Eligibility criteria and study selection process

The inclusion criteria were based on the PICO strategy [25]. Two researchers (CMA and BLFP) independently screened the titles and abstracts of the studies identified in the electronic databases. Articles appearing in more than one database were considered only once. Any disagreement between the researchers was resolved *via* discussion and consensus. If necessary, a third researcher was consulted (CMS). For studies appearing to meet the inclusion criteria or for which there were insufficient data in the title and abstract to make a clear decision, the full-text article was obtained and reviewed. Only studies meeting the following criteria were included:

- Participants: Humans with DH not associated with post-bleaching hypersensitivity.
- Intervention: n-HAP-containing desensitizing formulations, in topical form and any modality.
- Comparison: n-HAP-free treatments or placebo/negative control (glycerin and toothpaste without fluoride respectively).
- Outcomes: relief of DH pain in response to routine activities or to cold, thermal, tactile or evaporative stimuli.
- Studies: Randomized controlled trials (RCTs).

A manual search was performed on the bibliographic references of the RCTs that met all the inclusion criteria and were considered potentially relevant for this review. Two researchers (CMA and BLFP) independently screened all references to these RCTs.

2.4. Risk of bias

The full-texts that satisfied the eligibility criteria were thoroughly evaluated by two researchers independently (CMA and BLFP) for methodological risk of bias according to the Cochrane Collaboration common scheme for bias: selection, performance, attrition, detection, and reporting bias [26]. Disagreements were resolved *via* discussion, and a third researcher was consulted if necessary (CMS).

The overall risk of bias was classified as low, unclear, or high, and the researchers defined six key domains for the Risk of Bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. When the study was judged as "unclear" in one key domain, the authors of the article in question were contacted for additional information to make a definitive judgment of "low" or "high". Two criteria were considered for classification of "other bias": sample calculation and location and date of the study.

2.5. Data synthesis

Data were extracted from the eligible studies. Information on author, year of publication, number of patients and age of the clinical trial participants, study design, manufacturer and n-HAP concentration in the evaluated products, statistical analysis, follow-up time and results were tabulated.

2.6. Summary measures and synthesis of the results

The study data were analysed using RevMan software (Review Manager v. 5.3, The Cochrane Collaboration; Copenhagen, Denmark) to evaluate the efficacy of n-HAP for the treatment of DH. This desensitizing agent (n-HAP) was compared to other treatments, placebo or control (n-HAP-free). Five meta-analyses were performed:

- The first meta-analysis evaluated the efficacy of n-HAP-containing treatment for relief of DH, the main outcome of this systematic review. This analysis was subgrouped according to the stimuli applied and analyzed: evaporative, tactile and cold.

As a secondary outcome, in an attempt to evaluate the influence of some variables on the outcomes, the second, third and fourth meta-analyses were performed.

- The second analysis evaluated the influence of the comparison group on the efficacy of n-HAP-containing treatment in relation to evaporative stimuli. Two subgroups were created: one including studies that compared n-HAP-containing treatment *versus* other DA-containing treatments, and another subgroup including studies that compared n-HAP-containing treatment *versus* DA-free products (placebo or negative control).
- The third analysis evaluated the influence of pain scale used on the efficacy of n-HAP-containing treatment in relation to evaporative stimuli. Two subgroups were created: one including studies that

Table 1
Search strategy in different databases.

Database	Search strategy
Cochrane	*#1MeSH descriptor: [Dentin Sensitivity] explode all trees* *#2dentin* sensitivit* or dentin* hypersensitivit** *#3#1 or #2* *#4Dental Hypersensitivit** *#5#3 or #4* *#6MeSH descriptor: [Dentin Desensitizing Agents] explode all trees* *#7dentin* desensitizing agent* or desensitizing agent** *#8#6 or #7* *#9MeSH descriptor: [Hydroxyapatites] explode all trees* *#10Hydroxyapatite** *#11#9 or #10* *#12Nanohydroxyapatite or nano-hydroxyapatite* *#13#8 or #11 or #12* *#14#5 and #13*
PubMed	*#1 (((((dentin sensitivity[MeSH Terms]) OR dentin* sensitivit*[Title/Abstract]) OR dentin* hypersensitivit*[Title/Abstract]) OR Dental Hypersensitivit*[Title/Abstract])) #2 (((((((dentin desensitizing agents[MeSH Terms]) OR Hydroxyapatites[MeSH Terms]) OR dentin* desensitizing agent*[Title/Abstract]) OR desensitizing agent*[Title/Abstract]) OR Hydroxyapatite*[Title/Abstract]) OR Nanohydroxyapatite[Title/Abstract]) OR nano-hydroxyapatite[Title/Abstract]) #1 and #3*
Web of Science	*#1 TS = (dentin* sensitivit*) OR TS = (dentin* hypersensitivit*) OR TS = (Dental Hypersensitivit*) #2 TS = (dentin* desensitizing agent*) OR TS = (desensitizing agent*) OR TS = (Hydroxyapatite*) OR TS = (Nanohydroxyapatite) OR TS = (nano-hydroxyapatite)* #1 AND #2
Scopus	(TITLE-ABS-KEY (dentin*AND sensitivit*) OR TITLE-ABS-KEY (dentin*AND hypersensitivit*) OR TITLE-ABS-KEY (dentalAND hypersensitivit*)) AND (TITLE-ABS-KEY (dentin*AND desensitizingAND agent*) OR TITLE-ABS-KEY (desensitizingAND agent*) OR TITLE-ABS-KEY (hydroxyapatite*) OR TITLE-ABS-KEY (nanohydroxyapatite) OR TITLE-ABS-KEY (nano-hydroxyapatite))
Lilacs	*(mh:(dentin sensitivity)) OR (tw:(dentin* sensitivit*)) OR (tw:(dentin* hypersensitivit*)) OR (tw:(Dental Hypersensitivit*)) AND (mh:(dentin desensitizing agents)) OR (mh:(Hydroxyapatites)) OR (tw:(dentin* desensitizing agent*)) OR (tw:(desensitizing agent)) OR (tw:(Hydroxyapatite*)) OR (tw:(nano-hydroxyapatite)) OR (tw:(Nanohydroxyapatite))*
Open Grey	*(dentin* sensitivit* OR dentin* hypersensitivit* OR Dental Hypersensitivit*) AND (dentin* desensitizing agent* OR desensitizing agent OR Hydroxyapatite* OR nano-hydroxyapatite OR Nanohydroxyapatite)*
Clinical Trials	*Search 1: Condition or disease: dentin sensitivity x Other terms: Nanohydroxyapatite;* *Study type: Interventional Studies (Clinical trials)* *Study Results: Studies With Results* *Search 2: Condition or disease: dentin sensitivity x Other terms: nano-hydroxyapatite* *Study type: Interventional Studies (Clinical trials)* *Study Results: Studies With Results*

evaluated the pain using a 0–10 scale, and another subgroup including studies that evaluated the pain using a 0–3 scale.

- The fourth analysis evaluated the influence of the comparison group and pain scale used on the efficacy of n-HAP-containing treatment in relation to tactile stimuli. Two subgroups were created: one including studies that compared n-HAP-containing treatment *versus* other DA-containing treatments and used a 0–3 pain scale, and another subgroup including studies that compared n-HAP-containing treatment *versus* DA-free products and used a 0–10 pain scale.
- The fifth analysis evaluated the influence of application protocol on the efficacy of n-HAP-containing treatment in relation to tactile stimuli. Two subgroups were created: studies that performed at-home application *versus* in-office application.

Since the two studies that presented results for cold stimulus had the same comparison group (both used other DA-containing products) and used the same pain scale (both used a 0–10 pain scale), a separate analysis for this stimulus was not performed. Likewise no analysis of application protocol for tactile and cold stimuli was performed as there was only one study in the in-office subgroup.

Mean differences (MD), 95% confidence intervals (CIs), and standard errors (SEs) were calculated for all studies included in this systematic review, in an attempt to combine data from parallel and split-mouth studies [27]. In split-mouth studies [28], an intrapatient correlation coefficient of 0.5 was assumed [29]. The pooled effect size was calculated by the generic inverse variance standardized mean difference (SMD), since the outcome presented methodological variables between studies in all meta-analyses, as seen in the second, third and fourth meta-analysis. Heterogeneity was tested using the I^2 index. If the heterogeneity was substantial (50 to 100%) ($p < 0.05$), a sensitivity analysis was employed to verify the influence of each study on the pooled meta-analysis results [29].

If necessary, study authors were contacted to provide missing data (five attempts to make contact for each study). “Unclear” or “high” risk of bias studies, or those that still had insufficient data after contacting the authors, were excluded from the meta-analysis.

Since some studies presented more than one time point of evaluation, in an attempt to reduce variables and make the analyses more uniform, only the results at 30 days or 4 weeks of follow-up were included in the meta-analyses.

2.7. Grading the quality of evidence

The quality of evidence (certainty in the estimates of effect) was determined for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Using the GRADE approach, RCTs are initially considered as providing high-quality evidence, however, the quality or certainty of evidence decreases to moderate, low, or very low if serious or very serious issues related to risk of bias, imprecision, inconsistency, indirectness, and publication bias are identified [30].

3. Results

3.1. Study selection

The initial search of all sources yielded 1759 records. Of these, 844 duplicated studies were removed using the reference manager EndNote. Another 899 irrelevant studies were removed after scanning the retrieved studies on the basis of their titles and abstracts. Sixteen studies of potential interest were read and analysed in their full-text form and, of these, eight met the inclusion criteria and were included in the systematic review; six studies were included in the meta-analysis (Fig. 1).

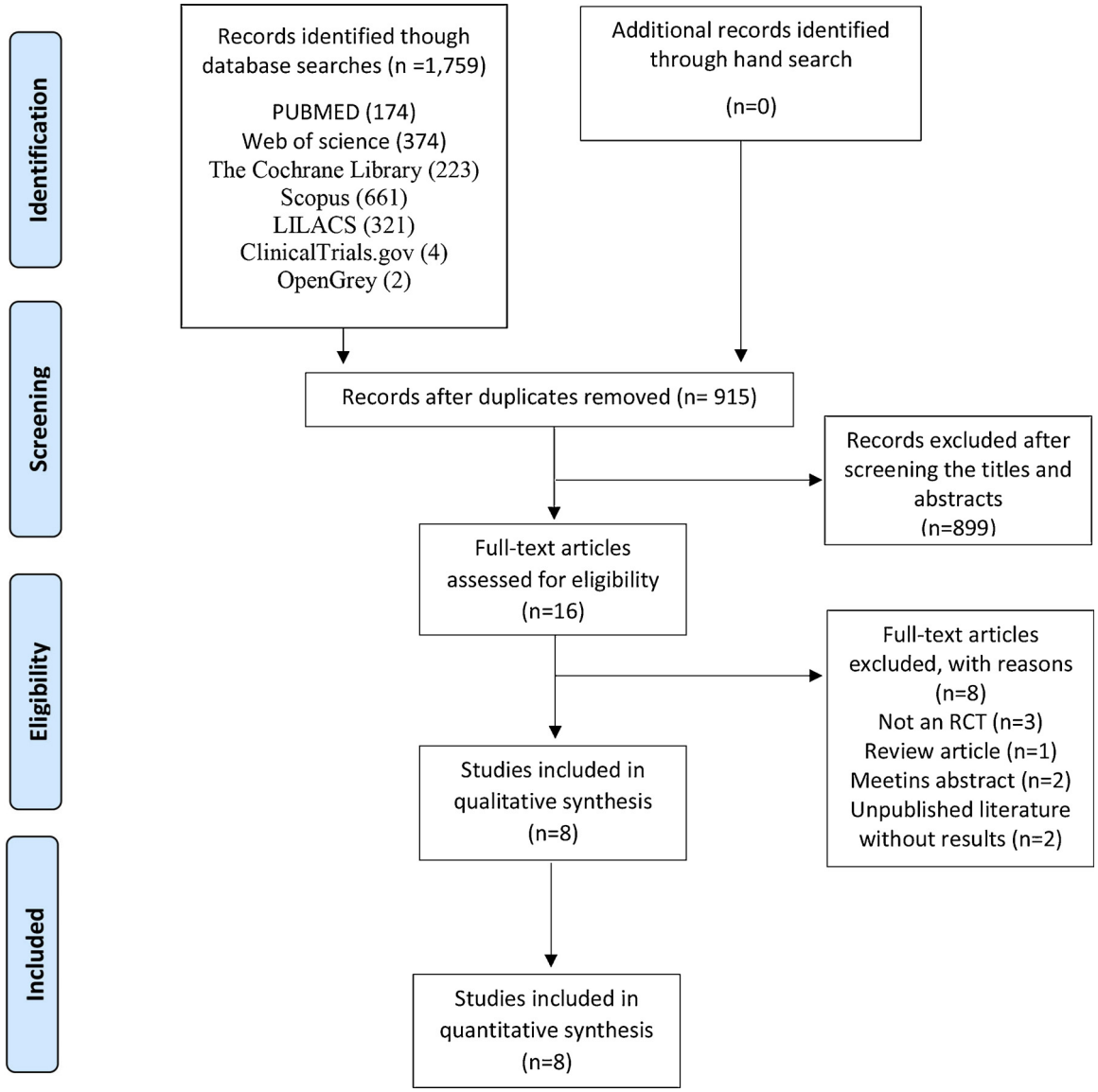

Fig. 1. PRISMA flow diagram of the search results from the databases.

3.2. Analysis of the risk of bias

Only one clinical trial did not clearly mention the random sequence generation and allocation concealment [16]. The other seven studies correctly employed these approaches [13,14,17,18,28,31,32]. All eight studies presented appropriate blinding of participants and personnel and blinding of outcome assessment. All studies were classified as having a 'low' risk of bias to selective reporting. The risk of other bias was considered present in three studies: Bevilacqua et al. did not report the sample size in his study; Gopinath et al. [17] and Jena et al. [31] did not report the sample size and did not report the location or date of the study (Figs. 2 and 3).

3.3. Descriptions of the included studies

Detailed data from the eight included studies are listed in Table 2. n-HAP was used in the form of self-administered toothpaste in five studies [13,14,17,31,32] and was applied in-office in three studies [16,18,28], with concentrations ranging from 1% [14,17] to 20% [16,18,28].

The follow-up times ranged from 4 weeks [13,14,17,28,31,32] to 3 months [16,18]. DH pain was elicited by evaporative [13,14,17,18,28,31,32], tactile [13,17,31,32], thermal [17,28] or electric stimuli [16] and two scales were used to quantify DH. Six studies used a 10-cm visual analogue scale (VAS) [14,16–18,28,31] and two studies used a scale from 0 to 3 for measurements [31,32].

Three of the studies included a placebo or control group [13,28,32] and all others compared n-HAP with other desensitizing agents [14,16–18,31]. All studies reported equivalence between treatment groups at baseline. Five studies showed no significant difference between n-HAP and other treatments for all outcomes measured [14,16–18,28] and three studies reported a significant difference between n-HAP and the other treatments for all outcomes measured [13,31,32]. Three studies included in this systematic review used the number of teeth as the sample unit [18,28,31] and five used the individuals' responses [13,14,16,17,32].

3.4. Meta-analysis and quality of evidence

The meta-analysis was conducted using the data available in the studies classified as having a "low" risk of bias for key domains. One study was classified as having an "unclear" risk of bias [16] and another study did not provide the mean or standard deviation values required to perform the meta-analysis. [14]. These two studies were excluded from the meta-analysis.

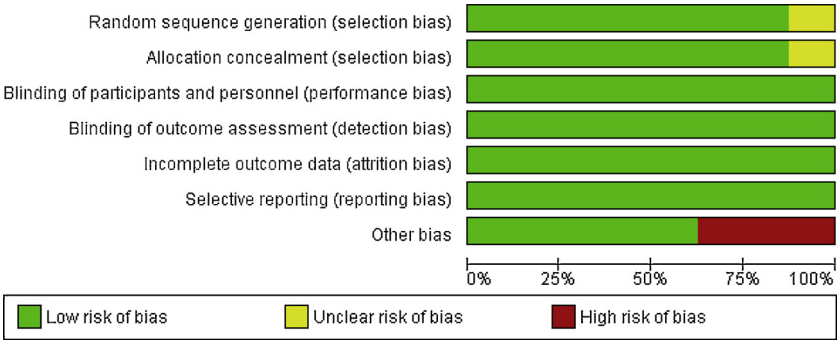

Fig. 2. Risk of bias graph.

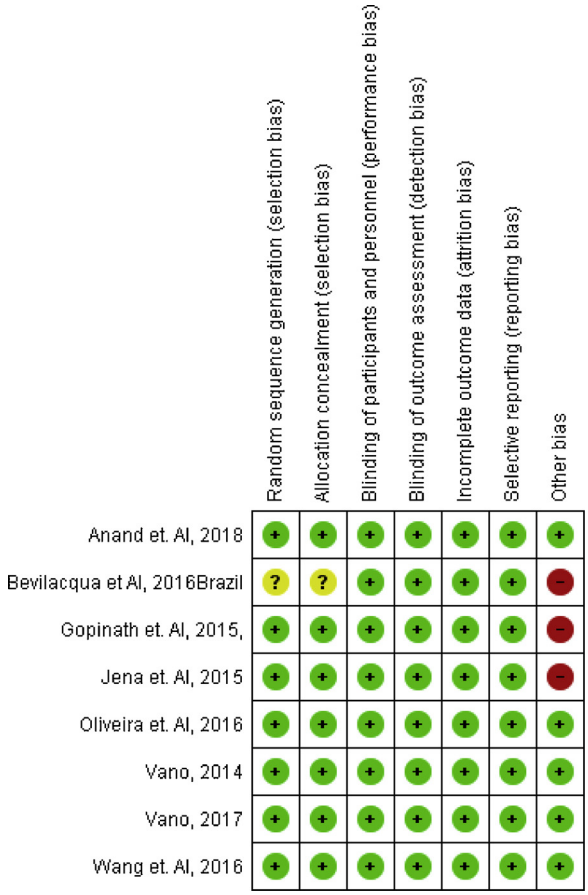

Fig. 3. Risk of bias summary.

Six studies were included in the first meta-analysis (to evaluate the efficacy of n-HAP-containing treatment for the relief of dentin sensitivity) [13,17,18,28,31,32]. The overall and subgroup (evaporative, tactile and cold stimuli) heterogeneity varied from considerable to null (I^2 = 91%, I^2 = 86%, I^2 = 95% and I^2 = 0%, respectively). During the sensitivity analysis, the overall heterogeneity ranged from 86 to 92%, evaporative stimuli heterogeneity ranged from 0 to 86% and tactile stimuli heterogeneity ranged from 90 to 97%. Although no substantial reduction in overall heterogeneity was observed, the study by Gopinath *et al* [17] was excluded from the evaporative stimuli subgroup to reduce this subgroup's heterogeneity.

The n-HAP-containing treatment had a better desensitizing effect for evaporative stimuli (SMD -1.09 [-1.24, -0.94], p < 0.00001, I^2 = 0% (I^2 p = 0.95)) and tactile stimuli (SMD -0.93 [-1.42, -0.43], p = 0.0002, I^2 = 91% (I^2 p < 0.00001)) in compared with n-HAP-free treatments. However, there was no significant difference between n-HAP and the other treatments for the cold stimulus (SMD -0.17 [-0.81, 0.48], p = 0.61, I^2 = 0% (I^2 p = 0.87)). In the overall analysis, the n-HAP-containing treatment had a significant desensitizing effect when compared to n-HAP-free treatments (SMD -0.93 [-1.19, -0.68], p < 0.00001, I^2 = 77% (I^2 p < 0.00001)) (Fig. 4). The assessed quality of evidence for the overall outcome was moderately high; for the evaporative subgroup it was moderate due to serious issues related to imprecision; for the tactile subgroup it was low due to serious issues related to inconsistency and imprecision; and for the cold subgroup it was high (Table 3).

The same six studies were included [13,17,18,28,31,32] in the second meta-analysis (to evaluate the influence of the comparison group on the efficacy of n-HAP-containing treatment in relation to evaporative stimuli). The overall and subgroup (other DA-containing and DA-free treatments) heterogeneity was considerable or null (I^2 = 86%, I^2 = 0% and I^2 = 90%, respectively).

During the sensitivity analysis, the overall heterogeneity ranged from 0 to 86% and in the subgroup using products with other DA-containing treatment heterogeneity ranged from 58 to 95%. In an attempt to reduce overall and subgroup heterogeneity, the study by Gopinath *et al.* [17] was excluded.

The n-HAP-containing treatment had a better desensitizing effect for evaporative stimuli in the overall analysis (SMD -1.09 [-1.24, -0.94], P < 0.00001, I^2 = 0% (I^2 p = 0.95)) when compared with other DA-containing (SMD -1.02 [-1.49, -0.56], p < 0.0001, I^2 = 0% (I^2 p = 0.43)) and DA-free treatments (SMD -1.10 [-1.25, -0.94], p < 0.00001, I^2 = 0% (I^2 p = 0.99)) (Fig. 5).

The same six studies were included [13,18,28,31,32] in the third meta-analysis (to evaluate the influence of pain scale used on efficacy of n-HAP-containing treatment in relation to evaporative stimuli). The overall and subgroup (0–10 and 0–3 pain scale) heterogeneity was considerable or null (I^2 = 86%, I^2 = 56% and I^2 = 0%, respectively). During the sensitivity analysis, the overall heterogeneity ranged from 0 to 86% and in the 0–10 pain scale subgroup heterogeneity ranged from 0 to 78%. In an attempt to reduce overall and subgroup heterogeneity, the study by Gopinath et al. [17] was excluded from the 0–10 pain scale subgroup.

The n-HAP-containing treatment showed a similar desensitizing effect against evaporative stimuli as the comparison groups when a 0–10 pain scale was applied (SMD -0.02 [-3.01, 3.05], p = 0.99, I^2 = 0% (I^2 p = 0.69)) and a better desensitizing effect when a 0–3 pain scale was applied (SMD -1.09 [-1.24, -0.94], p < 0.00001, I^2 = 0% (I^2 p = 0.98)) and in the overall analysis (SMD -1.09 [-1.24, -0.94], p < 0.00001, I^2 = 0% (I^2 p = 0.95)) (Fig. 6).

The assessed quality of evidence in the second and third meta-analysis is described in Table 4 (supplementary file). The quality of evidence for the overall evaporative outcome, as well as for most of the subgroups (treatments without DA, treatments with DA and 0–3 pain scale subgroups) was moderate due to serious issues related to imprecision, and high for the '0–10 pain scale' subgroup.

Four studies were included [13,17,31,32] in the fourth meta-

Table 2
Description of included studies.

Author, Year, Cowntry	No. of participants/ Teeth	Age range	Study design	Manufacturer of desensitizers	Ingredients	Data analysis	Follow-up	Results
Anand et. Al, 2018, India	N = 60	18-50 years	RCT, parallel, DB	Aclaim™, Group Pharmaceuticals, Bangalore, India	Toothpaste contains 1% n-HAP associated with xylitol and Fluoride-Free	ANOVA and Bonferroni	4 weeks	There was no significant difference between n-HAP and arginine for all outcomes measured.
Bevilacqua et Al, 2016 Brazil	N = 35	18-60 years	RCT, parallel, DB	Nano-P®, FGM-Dentscare, Joinville, Brazil)	Desensitizing agent contains 20% Nano-hydroxyapatite associated with 9000 ppm SF and 5% PN	ANOVA and post-hoc Turkey	3 months	There was no significant difference between n-HAP, fluoride and biosilicate for all outcomes measured.
Copinath et. Al, 2015, India	N = 36	18-60 years	RCT, parallel, DB	Aclaim™, Group Pharmaceuticals, Bangalore, India	Toothpaste contains 1% n-HAP associated with xylitol and Fluoride-Free	Paired and unpaired t-test	4 weeks	There was no significant difference between n-HAP and Novamin for all outcomes measured.
Jena et. Al, 2015, India	n = 45 Hypersensitivity teeth = 122	18-50 years	RCT, parallel, DB	NanoXIM®, Fluidinova Technologies, Moreira de Maia, Portugal	Toothpaste contains 15% n-HAP associated with 2% PC and fluoride-free	ANOVA and post-hoc Turkey	4 weeks	There was significant difference between n-HAP, arginine and Novamin for all outcomes measured. n-HAP was found to be most effective followed by 8% arginine and 5% NovaMin.
Oliveira et. Al, 2016, Brazil	N = 8 Hypersensitivity teeth = 140	18 years or older	RCT, split-mouth, TB	Nano-P®, FGM-Dentscare, Joinville, Brazil)	Desensitizing agent contains 20% Nano-hydroxyapatite associated with 9000 ppm SF and 5% PN	Kruskall-Wallis and Friedma	4 weeks	There was no significant difference between n-HAP, arginine and Strontium acetate for all outcomes measured. But, just n-HAP provided an immediate relief.
Vano, 2017, Italy	n = 105	20-70 years	RCT, parallel, DB	Cavex Bite&White®, ExSense, Cavex Holland BV	Toothpaste contains 5% n-HAP associated with 2% PC and Fluoride-Free	t-test and Kruskall-Wallis	4 weeks	There was significant difference between n-HAP and a placebo group for all outcomes measured.
Vano, 2014, Italy	n = 105	20-70 years	RCT, parallel, DB	PREvDent® toothpaste, Prev Dent, California, United State	Toothpaste contains 15% n-HAP and associated with 2% PC and Fluoride-Free	t-test and Kruskall-Wallis	4 weeks	There was significant difference between n-HAP and a placebo group for all outcomes measured.
Wang et. Al, 2016, Brazil	n = 28 Hypersensitivity teeth = 137	18-60 years	RCT, parallel, DB	Nano-P®, FGM-Dentscare, Joinville, Brazil)	Desensitizing agent contains 20% Nano-hydroxyapatite associated with 9000 ppm SF and 5% PN	ANOVA	3 months	There was no significant difference between n-HAP, arginine and a fluoride varnish

RCT, Randomized Clinical Trial; DB, Double-blind; TB, Triple-blind; n-HAP, nano-hidroxyapatite; SF, sodium fluoride; PN, potassium nitrate; PC potassium chloride.

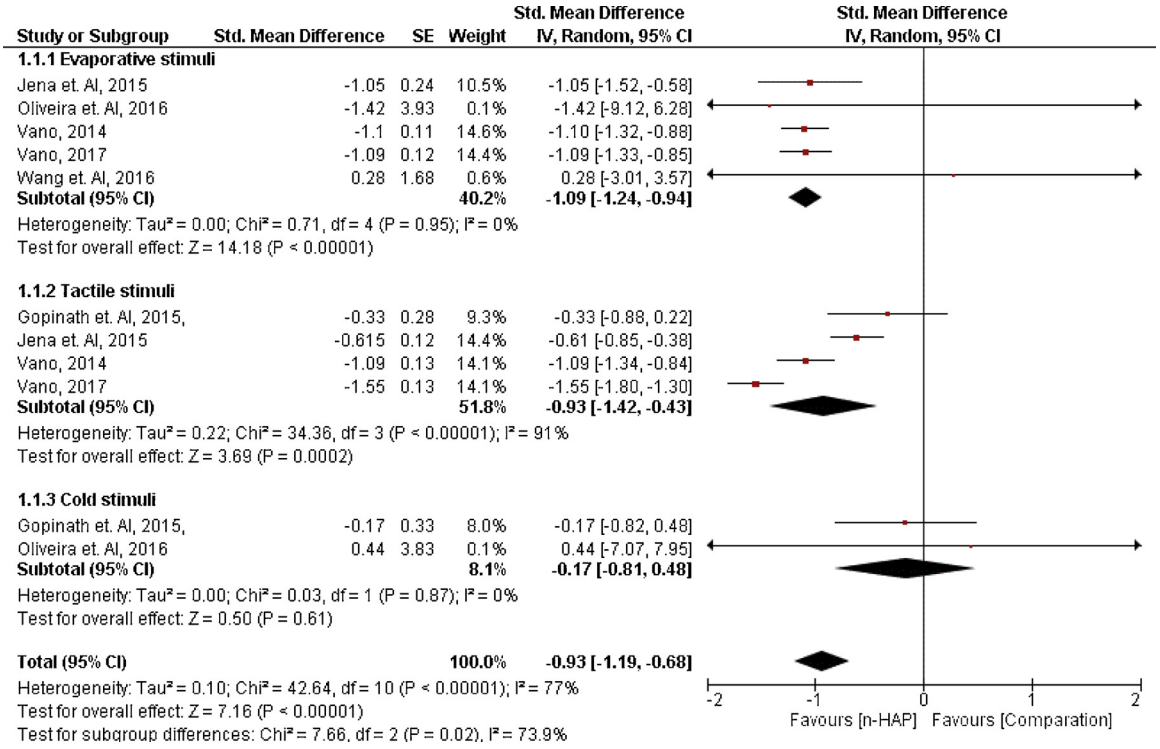

Fig. 4. Forest plot of the desensitizing effect of n-HAP-containing treatment, according to stimuli applied.

analysis (to evaluate the influence of the comparison group and pain scale used on the efficacy of n-HAP-containing treatment in relation to tactile stimuli). The overall and subgroup heterogeneity was considerable or moderate (I^2 = 95%, I^2 = 94% and I^2 = 32%, respectively). During the sensitivity analysis, the overall heterogeneity ranged from 90 to 97%. Since no substantial reduction in heterogeneity was observed following removal of individual studies from the analysis, no study was excluded.

The n-HAP-containing treatment had a better desensitizing effect for tactile stimuli in the overall analysis (SMD -1.01 [-1.15, -0.87], $p < 0.00001$, I^2 = 91% (I^2 $p < 0.00001$)) compared to treatments without DA / 0–3 pain scale (SMD -1.33 [-1.50, -1.14], $p < 0.00001$, I^2 = 84% (I^2 p = 0.01)) or with DA/ 0–10 pain scale (SMD -0.57 [-0.79, -0.35], $p < 0.00001$, I^2 = 0% (I^2 p = 0.35)) (Fig. 7). The quality of evidence for this overall outcome is moderate, owing to serious issues related to imprecision; and for subgroups it was low due to serious issues related to suspected imprecision and publication bias in each subgroup (Table 5 – supplementary file).

Four studies were included [13,17,31,32] in the fifth meta-analysis (to evaluate the influence of application protocol on the efficacy of n-HAP-containing treatment in relation to evaporative stimuli). The overall and subgroup (at-home and in-office) heterogeneity was considerable or null (I^2 = 84%, I^2 = 94% and I^2 = 0%, respectively). During the sensitivity analysis, the overall heterogeneity ranged from 0 to 87% and the at-home subgroup heterogeneity ranged from 0% to 97%. In an attempt to reduce overall and subgroup heterogeneity, the study by Gopinath et al. [17] was excluded.

The n-HAP-containing treatment had a better desensitizing effect than others treatments for the evaporative stimuli in the overall analysis (SMD -1.09 [-1.24, -0.94], $P < 0.00001$, I^2 = 0% (I^2 p = 0.95)) both in at-home (SMD -1.10 [-1.25, -0.94], $p < 0.0001$, I^2 = 0% (I^2 p = 0.95)) and in-office products (SMD -1.02 [-1.49, -0.56], $p < 0.00001$, I^2 = 0% (I^2 p = 0.73)) (Fig. 8). The assessed quality of evidence for the overall outcome and in-office subgroup was moderate due to serious issues related to imprecision, and for the at-home subgroup it was high (Table 6 – supplementary file).

4. Discussion

Based on the results of the meta-analysis, n-HAP-containing treatment are more effective than n-HAP-free treatments and placebo in relieving DH when used either at home or in office. Therefore, H0 was rejected.

Despite the low number of studies included in the present systematic review (eight studies) [13,14,16–18,28,31,32] it is important to highlight that seven of them were classified as having a “low” risk of bias [13,14,17,18,28,31,32]. For this reason, the present systematic review and meta-analysis results should be considered reliable. Furthermore, the GRADE approach showed a moderate or high quality of evidence for these results. The studies what evaluated the tactile stimulus showed a low quality of evidence, further clinical investigations of DH through tactile stimulation are necessary to reach a definitive conclusion.

All studies evaluating bleaching-induced tooth sensitivity (TS) were excluded from the present systematic review because the pain characteristics differ from the DH [33,34]. In the tooth bleaching procedure, upon penetrating the dental tissues the peroxides quickly diffuse to reach the chemosensitive ion channels (TRPA1), activating the intradental nerves and causing discomfort [34,35]. In contrast, the DH mechanism is more often explained by the hydrodynamic theory [8] and no inflammatory process is implicated.

In the first meta-analysis, the n-HAP-containing treatment had a more significant desensitizing effect against evaporative and tactile stimuli and in pooled results than the other treatments, placebo and control. However, it did not appear to be effective against cold stimuli because the values reported for this stimulus were high regardless of the treatment and time of evaluation when compared to the other stimuli. It was hypothesized by Tokuda et al. [36] that TRPM8 channels in odontoblasts might be candidates for generating dentinal sensation as they have a long latency following cool- and/or cold-stimuli applied to the dentin surface. This implies that DH caused by the cold stimulus could involve not only the hydrodynamic theory but also other as yet unknown factors.

Table 3
Quality of the evidence for the overall outcomes.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	n-HAp	Comparison	Relative (95% CI)	Absolute (95% CI)	
Overall (follow up: mean 4 weeks)											
6	randomized trials	not serious	not serious [a]	not serious	not serious [b]	none	112	112	–	SMD 0.93 lower (1.19 lower to 0.68 lower)	⨁⨁⨁⨁ HIGH
Evaporative stimuli (follow up: mean 4 weeks)											
5	randomized trials	not serious	not serious	not serious	serious [c]	none	94	94	–	SMD 1.09 lower (1.24 lower to 0.94 lower)	⨁⨁⨁◯ MODERATE
Tactile stimuli (follow up: mean 4 weeks)											
4	randomized trials	not serious	serious [d]	not serious	serious [b]	none	103	103	–	SMD 0.93 lower (1.42 lower to 0.43 lower)	⨁⨁◯◯ LOW
Cold stimuli (follow up: mean 4 weeks)											
2	randomized trials	not serious	not serious	not serious	very serious [e]	very strong association	20	20	–	SMD 0.17 lower (0.81 lower to 0.48 higher)	⨁⨁⨁⨁ HIGH

CI: Confidence interval; **SMD:** Standardized mean difference.
a. Although the overall heterogeneity is 77%, the subgroup analysis detected that it is related only with tactile stimuli. So, the authors did not considered it a serious or very serious inconsistency.
b. Total number of participants is less than 400 and Gopinath et al. and Jena et al. did nor performed sample size.
c. Total number of participants is less than 400 and Jena et al. did not performed sample size calculation.
d. The heterogeneity was high (91%), but there is no wide variation in the effect estimates across studies and there is some overlap of confidence intervals associated with the effect estimates.
e. Total number of participants is less than 400, Gopinath et al. did not performed sample size and upper or lower confidence limit crosses the effect size of 0.5 in either direction (Minimal important difference).

In the first meta-analysis, all stimuli were considered (tactile, cold and evaporative) in the quantitative analysis. The patient with DH is susceptible to all sorts of painful stimulation daily, for which reason the performance of all three forms of pain evaluation is recommended [37]. However, the air blast test is the most accurate method of evaluating DH because it involves a wider area of dentin and has also been used more often than the tactile test, thermal test, or subject assessment in clinical trials [38]. For this reason, the comparative analysis between n-HAP-containing and n-HAP-free treatments was performed by considering the evaporative stimulus (second meta-analysis). In this meta-analysis it was demonstrated that n-HAP was more effective at reducing DH both compared to other desensitizing agents and compared to placebo or negative controls.

In an attempt to reduce overall heterogeneity and subgroups in this meta-analysis, the study by Gopinath et al. [17] was excluded. In this RCT, n-HAP was compared with amorphous sodium calcium phosphosilicate (NovaMin) while all other RCTs compared with arginine or placebo/negative control. For this reason, arginine was the only desensitizing agent considered for comparison in this meta-analysis. This material is an amino acid that is found naturally in saliva. The combination of arginine and calcium carbonate mimics saliva's ability to occlude and seal open dentinal tubules; the result is a plug that renders that tooth surface resistant to acid and thermal attacks, thereby reducing fluid movement [39]. Two previous meta-analyses and one systematic review have already evaluated the desensitization efficiency of arginine and presented promising results regarding the use of this bioactive agent [40–42]. However, in the present meta-analysis, n-HAP showed better results than those presented by arginine in the treatment of DH.

An important methodological difference between studies was the different scales used to measure sensitivity. Half of the studies used a visual scale from 0 to 10 and the other half used the Schiff Cold Air Sensitivity Scale [43] (0–3). For this reason, a meta-analysis was performed to evaluate the influence of pain scale on the efficacy of n-HAP-containing treatment in relation to evaporative stimuli. The results of the quantitative analysis (third meta-analysis) of the studies showed that all studies that used the scale of 0 to 3 presented a statistically significant difference between n-HAP-containing and n-HAP-free treatments and all studies that used the scale of 0 to 10 demonstrated equivalence among treatments. This result could be a consequence of the possible greater representativeness of the scale of 0 to 3, as a smaller interval between one score and another can facilitate the patient's choice when it comes to representing their pain. However, the perception of pain arising from exposed dentin surfaces is influenced by a number of different aspects, including the individual parameters of each patient, psychological factors, cultural aspects, and situational and emotional factors [44,45]. For this reason, the hypothesis that the Schiff Cold Air Sensitivity Scale is more sensitive than the scale of 0 to 10 could not be confirmed based on the results of this meta-analysis.

The fourth meta-analysis was performed to evaluate the desensitizing effect of n-HAP-containing and n-HAP-free treatments for tactile stimuli. However, after clustering it was noted that, coincidentally, all studies comparing placebo or negative controls with n-HAP were also those that used the Schiff Cold Air Sensitivity Scale. In addition, all studies comparing n-HAP with other DA used the 0–10 scale. A double response was thus obtained. The n-HAP-containing treatment showing a better desensitizing effect for tactile stimuli in overall analysis, for both DA-free/0–3 pain scale and DA-containing/0–10 pain scale. The results of the second and fourth meta-analyses showed that, regardless of the applied stimulus, n-HAP presented better results than the placebo, control and other DA in DH treatment.

The fifth meta-analysis showed that both at-home and in-office n-HAP showed satisfactory results in the treatment of HD. However, the RCTs that evaluated at-home n-HAP were performed by the same author [13,32]. This demonstrates the need for more RCTs to consistently address this topic, although the studies included had a low risk of bias.

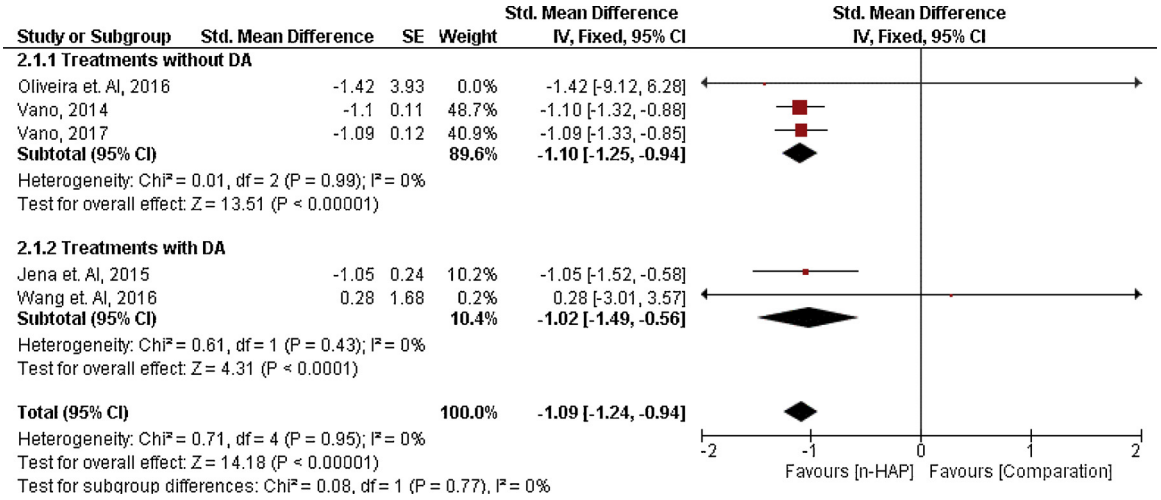

Fig. 5. Forest plot of the desensitizing effect of n-HAP-containing treatment and treatments with and without DA, for evaporative stimuli.

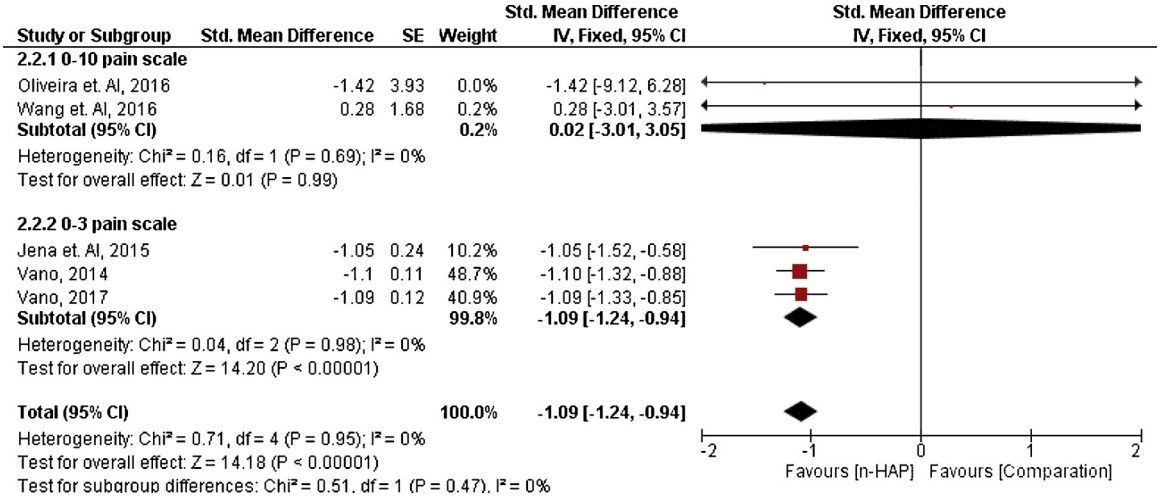

Fig. 6. Forest plot of the desensitizing effect of n-HAP-containing treatment evaluated using a 0–3 or 0–10 pain scale, for evaporative stimuli.

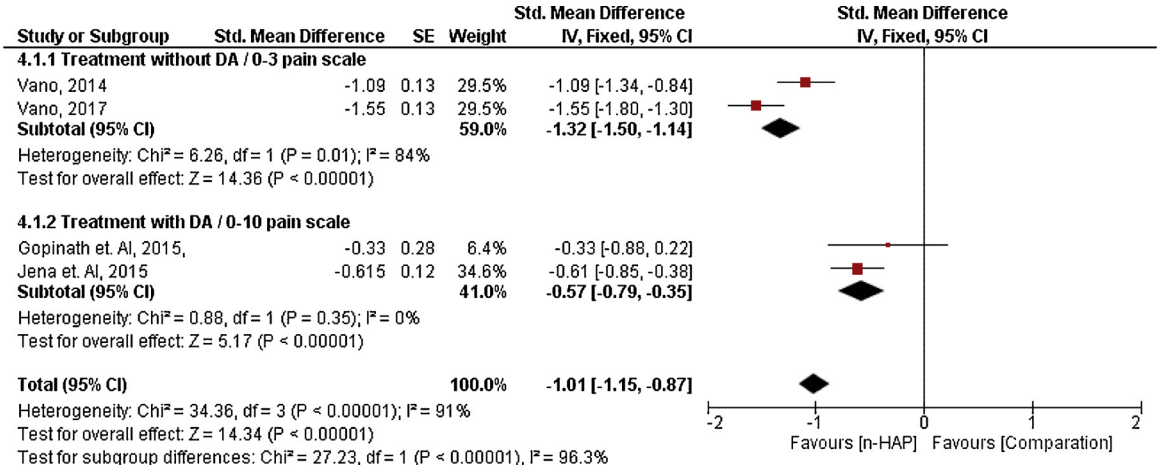

Fig. 7. Forest plot of the desensitizing effect of n-HAP-containing treatment and treatments without DA/0–3 pain scale or with DA / 0–10 pain scale, for tactile stimuli.

Remaining on the subject of the tactile stimulus, although the final heterogeneity in the statistical results was not significant for most analyses, this specific stimulus subgroup had high heterogeneity in the first meta-analysis and overall in the fourth meta-analysis (I^2 = 95%). The studies included in this systematic review have enough in common that it makes sense to synthesize the information, but there is no reason to assume that they are identical, since they present some methodological differences. The high heterogeneity in the tactile stimulus subgroup (in the first analysis) and in the fourth meta-analysis could be related to the application of the force of the probe on the patient's tooth,

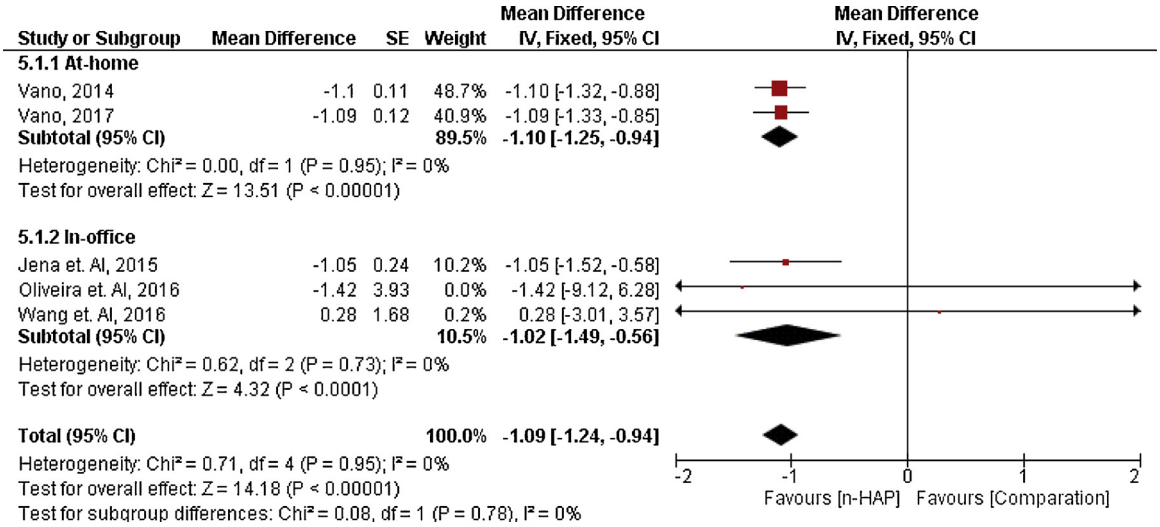

Fig. 8. Forest plot of the desensitizing effect of in-office *versus* at-home n-HAP-containing treatment, for evaporative stimuli.

which depends on the pressure exerted by the operator, and there was no standardization of this variable among the included studies. In addition, of the four studies included in the meta-analysis, two compared n-HAP with placebo and two compared it with other desensitizing treatments. These associated factors contributed to the increase in heterogeneity.

Three studies used the painful response of each tooth as a sample unit [18,28,31], that is, the individuals were randomized as a cluster [46]. In this case, it is important to consider that the tooth sample unit is a dependent variable when present in the same individual or cluster [47]. However, all three articles used statistical tests for independent variables, disregarding the clustering effect of dental clusters. These studies performed randomization in an appropriate manner, considering the individual as a sample unit of randomization and, for this reason, each group presented different sample numbers. In the present meta-analysis, all data were considered such as independent samples (individuals) to decrease the heterogeneity and to provide stronger comparisons. In addition, one study [16] used a split mouth-design to set up paired samples. For this specific study an intrapatient correlation coefficient of 0.5 was assumed in the quantitative analysis, as previously suggested by Higgins and Green [29].

Many systematic reviews and meta-analyzes have been performed to evaluate the efficacy of desensitizing treatments with arginine [20], Novamin [22], amorphous calcium phosphate [23], strontium [19,48], potassium [49], oxalates [50], laser photobiomodulation [51] and others [40,52]. Although some promising responses have been demonstrated, most studies have shown inconclusive results indicating the most diverse treatments available. Therefore, it is clear that more RCTs with low risk of bias are necessary for consistent systematic responses to be generated.

The strength of this meta-analysis lies in the rigour of its methodology, which followed the recommendations in the Cochrane Handbook for Systematic Reviews of Intervention and evaluated the quality of the evidence using the GRADE approach. Most studies included 4 weeks of follow-up, but in one study follow-up lasted for up to 3 months. For the calculation of the meta-analysis it was possible to standardize all studies included in the 4-week follow-up. None of the included studies reported funding or conflicts of interest.

5. Conclusions

This systematic review and meta-analysis indicate that desensitizing agents containing n-HAP are effective for the relief of dentin hypersensitivity in both at-home and in-office treatments when compared with others desensitizing agents or placebo/negative control. However, the evidence generated by this review was based on a small number of studies. In addition, long-term follow-up clinical trials are required in the future before definitive recommendations can be made.

Acknowledgements

The authors of this study thank the following authors who kindly collaborated by answering e-mails and providing the information requested: Nithin Manchery Gopinath, Douglas de Oliveira, Amit Jena and Linda Wang. This study was financially supported by the Brazilian National Council for Scientific and Technological Development (CNPq).

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.2018.12.014.

References

[1] G.R. Holland, M.N. Narhi, M. Addy, L. Gangarosa, R. Orchardson, Guidelines for the design and conduct of clinical trials on dentine hypersensitivity, J. Clin. Periodontol. 24 (1997) 808–813.
[2] K. Bekes, C. Hirsch, What is known about the influence of dentine hypersensitivity on oral health-related quality of life? Clin. Oral Investig. 17 (2013) S45–S51.
[3] D.W. Douglas-de-Oliveira, G.P. Vitor, J.O. Silveira, C.C. Martins, F.O. Costa, L.O.M. Cota, Effect of dentin hypersensitivity treatment on oral health related quality of life — a systematic review and meta-analysis, J. Dent. 71 (2018) 1–8.
[4] M. Mantzourani, D. Sharma, Dentine sensitivity: past, present and future, J. Dent. 41 (2013) S3–S17.
[5] R. Rapp, J.K. Avery, D.S. Strachen, Possible role of the acetylcholinesterase in neural conduction within the dental pulp, in: S.B. Finn (Ed.), Biology of Dental Pulp Organ, University of Alabama Press, Birmingham, 1968pp. 309.
[6] N.X. West, A. Lussi, J. Seong, E. Hellwig, Dentin hypersensitivity: pain mechanisms and a etiology of exposed cervical dentin, Clin. Oral Investig. 17 (2013) S9–S19.
[7] M. Brännström, G. Johnson, K.J. Nordenvall, Transmission and control of dentinal pain: resin impregnation for the desensitization of dentin, J. Am. Dent. Assoc. 99 (1979) 612–618.
[8] M. Brännström, L.A. Linden, A. Astrom, The hydrodynamics of the dental tubule and of pulp fluid. A discussion of its significance in relation to dentinal sensitivity, Caries Res. 1 (1967) 310–317.
[9] M. Brännström, A hydrodynamic mechanism in the transmission of pain-produced stimuli through the dentine, in: D.J. Anderson (Ed.), Sensory Mechanisms in Dentine, Pergamon, Oxford, 1966, pp. 73–79.
[10] M. Brännström, The surface of sensitive dentine, Odontol. Rev. 16 (1965) 293–299.
[11] M. Brännström, The sensitivity of dentine, Oral Surg. Oral Med. Oral Pathol. 21 (1966) 517–526.
[12] L.M. Sykes, Dentine hypersensitivity: a review of its aetiology, pathogenesis and management, S.A.D.J. 62 (2007) 66–71.
[13] M. Vano, G. Derchi, A. Barone, R. Pinna, P. Usai, U. Covani, Reducing dentine hypersensitivity with nano-hydroxyapatite toothpaste: a double-blind randomized controlled trial, Clin. Oral Investig. 22 (2018) 313–320.

[14] S. Anand, F. Rejula, J.V.G. Sam, R. Christaline, M.G. Nair, S. Dinakaran, Comparative evaluation of effect of nano-hydroxyapatite and 8% arginine containing toothpastes, Acta Medica (Hradec. Kralove) 60 (2017) 114–119.
[15] M. Hanning, C. Hanning, Nanomaterials in preventive dentistry, Nat. Nanotechnol. 5 (2010) 565–569.
[16] F.M. Bevilacqua, A. Catelan, G.S.A. Araújo, C.H.C. Saraceni, J.E.C. Sampaio, Efficacy of a bioactive material and nanostructured desensitizing on dentin hypersensitivity treatment, Rev. Odontol. UNESP 45 (2016) 127–131.
[17] N.M. Gopinath, J. John, N. Nagappan, S. Prabhu, E.S. Kumar, Evaluation of dentifrice containing nano-hydroxyapatite for dentinal hypersensitivity: a randomized controlled trial, J. Int. Oral Health 7 (2015) 118–122.
[18] L. Wang, A.C. Magalhães, L.F. Francisconi-Dos-Rios, M.P. Calabria, D. Araújo, M. Buzalaf, J. Lauris, J.C. Pereira, Treatment of dentin hypersensitivity using nano-hydroxyapatite pastes: a randomized three-month clinical trial, Oper. Dent. 41 (2016) E93–E101.
[19] B.F. Karim, D.G. Gillam, The efficacy of strontium and potassium toothpastes in treating dentine hypersensitivity: a systematic review, Int. J. Dent. 2013 (2013) 573258.
[20] M.O. Sharif, S. Iram, P.A. Brunton, Effectiveness of arginine-containing toothpastes in treating dentine hypersensitivity: a systematic review, J. Dent. 41 (6) (2013) 483–492.
[21] L. Gendreau, A.P. Barlow, S.C. Mason, Overview of the clinical evidence for the use of NovaMin in providing relief from the pain of dentin hypersensitivity, J. Clin. Dent. 22 (3) (2011) 90–95.
[22] M.J. Zhu, J.L. Li, B. Chen, L. Mei, L. Yao, J.H. Tian, H. Li, The effect of calcium sodium phosphosilicate on dentin hypersensitivity: a systematic review and meta-analysis, PLoS One 10 (11) (2015).
[23] M.L. Hu, G. Zheng, Y.D. Zhang, X. Yan, X.C. Li, H. Lin, Effect of desensitizing toothpastes on dentine hypersensitivity: a systematic review and meta-analysis, J. Dent. 19 (2018) 12–21.
[24] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Int. J. Surg. 8 (2010) 336–341.
[25] L.C. Maia, A.G. Antonio, Systematic reviews in dental research. A guideline, J. Clin. Pediatr. Dent. 37 (2012) 117–124.
[26] X. Zeng, Y. Zhang, J.S. Kwong, C. Zhang, S. Li, F. Sun, Y. Niu, L. Du, The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review, J. Evid. Med. 8 (2015) 2–10.
[27] E. Lesaffre, M.-J.G. Zattera, C. Redmond, H. Huber, I. Needleman, Reported methodological quality of split-mouth studies, J. Clin. Periodontol. 34 (2007) 756–761.
[28] D.W. Douglas-de-Oliveira, E.S. Oliveira, A.F. Mota, V.W. Pereira, V.O. Bastos, J.C. Glória, P.F. Gonçalves, O.D. Flecha, Effectiveness of three desensitizing dentifrices on cervical dentin hypersensitivity: a pilot clinical trial, J. Int. Acad. Periodontol. 8 (2016) 57–65.
[29] J.P. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions, (2011) (Accessed 10 March 2017), https://training.cochrane.org/handbook.
[30] R. Ryan, S. Hill, How to GRADE the Quality of the Evidence, Cochrane Consumers and Communication Group, 2016 Version 3.0, (Accessed 20 April 2017) http://cccrg.cochrane.org/author-resources.
[31] A. Jena, G. Shashirekha, Comparison of efficacy of three different desensitizing agents for in-office relief of dentin hypersensitivity: a 4 weeks clinical study, J. Conserv. Dent. 18 (2015) 389–393.
[32] M. Vano, G. Derchi, A. Barone, U. Covani, Effectiveness of nano-hydroxyapatite toothpaste in reducing dentin hypersensitivity: a double-blind randomized controlled trial, Quintessence Int. (Berl) 45 (2014) 703–711.
[33] W.D. Browning, S.D. Cho, E.J. Deschepper, Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity, J. Esthet. Restor. Dent. 24 (2012) 268–276.
[34] K. Markowitz, Pretty painful: why does tooth bleaching hurt? Med, Hypotheses 74 (2010) 835–840.
[35] M. Nähri, The neurophysiology of the teeth, Dent. Clin. North Am. 34 (1990) 439–448.
[36] M. Tokuda, S. Tatsuyama, M. Fujisawa, Y. Morimoto-Yamashita, Y. Kawakami, Y. Shibukawa, M. Torii, Dentin and pulp sense cold stimulus, Med. Hypotheses 84 (2015) 442–444.
[37] G.R. Holland, M.N. Narhi, M. Addy, L. Gangarosa, R. Orchardson, Guidelines for the design and conduct of clinical trials on dentine hypersensitivity, J. Clin. Periodontol. 24 (1997) 0808–0813.
[38] P.Y. Lin, Y.W. Cheng, C.Y. Chu, K.L. Chien, C.P. Lin, Y.K. Tu, In-office treatment for dentin hypersensitivity: a systematic review and network meta-analysis, J. Clin. Periodontol. 40 (2013) 53–64.
[39] I. Petrou, R. Heu, M. Stranick, S. Lavender, L. Zaidel, D. Cummins, R.J. Sullivan, C. Hsueh, J.K. Gimzewski, A breakthrough therapy for dentin hypersensitivity: how dental products containing 8% arginine and calcium carbonate work to deliver effective relief of sensitive teeth, J. Clin. Dent. 20 (2009) 23–31.
[40] J.H. Bae, Y.K. Kim, S.K. Myung, Desensitizing toothpaste versus placebo for dentin hypersensitivity: a systematic review and meta-analysis, J. Clin. Periodontol. 42 (2015) 131–141.
[41] Z.Y. Yang, F. Wang, K. Lu, Y.H. Li, Z. Zhou, Arginine-containing desensitizing toothpaste for the treatment of dentin hypersensitivity: a meta-analysis, Clin. Cosmet. Investig. Dent. 7 (2016) 1–14.
[42] M.O. Sharif, S. Iram, P.A. Brunton, Effectiveness of arginine-containing toothpastes in treating dentine hypersensitivity: a systematic review, J. Dent. 41 (2013) 483–492.
[43] T. Schiff, M. Dotson, S. Cohen, W.D. Vizio, J. McCool, A. Volpe, Efficacy of a dentifrice containing potassium nitrate, soluble pyrophosphate, PVM/MA copolymer, and sodium fluoride on dentinal hypersensitivity: a twelve-week clinical study, J. Clin. Pediatr. Dent. 5 (1994) 87–92.
[44] D.G. Gillam, R. Orchardson, M.V.O. Närhi, V. Kontturi-Närhi, Present and future methods for the evaluation of pain associated with dentine hypersensitivity, in: M. Addy, G. Embery, W.M. Edgar, R. Orchardson (Eds.), Tooth Wear and Sensitivity, Martin Dunitz Ltd., London, 2000, pp. 283–297.
[45] D.G. Gillam, H.N. Newman, Assessment of pain in cervical dentinal sensitivity studies. A review, J. Clin. Periodontol. 20 (1993) 383–394.
[46] G.J.P. Van Breukelen, M.J.J.M. Candel, Efficient design of cluster randomized trials with treatment-dependent costs and treatment-dependent unknown variances, Stat. Med. 10 (2018) 1–20.
[47] M.J. Campbell, Challenges of cluster randomized trials, J. Compar. Effect. Res. 3 (2014) 271–281.
[48] M.B. Magno, G.C. Nascimento, N.K. Da Penha, O.F. Pessoa, S.C. Loretto, L.C. Maia, Difference in effectiveness between strontium acetate and arginine-based toothpastes to relieve dentin hypersensitivity. A systematic review, Am. J. Dent. 28 (2015) 40–44.
[49] Y. Wang, J. Gao, T. Jiang, S. Liang, Y. Zhou, B.A. Matis, Evaluation of the efficacy of potassium nitrate and sodium fluoride as desensitizing agents during tooth bleaching treatment—a systematic review and meta-analysis, J. Dent. 43 (2015) 913–923.
[50] J. Cunha-Cruz, J.R. Stout, L.J. Heaton, J.C. Wataha, Dentin hypersensitivity and oxalates: a systematic review, J. Dent. Res. 90 (2011) 304–310.
[51] A.C. Machado, I.E.L. Viana, A.M. Farias-Neto, M.M. Braga, C. de Paula Eduardo, P.M. de Freitas, A.C.C. Aranha, Is photobiomodulation (PBM) effective for the treatment of dentin hypersensitivity? A systematic review, Lasers Med. Sci. 33 (2018) 745–753.
[52] V. Moraschini, L.S. da Costa, G.O. Dos Santos, Effectiveness for dentin hypersensitivity treatment of non-carious cervical lesions: a meta-analysis, Clin. Oral Investig. 22 (2018) 617–631.