REVIEW ARTICLE

Effectiveness of Nano-hydroxyapatite in Reducing Bleaching-related Tooth Sensitivity: A Systematic Review and Meta-analysis

Zainab Haji[1], Shizrah Jamal[2], Robia Ghafoor[3]

Abstract

Introduction: Vital tooth bleaching is a popular, conservative treatment option, easily accepted by patients for improved esthetics. This has few demerits, but managing bleaching-related tooth sensitivity remains a clinical challenge. Various materials reduce this outcome, of which nano-hydroxyapatite (n-HAP) showed promising long-term protective effects. The current systematic review aims to evaluate the effectiveness of n-HAP in the reduction of bleaching-related hypersensitivity.

Methodology: A detailed literature search was carried out on various electronic databases (CINAHL-Plus, PubMed (NLM), EBSCO Dent and Oral Science, Cochrane central register of Controlled Trials). The objective was to assess the effectiveness of n-HAP compared to placebo for the reduction in hypersensitivity. A secondary outcome of color change was noted. The risk of bias was assessed using the Cochrane collaboration tool. A meta-analysis was run on the primary outcome.

Results: Out of total 4,352 articles, five randomized controlled trials (RCTs) were selected for review. One trial reported a significant difference between the two groups and favored n-HAP, whereas one trial reported a significant number of days without sensitivity favoring n-HAP. One trial reported a significant difference in color change among the groups. Two trials were at low risk of bias; however, three had a moderate risk of bias. A meta-analysis forest plot showed an insignificant difference in reduction of bleaching-related sensitivity with n-HAP (p-value = 0.17).

Conclusions: The use of n-HAP is equally effective in reducing bleaching-related sensitivity and affecting tooth shade. However, the results of this systematic review and meta-analysis should be cautiously interpreted as limited studies were available. An increased number of good quality RCTs are required to generate robust conclusions.

Clinical significance: Tooth sensitivity is an adverse effect faced by many patients who undergo dental bleaching. The n-HAP is one of the most biocompatible and bioactive materials. This study highlights the effect of n-HAP on bleaching-related sensitivity and tooth shade, affecting the quality of patient care and clinical application of n-HAP.

Keywords: Dentin hypersensitivity, Esthetics, Nano-hydroxyapatite, Tooth bleaching, Tooth shade.

Journal of Contemporary Dentistry (2021): 10.5005/jp-journals-10031-1304

Introduction

Tooth discoloration creates a vast array of concerns that have been positively correlated with social competence, intellectual ability, and psychological status.[1] This can impart psychosocial adverse effects on patients and can create an esthetic challenge.[2] Dental stains of intrinsic and extrinsic origin have been studied in great detail over the years.[3] While several treatment options are available for teeth that have a vital pulp, bleaching offers a successful, minimally invasive, and esthetic treatment modality.[4] Vital tooth bleaching, offered either in office or at home, is a popular choice to manage mild or moderate extrinsic stains.[5] This provides instant results with reduced patient chair time.[5] In spite of being glorified in its use, this has some demerits, including hypersensitivity, enamel demineralization, gingival irritation, uneven shade, and cervical resorption.[6] Although it resolves over time, tooth sensitivity due to bleaching is sometimes responsible for patients' withdrawal from treatment.[7]

According to a study by Haywood et al., 52% of participants reported bleaching-related hypersensitivity. Whereas the study of Tam et al. reported 64% participants with sensitivity after vital tooth bleaching.[8] Jorgensen et al. concluded that tooth sensitivity can be expected in approximately half or more of patients who undergo dental bleaching treatment.[6] The effectiveness of whitening products depends on the concentration of peroxides they contain. These peroxides diffuse into the tooth and reach the transient receptor potential ankyrin-1 chemosensitive ion channels activating the nerve endings in dentin causing discomfort.[9] This differs from dental hypersensitivity, which is well-explained in the literature by the hydrodynamic theory.[10] To combat this side effect, several materials have been made available for desensitization of the dentin, which work on one of the three principles to reduce bleaching-related hypersensitivity: nerve depolarization, dentinal tubule coverage, and dentinal tubule occlusion.[11] The use of commercially available products to occlude dentinal tubules includes sodium fluorides,[12] potassium nitrate,[13] arginine,[13] casein phosphopeptide-acidulated calcium

[1–3]The Aga Khan University Hospital, Karachi, Pakistan

Corresponding Author: Robia Ghafoor, The Aga Khan University Hospital, Karachi, Pakistan, Phone: +92 300 8246414, e-mail: robia.ghafoor@aku.edu

How to cite this article: Haji Z, Jamal S, Ghafoor R. Effectiveness of Nano-hydroxyapatite in Reducing Bleaching-related Tooth Sensitivity: A Systematic Review and Meta-analysis. J Contemp Dent 2021;x(x):xx–xx.

Source of support: Nil

Conflict of interest: None

phosphate (CPP-ACP),[14] lasers,[15] and nano-hydroxyapatite (n-HAP).[14]

The n-HAP is considered one of the most biocompatible and bioactive materials. The increased nanoparticles superficial area of n-HAP may facilitate the availability of the material and the reorganization of calcium phosphate ions in the form of hydroxyapatite.[16] The n-HAP paste showed promising long-term protective effects in terms of surface deposition and maintaining a smooth surface compared with fluoride varnish.[17]

Application of desensitizers to reduce bleaching sensitivity may deteriorate the bleaching effect. The mechanism of this is not known. However, it is theorized that desensitizing agents obliterate the dentinal tubule, which could possibly impair permeability through the peroxide diffusion in subsequent cycles and can cause a change in shade. Reduced bleaching effect was noted by application of sodium fluoride in a study by Kyaw et al.[18] Therefore, analysis of color change has become necessary to assess the efficacy of desensitizer in use.

To the best of our knowledge, systematic reviews that were conducted in the past exclusively focused on desensitizing hypersensitivity other than bleaching. A recent systematic review on bleaching gel concentration was published by Pontes et al., which concluded that less concentration of bleaching gel resulted in the reduction of hypersensitivity.[19] However, that review did not take into account the use of desensitizer. The mechanism of bleaching-related hypersensitivity differs from dentin hypersensitivity as explained earlier.[9,10] Over the years, trials have been conducted on bleaching to report this hypersensitivity and the use of newer materials to reduce it. A study by Vano et al.[20] states no difference in the compared groups for reducing dentinal hypersensitivity by n-HAP as a desensitizer, in contrast to Browning et al.,[21] who concluded a significant reduction in a number of hypersensitive days in the n-HAP group. This brings us to our review question if n-HAP is effective in the reduction of bleaching-related tooth sensitivity. The objective of the current review was to determine the effect of n-HAP in reducing bleaching-related hypersensitivity. The parameters of interest were pain reduction on using n-HAP and change in color associated with the use of n-HAP as desensitizer.

Material and Methods

Registration of Protocol

This systematic review was registered with the International Prospective Register of Systematic Review (PROSPERO) REG# CRD42020196800 to avoid any unplanned duplication. Data were extracted and collected after the registration was completed. This systematic review was conducted in obedience to the guidelines of the Cochrane Handbook of Systematic Reviews of Intervention and is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) principles.

Research Question: is nano-hydroxyapatite effective in the reduction of bleaching-related tooth sensitivity?

Eligibility Criteria

The eligibility criteria were formulated using the Population, Intervention, Comparison, Outcomes and Study (PICOS) approach where the population was patients who had undergone bleaching procedures. The intervention included the use of n-HAP compared to placebo. The primary outcome of reduction in bleaching-related sensitivity reported on the visual analog scale (VAS) was assessed and the secondary outcome of change in color was also noted in included studies. All data were extracted by the primary authors (ZH and SJ). Only randomized controlled trials (RCTs) done on human participants, published in the English language, were included in this systematic review. All longitudinal, single-arm, non randomized clinical studies, including case controls and cohort, reviews, in vitro, and animal studies were excluded. There were no preset limitations on the timeline of RCTs publication.

Search Strategy

An extensive electronic search of the literature was carried out by the primary investigators on major health databases, including PubMed (NLM), CINHAL Plus (EBSCO), Cochrane, Web of Science, and Dental and Oral Science. A manual hand search was performed on Google Scholar and www.clinicaltrials.gov databases to identify any gray literature and unpublished data. Medical Subject Headings (MeSH) terms included permutations of (Nano-hydroxyapatite) OR (n-HAP) AND (Dentin Desensitizing Agents) OR (Calcium Phosphate) OR (Bleaching) OR (Hydrogen Peroxide) OR (Carbamide OR Peroxide).

Screening and Data Collection

Initial search displayed 4,352 articles that were then evaluated for inclusion by primary authors (ZH and SJ) using Endnote version X9. After eliminating duplicates, studies were further scrutinized and excluded on the basis of language, title, abstract, irrelevant object, study design, in vitro, or animal study. Only those articles with full text available in English were included as per the preset PICOS model and summarized in the PRISMA flowchart (Fig. 1). Data were extracted from the studies after a full-text review on a customized proforma to tabulate author characteristics, including author name, year, and journal of publication and study characteristics, including sample size, study design, randomization, intervention group, control group, follow-up time, and measuring tool used to evaluate primary and secondary outcomes.

Summary Measures

Relevant data were extracted from the included articles after reviewing of the full text by both authors (ZH and SJ), which were checked by the third author (ROBG). The meta-analysis was based on Der Simonian and Laird method. Bleaching-related sensitivity by VAS was taken as a continuous outcome and evaluated using mean difference with 95% confidence interval (CI). The values were considered significant when p-value ≤ 0.05. Considering heterogeneity among the studies, the random effect model was applied for the computation of a summary effect for the outcome. The software Review Manager 5.4 (The Nordic Cochrane Center, the Cochrane Collaboration, Copenhagen, Denmark) was used for meta-analysis.

Risk of Bias

The quality of RCTs was evaluated using the risk of bias assessment tool (The Cochrane collaboration's tool). This tool includes seven categories that assess RCTs as low, unclear, or high risk of bias. Insufficient information in any category was considered to be an unclear risk of bias. Any disagreement among individual reviews by the primary authors was then resolved via discussion with all authors.

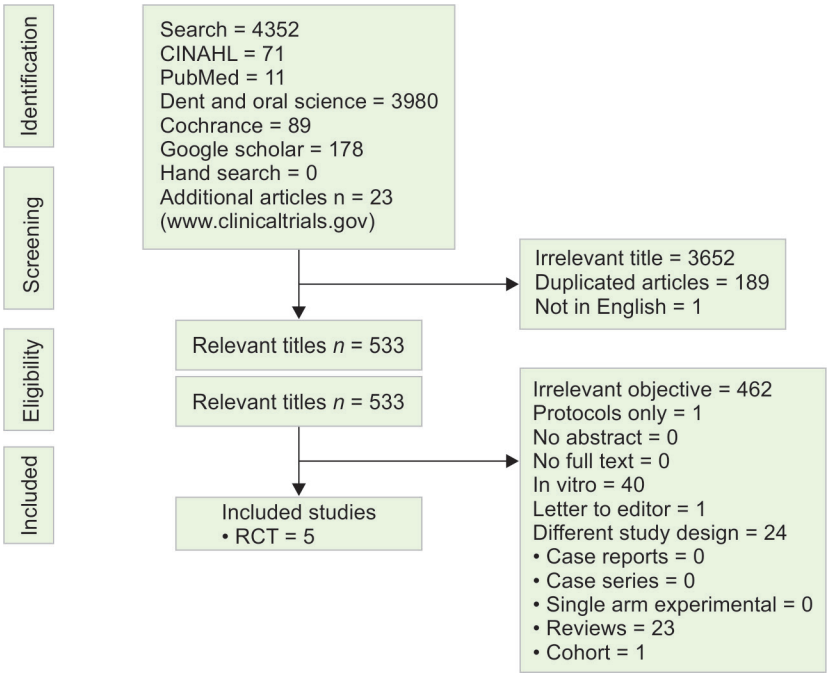

Fig. 1: PRISMA flowchart

Results

Study Characteristics

This systematic review included only five studies that fulfilled the criteria of selection. All included studies were comparable in terms of study design, intervention, and control. All the RCTs that were included in this study evaluated the reduction in bleaching-related sensitivity between n-HAP and placebo as described in Table 1.

Study Design

Five RCTs were selected. A total of 202 individuals were subjected to the bleaching treatment to evaluate the effect of n-HAP on post-bleaching sensitivity with 101 per group for n-HAP and control. A maximum number of study participants ($n = 60$) were contributed by Vano et al.[20] and the least number of participants ($n = 20$) were from Palomino et al.[22] The control group in all the studies included was a placebo for comparable results. The most common inclusion criteria in the selected studies were consenting adults with good general and oral health,[20-24] having all six maxillary anterior teeth[20,22,23] free of caries, no loss of vitality,[20,24] free of restoration with initial shade of A2, or darker on Vitapan Classic Shade guide.[20,21,24] Two studies took the loss to follow-up or dropouts during the studies into account.[22,24] The most common exclusion criteria in included studies were previous bleaching procedures,[20,22–24] pregnancy/lactation,[20,22-24] discolored teeth (tetracyclin stain, hypoplastic, or developmental anomaly),[20,22–24] bruxism, or any pathology that causes prior sensitivity,[20,22–24] continuous use of anti-inflammatory drugs,[20,22-24] heavily restored labial surfaces,[20,22,24] endodontically treated teeth,[22,24] orthodontic appliance in use,[22,24] or use of desensitization therapy prior to the study.[20,22,24] The follow-up period of included studies ranged from 2 days to 9 months.

Bleaching Protocol

In-office bleaching was performed in four studies.[20–23] The bleaching protocol varied in the included studies as described in Table 1. Some studies also mentioned previous prophylaxis before treatment.[20,21,24]

Tooth Sensitivity Evaluation

The VAS was used to measure bleaching-related tooth sensitivity in the included studies.[20–24] The degree of sensitivity was rated on an ordinal scale from 0 to 10 where 0 was no pain and 10 was intolerable pain.[22] Other measures were also used, including a 100 mm continuous line,[20,21] five-point verbal scale (none, mild, moderate, considerable, severe),[23] and a three-point VAS (four levels were considered: absent, mild, moderate, severe).[24] Airjet,[24] Schiff cold air,[20] and tactile[20] methods were also used in some studies to evaluate sensitivity as mentioned in Table 2. Tooth sensitivity was evaluated after each bleaching cycle in these studies.[20–24]

Shade Evaluation

Shade was evaluated by variable methods in four of the included studies.[20,21,23] Some used subjective Shade Guide Units (DSGU) like Vita,[20,21,23] bleachguide 3D[21] while others used objective color analysis.[24] Lack of standardized uniformity in evaluation of shade was noted among the spread of included studies described in Table 2.

Risk of Bias

The risk of bias of the included studies was assessed by the Effective Practice and Organisation of Care (EPOC) criteria proposed by the Cochrane Handbook for Systematic Reviews of Interventions.[25] The quality assessment score is summarized in Figures 2 and 3. Figure 2 reports the risk of bias of individual studies. Out of all, one study[21] failed to mention about randomization in the full text while two studies failed allocation concealment.[21,24] One out of all presented high risk on blinding of outcome assessment and unclear risk of bias on participant blinding.[22] For the remaining categories, included studies presented a low risk of bias as summarized in Figures 2 and 3.

Table 1: Study characteristics

Author, year	*Journal*	*Study type*	*Sample size*	*Study design*	*Mean age (years)*	*Male:Female*	*Follow-up*
Browning et al., 2012	Journal of Esthetic and Restorative Dentistry	RCT	42	**Group 1**: 7% HP for 30 minutes + Zero-HAP for 5 minutes	Not specified	Not specified	4 weeks
				Group 2: 7% HP for 30 minutes + n-HAP for 5 minutes			
Vano et al., 2015	International Journal of Dental Hygiene	RCT	60	**Group 1:** 6 % HP for 10 minutes × 6 times	29 ± 10.5	13:17	9 months
				Group 2: 6 %HP for 10 minutes × 6 times + 2% n-HAP for 3 minutes	27 ± 9.7	14:16	
Loguercio et al., 2015	Brazilian Oral Research	RCT	40	**Group 1:** 35% HP (for 15 minutes until 45 minutes × 3) twice 1 week apart	24.3 ± 5.9	1:1	2 days
				Group 2: 20% n-HAP for 10 minutes then scrub for 20 sec + 35% HP (for 15 minutes until 45 minutes × 3) twice 1 week apart	22.3 ± 4.7	3:2	
Palomino et al., 2015	Journal of Dentistry	RCT	20	**Group 1:** 35% HP for 15 minutes × 3 times	Unclear	Unclear	2 weeks
				Group 2: 35% HP for 15 minutes × 3 times + n-HAP 10 sec			
Da Silva et al., 2018	Journal of Clinical and Diagnostic Research	RCT	40	**Group 1:** 22% CP 2 hours a day for 10 days + paste without desensitizer for 5 minutes	23.45 ± 2.26	9:11	3 months
				Group 2: 22% CP 2 hours a day for 10 days + 20% n-HAP paste for 5 minutes	24.30 ± 2.39	11:9	

RCT, randomized controlled trial; n-HAP, nano-hydroxyapatite; CP, carbamide peroxide; HP, hydrogen peroxide

Table 2: Included studies with primary and secondary outcome

Author, year	*Measuring tool (bleaching-related sensitivity)*	*Post-bleaching sensitivity, p-value*	*No. of days*	*Measuring tool (change in color)*	*Change in color p-value*	*Follow-up*
Browning et al., 2012	VAS	>0.05	<0.001*	Vita, bleachguide 3D	>0.05	4 weeks
Vano et al., 2015	Tactile Schiff cold air VAS	>0.05	—	Vita	<0.05*	9 months
Loguercio et al., 2015	Five-point verbal scale	>0.05	—	Vita	>0.05	2 days
Palomino et al., 2015	VAS	>0.05	—	—	—	2 weeks
Da Silva et al., 2018	Air jet, VAS	<0.05*	—	CIE Lab	>0.05	3 months

p-value <0.05 is significant; VAS, visual analog scale

Meta-analysis

Meta-analysis was conducted for the primary outcome of a reduction in bleaching-related sensitivity. Quantitative data on this primary outcome using the same measuring tool were available. Thus, three studies were subjected to the meta-analysis,[20–22] which was based on Der Simonian and Laird method to compute the summarized effect. The forest plot Figure 4 graphically represents the meta-analysis conducted on included RCTs. The left column enlists the studies in chronological order from 2012 to 2015. The column on the right is a plot for each of the included RCT represented by square and a horizontal line depicting the CI of each included study. As seen in the forest plot, the line of CI or the box passes over the y-axis, and the data are considered statistically insignificant. Data from multiple studies observing the same effect are demonstrated in the forest plot. The results that fail to overlap among these studies are termed heterogeneous ($I^2 = 91\%$ in Fig.4). The area of each square represents the weight of that particular study in the meta-analysis.

The overall meta-analyzed effect is represented by the diamond, lateral points of which indicate CI for the overall estimate. These lateral points of the diamond as seen in Figure 4 overlap the line of no effect (*y*-axis); therefore, the overall meta-analyzed result cannot be said to differ from no effect at that given level of confidence. Therefore, the forest plot in Figure 4 revealed no statistically significant difference between n-HAP and placebo in reducing bleaching-related sensitivity [*p*-value = 0.17; mean difference 0.59 (–1.45, 0.2)]. The secondary outcome of change in color had non-standardized qualitative data; therefore, the meta-analysis could not be done.

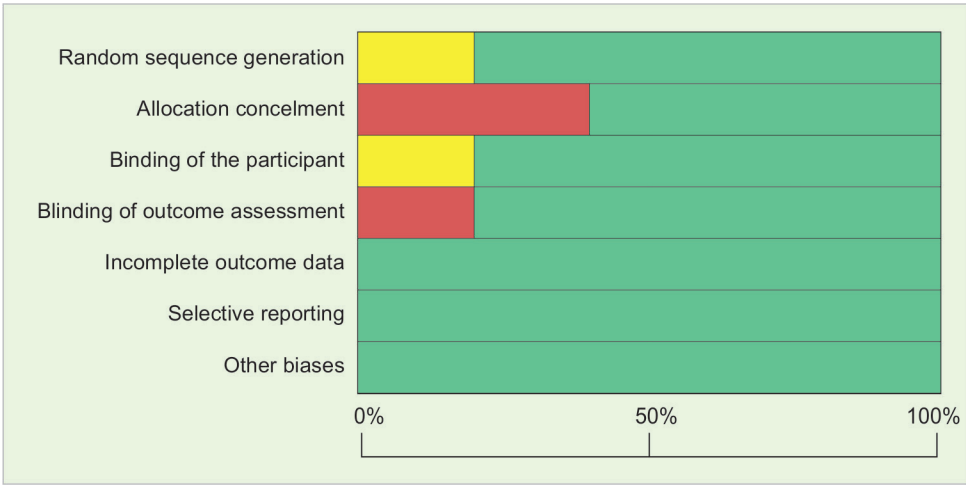

Fig. 2: Overall risk of bias

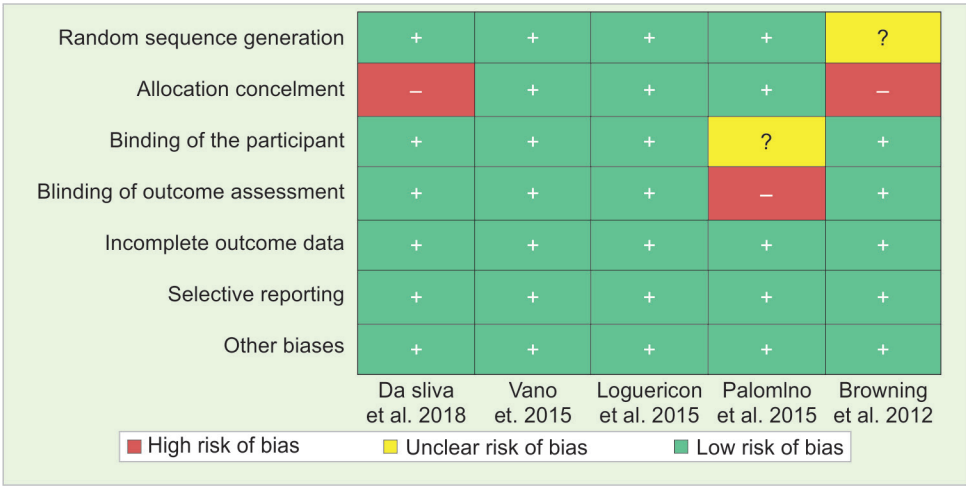

Fig. 3: Individual risk of bias

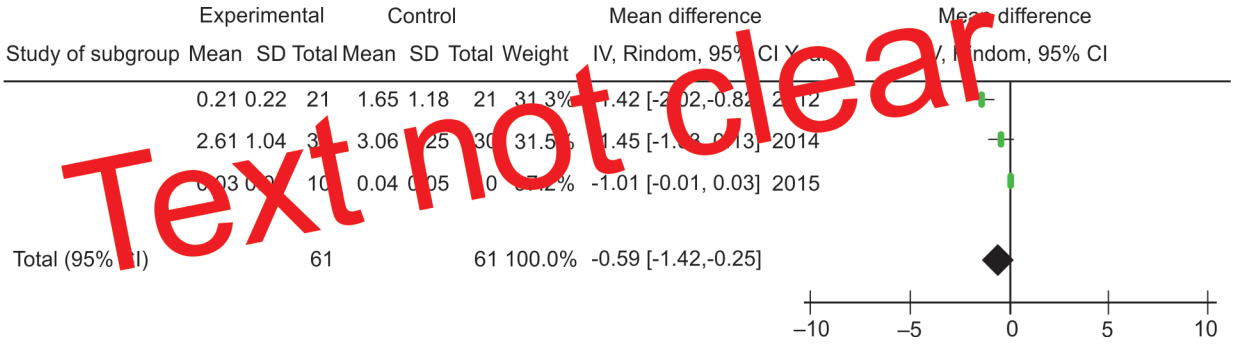

Fig. 4: Forest plot comparing reduction in bleaching related dentin hypersensitivity between experimental (n-HAP) and control (placebo) groups, using RevMan 5.4 Software

Discussion

The authors found that the present topic of reduction in bleaching-related hypersensitivity had no systematic review or meta-analysis done previously. Therefore, to the best of our knowledge, the present review may be the first systematic review and meta-analysis to address this topic of bleaching-related tooth sensitivity. The criteria for study inclusion were rigid as only comparable studies (intervention and control) were considered. Additionally, only bleaching-related sensitivity with n-HAP as a desensitizer was considered. Among five studies, four RCTs[20,21,23,24] focused on reduction in bleaching sensitivity as well as change in color, whereas one study[22] focused only on the

primary outcome of reduction in bleaching sensitivity. The control group in all studies in this review was placebo. An additional group of arginine was present in one study[24] but when results were assessed for comparable data that group was excluded. A total of 202 participants were included in all studies combined. All the included studies reported the primary outcome with a similar post-procedural pain scale, whereas no uniformity was observed in the four RCTs that qualitatively reported the change in color.[20,21,23,24]

The meta-analysis included three studies[20–22] that reported the primary outcome as the study by Da Silva et al.[24] had reported a zero value that cannot be included for the meta-analysis whereas Loguercio et al.[23] had not reported an equally quantifiable data compared to other studies. Meta-analysis revealed no statistically significant difference between n-HAP and placebo in reducing bleaching-related hypersensitivity, indicating that neither is superior to the other. This could be attributed to the variation in follow-up time periods of the included studies,[20–22] heterogeneous data as depicted by $I^2 = 91\%$, and a limited sample size that could have overshadowed if there was any comparable difference. Therefore, the use of n-HAP depends on the clinician's preference. Although the clinical outcome of both the groups in consideration appeared to be similar, meta-analysis statistically slightly favored the n-HAP group as seen by the position of diamond on the forest plot. The effect of a placebo may aggravate the discomfort while the concentration of n-HAP required to reduce bleaching-related sensitivity remains an unanswered question in the literature.

Assessments and measurement of tooth discoloration and bleaching can be performed by subjective comparisons or objective instruments. The effect of desensitizer on vital bleaching has been studied with significant results.[18] One possible cause could be the hindrance of the bleaching agent due to the use of desensitizer. While some studies report no effect of desensitizer on the shade, during bleaching.[26] The evaluation of tooth shade by color shade guide matching is simple to use. However, it is influenced by other factors including observers' experience, eye fatigue, and variation in ambient light. In the current review, there was a lack of standardization due to subjective analysis of color. Therefore, a meta-analysis cannot be applied to the included studies in order to generate a conclusion regarding that parameter. A need for standardized is easily available color measuring tool (CIE Lab or spectrophotometer) is required to quantify this outcome for uniform statistical analysis.

The risk of bias of all included five RCTs[20–24] was assessed with EPOC criteria. The highest risk of bias was reported in allocation concealment followed by blinding of outcome assessment. Participant blinding was seen in all studies except Palomino et al.[22] that failed to mention. There was no incomplete or selective data reporting, and details of randomization were given in four[20,22–24] out of five studies. No mention of random sequence generation in the study by Browning et al.[21]

The RCTs provide the highest level of evidence, and the included studies evaluated in the present review have a limited number of RCTs. The PICOS model implicated in this review could have been expanded to include nonrandomized clinical trials but that would negatively affect the risk of bias. While the search strategy was not limited by time frame, language restrictions could present with the possibility of missed articles. Therefore, only the quantifiable available data were evaluated in meta-analysis. However, the present current evidence is not sufficient.

Future considerations should be given to conducting high-quality RCT with a larger sample size and multiple comparable groups to generate robust evidence and a predictable answer to the review query.

Conclusion

A conclusion on the effectiveness of n-HAP in reducing bleaching-related hypersensitivity cannot be drawn due to limited number of studies. This was evident through the current systematic review and meta-analysis that this topic needs further research to generate a robust conclusion for clinical application. When a change in color was considered, subjective shade assessment in the included studies cannot conclude whether n-HAP affects the shade of bleaching

Clinical Significance

Tooth sensitivity is an adverse effect faced by many patients who undergo dental bleaching. The n-HAP is one of the most biocompatible and bioactive materials that has been recently under study. This study highlights the effect of n-HAP on bleaching-related sensitivity and tooth shade, affecting the quality of patient care and clinical application of n-HAP.

Acknowledgment

Khawaja Mustafa for helping in the literature search.

Orcid

Robia Ghafoor https://orcid.org/0000-0003-2335-4728

References

1. Kershaw S, Newton J, Williams D. The influence of tooth colour on the perceptions of personal characteristics among female dental patients: comparisons of unmodified, decayed and'whitened'teeth. Br Dent J 2008;204:E9. DOI: 10.1038/bdj.2008.134.
2. Kapadia Y, Jain V. Tooth staining: a review of etiology and treatment modalities. Acta Sci Dent Sci 2018;2:67–70.
3. Suchetha A, Khawar S, Sapna N, et al. All about dental stains: a review (Part II). Ann Dent Spec 2016;4(2):47.
4. Greenwall-Cohen J, Greenwall LH. The single discoloured tooth: vital and non-vital bleaching techniques. Br Dent J 2019;226(11):839–849. DOI: 10.1038/s41415-019-0373-9.
5. Bassett JL, Kurtzman GM. Simplified chairside whitening. Dent Today 2011;30:156, 158.
6. Jorgensen MG, Carroll WB. Incidence of tooth sensitivity after home whitening treatment. J Am Dent. 2002;133(8):1076–1082. DOI: 10.14219/jada.archive.2002.0332.
7. Schulte JR, Morrissette DB, Gasior EJ,et al. The effects of bleaching application time on the dental pulp. J Am Dent Assoc 1994;125(10):1330–1335. DOI: 10.14219/jada.archive.1994.0177.
8. Tam L. Clinical trial of three 10% carbamide peroxide bleaching products. J Can Dent Assoc 1999;65(4):201–207.
9. Markowitz K. Pretty painful: why does tooth bleaching hurt? Med Hypoth 2010;74(5):835–840. DOI: 10.1016/j.mehy.2009.11.044.
10. De Geus J, Wambier L, Kossatz S,et al. At-home vs in-office bleaching: a systematic review and meta-analysis. Oper Dent 2016;41(4):341–356. DOI: 10.2341/15-287-LIT.
11. West NX, Seong J, Davies M. Management of dentine hypersensitivity: efficacy of professionally and self-administered agents. J Clin Periodontol 2015;42(Suppl. 16):S256–S302. DOI: 10.1111/jcpe.12336.
12. Nanjundasetty JK, Ashrafulla M. Efficacy of desensitizing agents on postoperative sensitivity following an in-office vital tooth bleaching: A randomized controlled clinical trial. J Conserv Dent 2016;19(3):207–211. DOI: 10.4103/0972-0707.181927.

13. Thiesen CH, Rodrigues Filho R, Prates LH,et al. The influence of desensitizing dentifrices on pain induced by in-office bleaching. Braz Oral Res 2013;27(6):517–523. DOI: 10.1590/S1806-83242013000600012.
14. Kutuk ZB, Ergin E, Cakir FY,et al. Effects of in-office bleaching agent combined with different desensitizing agents on enamel. J Appl Oral Sci 2018;27:e20180233. DOI: 10.1590/1678-7757-2018-0233.
15. Rezazadeh F, Dehghanian P, Jafarpour D. Laser effects on the prevention and treatment of dentinal hypersensitivity: a systematic review. J Lasers Med Sci 2019;10(1):1–11. DOI: 10.15171/jlms.2019.01.
16. Demito CF, Costa JVD, Fracasso MLC,et al. Efficacy of fluoride associated with nano-hydroxyapatite in reducing enamel demineralization adjacent to orthodontic brackets: in situ study. Dent Press J Orthod 2019;24(6):48–55. DOI: 10.1590/2177-6709.24.6.048-055.oar.
17. Daas I, Badr S, Osman E. Comparison between fluoride and nano-hydroxyapatite in remineralizing initial enamel lesion: an in vitro study. J Contemp Dent Pract 2018;19(3):306–312. DOI: 10.5005/jp-journals-10024-2258.
18. Kyaw K, Otsuki M, Hiraishi N,et al. Effect of application of desensitizers before bleaching on change of tooth shade. Dent Mater J 2019;38(5):790–797. DOI: 10.4012/dmj.2018-129.
19. Pontes M, Gomes J, Lemos C,et al. Effect of bleaching gel concentration on tooth color and sensitivity: a systematic review and meta-analysis. Oper Dent 2020;45(3):265–275. DOI: 10.2341/17-376-L.
20. Vano M, Derchi G, Barone A,et al. Tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: a 9-month follow-up randomized clinical trial. Int J Dent Hygiene 2015;13(4):301–307. DOI: 10.1111/idh.12123.
21. Browning WD, Cho SD, Deschepper EJ. Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity. J Esthet Restor Dent 2012;24(4):268–276. DOI: 10.1111/j.1708-8240.2011.00437.x.
22. Pintado-Palomino K, Peitl Filho O, Zanotto ED,et al. A clinical, randomized, controlled study on the use of desensitizing agents during tooth bleaching. J Dent 2015;43(9):1099–1105. DOI: 10.1016/j.jdent.2015.07.002.
23. Loguercio AD, Tay LY, Herrera DR,et al. Effectiveness of nano-calcium phosphate paste on sensitivity during and after bleaching: a randomized clinical trial. Braz Oral Res 2015;29. DOI: 10.1590/1807-3107BOR-2015.vol29.0099.
24. Da Silva RC, Alencar CDM, Silva BHR,et al. A clinical, randomised, double-blind study on the use of nano-hydroxyapatite and arginine during at-home tooth bleaching. J Clin Diagn Res 2018;12. DOI: 10.7860/JCDR/2018/37325.12340.
25. Cochrane: EPOC-specific resources for review authors. Available from: http://epoc.cochrane.org/epoc-specific-resources-review-authors [Accessed on 26/8/2020].
26. Martins L, Lima e Souza L, Sutil E,et al. Clinical effects of desensitizing prefilled disposable trays in in-office bleaching: a randomized single-blind clinical trial. Oper Dent 2020;45(1):E1–E10. DOI: 10.2341/18-149-C.