LITHUANIAN UNIVERSITY OF HEALTH SCIENCES
MEDICAL ACADEMY
FACULTY OF ODONTOLOGY
DEPARTMENT OF DENTAL AND ORAL DISEASES

JENNIFER AZO TORRES

2022, OF 15

EVALUATION OF THE EFFECTIVENESS OF TOOTH BLEACHING WITH HYDROGEN PEROXIDE AND NANO-HYDROXYAPATITE: A SCIENTIFIC LITERATURE REVIEW

The Master's thesis of the Master's degree study programme "Odontology"

Supervisor: Assoc. Prof. Jolanta Siudikienė

Kaunas, 2022

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The thesis was done by graduate student ……..…….
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No.	MT parts	Evaluation criteria for the Master's thesis structural and methodological requirements	Evaluation (1-10 points)
1	Summary	Is summary informative and in compliance with the thesis content and requirements? Do the keywords match the essence of the thesis?	
2	Introduction	Are the novelty, relevance and significance of the work justified in the introduction of the thesis?	
3	Aim and objectives	Are the aim and objectives formulated properly and clearly? Are the aim and objectives interrelated?	
4	Criteria for articles selection	Were the eligibility criteria of articles determined? Are all the information sources (databases with dates of coverage, contact with the authors of article) described and is the last search day indicated? Is the electronic search strategy described in such a way that it could be repeated?	
5	Search methods and strategy	Is the selection process of articles (screening, eligibility for systematic review or, if applicable, for meta-analysis) described? Is the process of data selection from articles described (types of research, participants, interventions, factors analyzed, and indicators)? Were all the variables, for which data were searched and described, listed and described? What assumptions or simplifications were made? Were the key measurement indicators (relative risk, mean differences) identified?	

6	Systemization and analysis of data	Is the number of checked articles given: included (after their eligibility evaluation), and rejected (with reasons at each stage of rejection indicated)? Are the characteristics of the described studies (from the included articles according to which the data were taken) provided (e.g., study sample, observation period, type of subjects)? Are systemized publication data presented in tables according to individual objectives?	
7	Discussion	Are the main findings summarized and is their significance indicated? Are the limitations of the performed systematic review discussed? Does author present the interpretation of the results?	
8	Conclusions	Do the conclusions reflect the topic, aim and objectives of the Master's thesis and are they based only on the analyzed material? Are the conclusions clear and concise? Suggestions and practical recommendations (optional).	
9	List of references	Is the references list compiled according to the requirements and are the references to the text correct? Do the cited sources not older than 10 years compose at least 70% of the references, and the sources not older than 5 years make up at least 40%?	
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Evaluation of Effectiveness of Tooth Bleaching With Hydrogen Peroxide and Nano-Hydroxyapatite: A Scientific Literature Review

SUMMARY

Relevance: Tooth whitening with hydrogen peroxide (HP) is a common aesthetic dental procedure. However, this conventional bleaching agent has been associated with various adverse side effects. The scientific literature has documented the ability of biomimetic nano-hydroxyapatite (na-HA) to counteract these effects.

Aim: To analyze and describe the effects of nano-hydroxyapatite on dental enamel during dental bleaching with hydrogen peroxide.

Material and Methods: PRISMA guidelines were followed. The electronic databases PubMed®, Cochrane library, and Google Scholar were used in the search. The search was restricted to full text articles in English (using keywords) published between 2018 and 2022.

Results: The primary search identified 1052 publications, of which eight were included in this scientific literature review (based on the inclusion and exclusion criteria). Between two studies that used at-home bleaching, there was no significant difference in dental enamel microhardness values. Four studies using in-office bleaching discovered that enamel microhardness was significantly reduced following bleaching and that na-HA was able to significantly recover this loss. Three studies concluded that na-HA had no significant effect on the whitening ability of HP. Two studies discovered that na-HA significantly decreased dental sensitivity immediately following bleaching.

Conclusions: Nano-hydroxyapatite may be able to reduce dental enamel surface alterations and restore enamel microhardness loss caused by hydrogen peroxide bleaching. Furthermore, it can be used to prevent the post-bleaching dental sensitivity, while having no effect on the whitening efficacy of hydrogen peroxide.

Keywords: nano-hydroxyapatite, hydrogen peroxide, tooth whitening, dental enamel

Dantų balinimo efektyvumo, naudojant vandenilio peroksidą ir nano-hydroksiapatitą, įvertinimas: mokslinės literatūros apžvalga

SANTRAUKA

Aktualumas: Dantų balinimas vandenilio peroksidu yra įprasta estetinė odontologinė procedūra. Tačiau ši balinimo priemonė yra susijusi su nepageidaujamu balinimo poveikiu dantų emaliui. Mokslinėje literatūroje aprašomas biomimetinis nano-hidroksiapatito (na-HA) gebėjimas neutralizuoti šį poveikį.

Tikslas: išanalizuoti ir aprašyti nano-hidroksiapatito poveikį dantų emaliui, atliekant dantų balinimą vandenilio peroksidu.

Medžiaga ir metodai: Paieška viso teksto straipsnių anglų kalba (pagal pasirinktus raktažodžius) publikuotų 2018-2022 m., atlikta elektroninėmis duomenų bazėmis PubMed®, Cochrane library ir Google Scholar pagal PRISMA rekomendacijas.

Rezultatai: Atlikus pirminę paiešką buvo aptiktos 1052 publikacijos, iš kurių aštuonios publikacijos įtrauktos (remiantis įtraukimo-atmetimo kriterijais) į mokslinės literatūros apžvalgą. Dviejuose tyrimuose, kuriuose buvo atliekamas dantų balinimas namuose, nebuvo nustatyta statistiškai reikšmingų balinto emalio mikrokietumo dydžių skirtumai. Keturiuose tyrimuose, kuriuose taikytas dantų balinimo metodas odontologiniame kabinete, nustatyta, kad emalio mikrokietumas po balinimo statistiškai reikšmingai sumažėjo, tačiau pradinis mikrokietumas atkurtas panaudojus na-HA. Trijų tyrimų rezulatai rodo, kad na-HA neturėjo reikšmingos įtakos, keičiant dantų balinimo su HP efektyvumą. Dviejuose tyrimuose įrodyta, kad na-HA statiškai reikšmingai sumažino, iškart po balinimo atsiradusį, dantų jautrumą.

Išvados: Nano-hidroksiapatitas gali efektyviai sumažinti dantų emalio paviršiaus struktūrinius pokyčius, atsiradusius balinant dantis vandenilio peroksidu, ir atkurti balinto emalio mikrokietumą. na-HA apsaugo nuo po balinimo atsiradusio dantų jautrumo, nekeisdamas balinimo vandenilio peroksidu efektyvumo.

Reikšminiai žodžiai: nanohidroksiapatitas, vandenilio peroksidas, dantų balinimas, dantų emalis

ABBREVIATIONS

HP — Hydrogen Peroxide

CP — Carbamide Peroxide

HA — Hydroxyapatite

na-HA — Nano – Hydroxyapatite

VMH — Vickers micro-hardness

MHV — Microhardness value

SMH — Surface microhardness

INTRODUCTION

People are increasingly requesting tooth whitening as a treatment option from their dentists [1]. In response to public demand for brighter, more aesthetically pleasing smiles, tooth whitening alternatives have multiplied [1]. These whitening alternatives range from methods patients can use at home such as toothpaste and bleaching gels with lower concentrations to more potent concentrations which are administered by dental professionals in the clinic.

Teeth can become discolored in a variety of ways, and stains can be classified as either internal or external. Internal stains can be caused by heredity, advanced age, the use of medications such as antibiotics, an excess amount of fluoride, and developmental abnormalities [1]. External stains can be caused by environmental factors such as smoking, food and drink pigmentation, antibiotics, and metals [1].

Tooth whitening can be accomplished either physically with abrasives or chemically with bleaching agents. Typical bleaching agents contain varying concentrations of hydrogen peroxide (HP) or carbamide peroxide (CP). However, despite their widespread use, these chemicals have been associated with a myriad of adverse effects, including soft tissue irritation, alterations in surface morphology, reduced dental enamel microhardness, and increased dental sensitivity [2].

Recent clinical investigations show that there is still potential for improvement in current procedures for lowering the discomfort of tooth-whitening treatments [3]. Therefore, a more efficient therapy is still needed to produce an optimal whitening result without causing any long-term harm to the patient [2]. It has been demonstrated that adding remineralizing agents such as calcium, fluoride, and nano-hydroxyapatite before, after, or in addition to bleaching gels can help reduce demineralization and promote remineralization of teeth [4-9].

A major component of enamel is hydroxyapatite (HA), which gives it a bright white appearance and seals the enamel surface pores [10]. HA has long been one of the most researched biomaterials in medicine due to its demonstrated biocompatibility and role in bone and tooth mineralization [10].

The interactions of biomimetic hydroxyapatite particulates with tooth enamel have been studied *in vitro* and *in situ* [11-13]. It has been discovered that this interaction may have a whitening effect on the teeth [14], and unlike peroxide-based treatments, does not cause any harmful side effects when used on a regular basis, even for people under the age of 18 [15-17].

The novelty and significance of this review is that the use of nano-hydroxyapatite (na-HA) in dentistry may provide an additional benefit that combats the harmful effects of conventional bleaching methods.

Considering the available literature on the use of desensitizers in dental bleaching procedures, the aim of this systematic review was to analyze and describe the effects of nano-hydroxyapatite on dental enamel during dental bleaching with hydrogen peroxide.

The objectives of this review are as follows:

- To analyze the effect of nano-hydroxyapatite on dental enamel microhardness during hydrogen peroxide bleaching.
- To evaluate whether combining nano-hydroxyapatite with hydrogen peroxide improves hydrogen peroxide's whitening effectiveness.
- To analyze the effect of nano-hydroxyapatite on the surface morphology of dental enamel during hydrogen peroxide bleaching.
- To determine whether the use of nano-hydroxyapatite can reduce post-operative sensitivity of teeth after bleaching with hydrogen peroxide.

The hypothesis of this study is that the use of nano-hydroxyapatite when bleaching with hydrogen peroxide will increase dental enamel microhardness following bleaching, have no significant effect on the whitening efficacy of hydrogen peroxide, will reduce dental enamel surface morphology alterations, and decrease post-bleaching sensitivity.

1 CRITERIA FOR ARTICLES SELECTION. SEARCH METHODS AND STRATEGY

1.1 Protocol and registration

This systematic review has been approved by the Lithuanian University of Health Sciences' Bioethics Center with code Nr. BEC-OF-133 (Annex 1). The procedure for this review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting [18].

1.2 Information sources and search strategy

The search strategy's keywords were defined using the following PICO categories:

1. Population (P): Teeth subjected to bleaching
2. Intervention (I): Bleaching with hydrogen peroxide and nano-hydroxyapatite
3. Comparison (C): Bleaching without nano-hydroxyapatite
4. The outcome (O):
    - Effect on microhardness
    - Influence on whitening effectiveness
    - Effect on surphace morphology
    - Effect on dental sensitivity
5. Study design (S): *In vitro* and *in vivo* randomized controlled trials

PubMed/MEDLINE, Cochrane Library, and Google Scholar electronic databases were used to find studies published between 2018 and 2022. The following keywords were used in the search: hydroxyapatite, hydrogen peroxide, tooth whitening, dental bleaching, microhardness, color, and sensitivity. The keywords were presented in the search engine connected by a Boolean operator "AND" and "OR" in different combinations (Table 1).

1.3 Eligibility criteria

The titles and abstracts of studies were screened and selected. Articles that appeared in multiple databases were considered only once. The full-text articles were reviewed further if the title and abstract did not provide enough information to make a definitive decision. Eligibility was determined after a thorough review of the full text and the rejection of studies that did not meet the inclusion and exclusion criteria. (Table 2).

Table 1. Electronic database and search strategy.

Database	Keywords	Filters	Number of articles found	Date of last search
PubMed/MEDLINE	(hydroxyapatite AND hydrogen peroxide) AND (tooth whitening OR dental bleaching)	Articles from 2014-2022	24	28 March 2022
Google Scholar	(hydroxyapatite AND hydrogen peroxide) AND (tooth whitening OR dental bleaching) AND (microhardness OR color OR sensitivity)	Articles from 2018-2022	1020	28 March 2022
Cochrane Library	(hydroxyapatite AND hydrogen peroxide) AND (tooth whitening OR dental bleaching) AND (microhardness OR color OR sensitivity)	Trials	8	28 March 2022

Table 2. Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• Studies in English. • Studies from the past 5 years. • *In vitro* and *in vivo* studies. • Studies involving human permanent teeth. • Hydrogen peroxide as a bleaching agent (at-home and dental office bleaching). • Studies including comparison of dental bleaching with nano-hydroxyapatite.	• Studies involving animal teeth. • Studies involving primary teeth. • Studies involving teeth with extensive restorations or caries. • Bleaching agents other than hydrogen peroxide. • Studies where full texts were not available.

1.4 Data extraction and analysis

Three stages of screening were used to determine which articles would be included. To begin with, a preliminary search and the deletion of duplicates were performed. Second, independent title screening of search results. When a title appeared to be suitable, the abstract was evaluated for eligibility. Finally, when the title and abstract were deemed pertinent, the article's full text was reviewed. The data relevant to the review's aims and objectives was then manually extracted. To obtain any missing data, the authors were contacted via e-mail.

1.5 Risk of bias assessment of selected *in vitro* studies

Following a previous study [19], the risk of bias was assessed and adapted for the selected in vitro studies using the following parameters: randomization of teeth, use of teeth free of caries or extensive restorations, use of materials according to manufacturer's instructions, bleaching procedures performed by the same operator, and description of sample size calculation.

If the parameter was reported, a "Y" (yes) was given, while a "N" (no) was given if the information was not available. Articles with one to three items, four items, and five to six items were classified as having a high, medium, or low risk of bias, respectively. Table 4 contains a summary of the findings.

1.6 Risk of bias assessment of selected *in vivo* studies

The quality assessment of the selected *in vivo* studies were performed independently using JBI's critical appraisal tool [20], for assessing the risk of bias in randomized controlled trials. The results are described in Table 5.

2 SYSTEMIZATION AND ANALYSIS OF DATA

2.1 Study selection

The article selection procedure was carried out in accordance with the PRISMA flow diagram guidelines, as shown in Figure 1. During the search, 1052 publications from previously cited databases were retrieved. 28 papers were chosen following a preliminary screening that comprised title and abstract evaluations. The eligibility of 18 full-text articles was determined. Ten items were eliminated due to their incompatibility with the inclusion criteria. Finally, eight papers met the inclusion criteria and were included in this study.

2.2 Exclusion of studies

Six articles were excluded because they were more than five years old [21-26]. Two publications were omitted due to the absence of full texts [27-28]. One article was excluded due to the fact that the abstract was written in English but the full text was written in another language [29]. Another article was rejected as it was conducted on animal teeth [30].

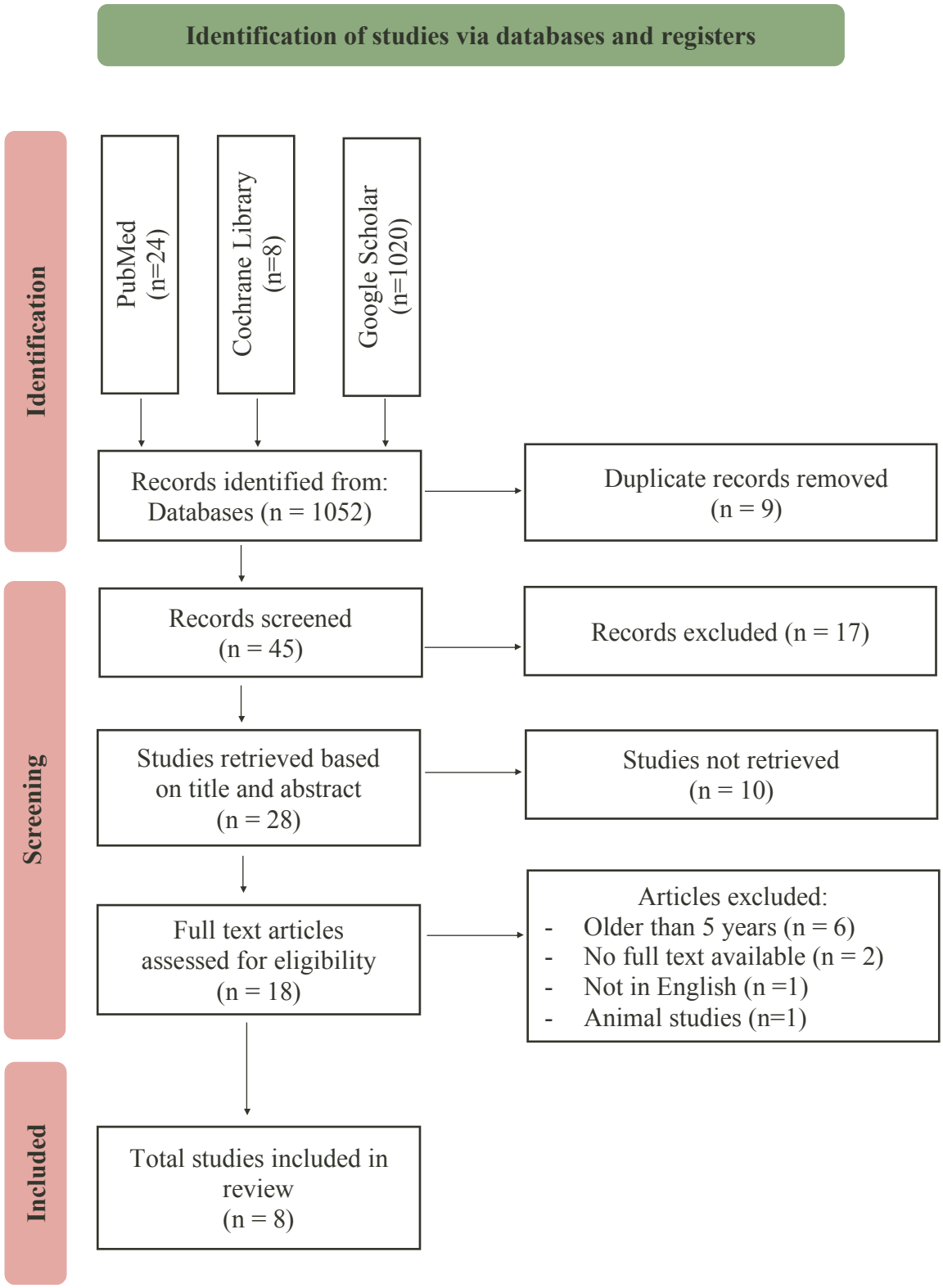

Fig 1. Flowchart depicting the search strategy and process of this systematic review.

2.3 Characteristics of the included studies

Six of the eight articles selected for this systematic review (Table 3) were *in vitro* investigations [31-36], whilst the other two were randomized controlled trials conducted *in vivo* [37-38]. Tables 6, 7, 8, and 9 provide a summary of the included studies.

Table 3. Articles included in the systematic review.

Author/Year	Title	Study design
Monterubbianesi R, et al. 2021 [31]	A Comparative Evaluation of Nanohydroxyapatite-Enriched Hydrogen Peroxide Home Bleaching System on Color, Hardness and Microstructure of Dental Enamel	*In Vitro*
Kunam D, et al. 2019 [32]	Effect of Indigenously Developed Nano-Hydroxyapatite Crystals from Chicken Egg Shell on the Surface Hardness of Bleached Human Enamel: An In Vitro Study	*In Vitro*
Ata MS, 2019 [33]	Influence of nano-silver fluoride, nano-hydroxyapatite and casein phosphopeptide-amorphous calcium phosphate on microhardness of bleached enamel: in-vitro study	*In Vitro*
Natsir N, et al. 2020 [34]	In situ Effects of Nanohydroxyapatite Paste Derived from Chicken Eggshell on Tooth Enamel During Two Bleaching Regimens	*In Vitro*
Parreiras SO, et al. 2020 [35]	Effect of Prior Application of Desensitizing Agent on the Teeth Submitted to In-Office Bleaching	*In Vitro*
Kutuk ZB, et al. 2018 [36]	Effects of in-office bleaching agent combined with different desensitizing agents on enamel	*In Vitro*
Mohamed H, et al. 2021 [37]	Impact of using nano-hydroxyapatite on postoperative hypersensitivity of two bleaching techniques – randomized controlled clinical trial	*In Vivo*
Gümüştaş B, et al. 2021 [38]	Effectiveness of remineralization agents on the prevention of dental bleaching induced sensitivity: A randomized clinical trial	*In Vivo*

2.4 Quality assessment of the included studies

Table 4. Evaluation of the risk of bias in *in-vitro* experiments based on previously reported aspects.

Author/Year	Randomization of teeth	Use of teeth free of caries	Use of materials according to manufacturer's instructions	Bleaching procedure performed by the same operator	Description of sample-size calculation	Blinding of the operator of the testing machine	Risk of bias
Monterubbianesi R, et al. 2021 [31]	UN	Y	Y	N	Y	UN	High
Kunam D, et al. 2019 [32]	Y	Y	Y	N	Y	UN	Medium
Ata, M.S., 2019 [33]	Y	Y	Y	Y	Y	UN	Low
Natsir N, et al. 2020 [34]	UN	UN	UN	UN	Y	UN	High
Parreiras SO, et al. 2020 [35]	Y	Y	Y	Y	Y	Y	Low
Kutuk ZB, et al. 2018 [36]	Y	Y	Y	UN	Y	UN	Medium

Abbreviations: N - no; Y - yes; UN - unclear

Table 5. Evaluation of the risk of bias in *in-vivo* studies following JBI's checklist for RCT.

Author/ Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Overall Appraisal
Mohamed H, et al. 2021 [37]	Y	Y	UN	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**Include**
Gümüştaş B, et al. 2021 [38]	Y	Y	UN	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	**Include**

Abbreviations: N – no; Y – yes; UN – unclear; NA – not applicable

Q1: Was true randomization used for assignment of participants to treatment groups?
Q2: Was allocation to treatment groups concealed?
Q3: Were treatment groups similar at the baseline?
Q4: Were participants blind to treatment assignment?
Q5: Were those delivering treatment blind to treatment assignment?
Q6: Were outcomes assessors blind to treatment assignment?
Q7: Were treatment groups treated identically other than the intervention of interest?
Q8: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
Q9: Were participants analyzed in the groups to which they were randomized?
Q10: Were outcomes measured in the same way for treatment groups?
Q11: Were outcomes measured in a reliable way?
Q12: Was appropriate statistical analysis used?
Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Table 6: A summary of the studies assessing dental enamel microhardness. Only groups analyzed are included in the table.

Author/ Year	Study Design	Samples (N=)	Bleaching System	Groups (n=)	Application Regimen	Micro-hardness Assessment	Analysis Period	Baseline	Post bleaching / treatment	Outcome
Monterubianesi R, et al. 2021 [31]	*In Vitro*	(N = 15) Extracted third molars	At home bleaching - 6% HP	Three groups (n=5) *6HP:* Bleaching only *6HP-nHA* Bleach & na-HA mixed together *Control (CTR)*	*6HP & 6HP-nHA:* Bleaching agent applied for 50 min/day for 7 days *CTR:* no treatment	Vickers micro-hardness (VMH)	(T0) – Baseline (T7) – 7 days after bleaching treatment	(T0) *6HP*: 320 *6HP-nHA*: 375 *CTR*: 345	(T7) *6HP*: 280 *6HP-nHA*: 320 *CTR*: 320	No statistically significant difference between (T0) and (T7) in all groups.
Kunam D, et al. 2019 [32]	*In Vitro*	(N=40) Maxillary anterior teeth	In office bleaching - 30% HP	Four groups (n=10) *Group A*: no bleaching *Group B*: bleaching only *Group D*: bleaching + na-HA	*Group A:* No bleaching *Group B & D:* Bleaching with HP for 30 min *Group D:* After bleaching, na-HA applied for 2 min/day for 14 days	Vickers micro-hardness (VMH)	(T0) – Baseline (T14) – 14 days after bleaching treatment	(T0) *Group A*: 306.66 ± 13.57 *Group B*: 311.14 ± 8.38 *Group D*: 301.60 ± 7.56	(T14) *Group A*: 306.27 ± 12.49 *Group B*: 291.84 ± 8.09 *Group D*: 308.46 ± 6.67	No significant difference between microhardness value (MHV) at T0 and T14 in Groups A and D ($P > 0.05$). A significant decrease in MHV was seen at T14 compared to T0 in Group B ($P < 0.05$). Group D showed a significant increase in enamel microhardness post bleaching compared to Group B .

Author/ Year	Study Design	Samples (N=)	Bleaching System	Groups (n=)	Application Regimen	Micro-hardness Assessment	Analysis Period	Baseline	Post bleaching / treatment	Outcome
Ata MS, 2019 [33]	*In Vitro*	(N=60) Extracted maxillary premolars	In office bleaching - 40 % HP	Four groups (n=15) *Group 1*: bleaching only *Group 3*: bleach & na-HA paste	*Group 1 & 3*: Samples bleached three times (20 min each time). *Group 1:* Control group, untreated. *Group 3*: na-HA paste applied 1 time/day for 10 days (2 min/day)	Vickers micro-hardness (VMH)	Baseline 24 hours after bleaching 24 hours after treatment with na-HA	*Group 1*: 323.38 ± 22.54 *Group 3*: 324.12 ± 18.76	Post-bleaching: *Group 1* : 117.32 ± 11.89 *Group 3*: 112.70 ± 19.95 Post-treatment: *Group 1:* 103.94 ± 29.76 *Group 3*: 171.98 ± 19.21	Post-bleaching surface microhardness (SMH) significantly lower than baseline in all groups. ($P \leq 0.001$). Post-treatment SMH significantly different from post-bleaching ones ($P \leq 0.001$) except for control group which was not statistically different ($P = 0.68$) SMH was increased in na-HA group but was decreased in control group
Natsir N, et al. 2020 [34]	*In Vitro*	(N=24) Maxillary central incisors	Two types of bleaching: At home bleaching - 15% HP In office bleaching - 40% HP	Four groups (n=6) *Group 1*: at-home bleaching and na-HA paste *Group 3*: in-office bleaching and na-HA paste	*Group 1*: Bleach applied for 20 min for 2 weeks *Group 3*: Bleach applied for 20 min over 3 cycles *Group 1 & 3*: Na-HA paste applied for 30 min/day, for 7 days.	Universal Hardness Tester	After bleaching After na-HA paste	N/A	Post-bleaching: *Group 1*: 105.95 ± 26.46 *Group 3*: 112.08 ± 36.25 Post-treatment: *Group 1*: 115.26 ± 30.95 *Group 3*: 124.44 ± 28.83	Group 1 showed no significant increase in microhardness values for tooth enamel ($p>0.05$). Group 3 showed a significant increase in the microhardness of tooth enamel ($p<0.05$)

Author/ Year	Study Design	Samples (N=)	Bleaching System	Groups (n=)	Application Regimen	Micro-hardness Assessment	Analysis Period	Baseline	Post bleaching / treatment	Outcome
Kutuk ZB, et al. 2018 [36]	*In Vitro*	(N=117) Anterior human teeth	In office bleaching - 38% HP	Nine groups (n=13) *Group 1*: bleaching only *Group 5*: bleaching and 30% na-HA *Group 9*: bleach and 30% na-HA mixed	*Group 1:* Three 15 min applications *Group 5:* NaHa applied for 2 min before and after Bleaching. The bleaching agent was applied in three 15-min applications. *Group 9*: Paste formed by mixing 1.5 mL bleach with 0.5 mL NaHa. The paste was applied 3 times for 15 min.	Vickers micro-hardness (VMH)	Before bleaching (BB) One day after bleaching (B1) 14 days after bleaching (B14)	(BB) *Group 1*: 417.9 ± 73.6 *Group 5*: 412.9 ± 57.6 *Group 9*: 413.0 ± 46.4	(B1) *Group 1*: 325.6 ± 95.0 *Group 5*: 328.5 ± 80.4 *Group 9*: 411.5 ± 115.0 (B14) *Group 1*: 420.4 ± 110.4 *Group 5*: 483.2 ± 63.0 *Group 9*: 461.3 ± 112.7	All groups showed a reduction in MHV one day after bleaching compared to baseline. However, only Group 1 and 5 showed a statistically significant difference. All groups showed statistically similar microhardness 14 days after bleaching procedure ($p>0.05$). All values were statistically different between groups 1, 5 and 9 after 14 days.

Table 7: A summary of the studies evaluating whitening efficacy. Only groups analyzed are included in the table.

Author/ Year	Study Design	Samples (N=)	Bleaching System	Groups (n=)	Application Regimen	Color Change Evaluation	Analysis Period	Baseline	Post bleaching / treatment	Outcome
Monterubbianesi R, et al. 2021 [31]	*In Vitro*	(N = 15) Extracted third molars	At home bleaching - 6% HP	Three groups (n=5) *6HP:* Bleaching only *6HP-nHA* Bleach & na-HA mixed together *Control (CTR)*	*6HP & 6HP-nHA:* Bleaching agent applied for 50 min/day for 7 days *CTR:* no treatment	Spectro-photometer ΔE The average values of L*, a*, and b* were calculated	(T0) – Baseline (T7) – 7 days after bleaching treatment	(T0) *6HP*: L*: 64.07 ± 2.88 a*: 3.62 ± 0.39 b*: 22.69 ± 2.10 *6HP-nHA*: L*: 64.91 ± 2.85 a*: 2.73 ± 1.17 b*: 19.02 ± 3.49 *CTR*: L*: 65.60 ± 6.59 a*: 3.56 ± 2.26 b*: 20.83 ± 3.00	(T7) *6HP*: L*: 74.44 ± 3.31 a*: 1.74 ± 0.96 b*:14.29 ± 2.35 *6HP-nHA*: L*: 75.88 ± 3.26 a*: 1.28 ± 0.65 b*: 11.25 ± 2.73 *CTR*: L*: 67.59 ± 6.03 a*: 3.76 ± 2.02 b*: 17.57 ± 3.48	CTR - lowest color variation between t0 and t7 6HP & 6HP-nHA - highest color variation; not statistically different ($p > 0.05$). Single color parameter: Δa - no difference between all groups ($p > 0.05$). ΔL & Δb of 6HP & 6HP-nHA statistically different than CTR ($p < 0.05$). At t7, 6HP & 6HP-nHA L* values were higher than CTR and b* values lower than CTR.
Parreiras SO, et al. 2020 [35]	*In Vitro*	(N=50) Extracted premolars	In office bleaching - 35% HP	Five groups (n=10) *Positive control:* Bleach only *Negative control*: No treatment *Nano-P®:* (na-HA & bleach)	Nano-P was applied according to manufacturer ’s recommendations. After, the bleaching gel was applied by three 15 min applications.	Spectro-photometer ΔE The average values of L*, a*, and b* were calculated	Before treatment 1 week after treatment	*Negative control*: L*: 84.2 ± 6.5 a*: -2.1 ± 0.6 b*: 22.1 ± 3.3 *Positive control*: L*: 85.4 ± 3.8 a*: -1.6 ± 2.0 b*: 27.2 ± 4.0 *Nano-P®:* L*: 83.5 ± 3.8 a*: -0.4 ± 1.4 b*: 26.4 ± 2.9	*Negative control*: 1.6 ± 0.6 *Positive control*: 9.3 ± 1.6 *Nano-P®*: 8.8 ± 2.8	A mean change of approximately 6 to 9 units of ΔE* was observed, except for the unbleached group. In the desensitizing group with Nano-P, no significant difference was detected. ($p<0.001$).

Author/ Year	Study Design	Samples (N=)	Bleaching System	Groups (n=)	Application Regimen	Color Change Evaluation	Analysis Period	Baseline	Post bleaching / treatment	Outcome
Kutuk ZB, et al. 2018 [36]	*In Vitro*	(N=117) Anterior human teeth	In office bleaching - 38% HP	Nine groups (n=13) *Group 1*: bleaching only *Group 5*: bleaching and 30% na-HA *Group 9*: bleach and 30% na-HA mixed	*Group 1:* Three 15 min applications *Group 5:* NaHa applied for 2 min before and after Bleaching. The bleaching agent was applied in three 15-min applications. *Group 9*: Paste formed by mixing 1.5 mL bleach with 0.5 mL NaHa. The paste was applied 3 times for 15 min.	Spectro-photometer ΔE The average values of L*, a*, and b* were calculated The overall color difference of specimen in each group was calculated	Before bleaching (BB) One day after bleaching (B1) 14 days after bleaching (B14)	N/A	(B1) *Group 1*: 21.8 ± 6.8 *Group 5*: 18.2 ± 5.1 *Group 9*: 21.2 ± 6.6 (B14) *Group 1:* 12 ± 12.1 *Group 5*: 10.6 ± 4.1 *Group 9*: 14.7 ± 3.8	Group 5 and 9 were statistically different compared to Group 1 one day after bleaching ($p<0.05$) The color change effect of all groups significantly decreased 14 days after the bleaching treatment when compared to 1 day after bleaching. No statisitically significant differences were seen between all groups after 14 days.

Table 8: A summary of the studies evaluating surface morphology alterations. Only groups analyzed are included in the table.

Author /Year	Study Design	Samples (N=)	Bleaching System	Groups (n=)	Application Regimen	Surface Morphology Change	Analysis Period	Outcome
Monterubbianesi R, et al. 2021 [31]	*In Vitro*	(N = 15) Extracted third molars	At home bleaching - 6% HP	Three groups (n=5) *6HP:* Bleaching only *6HP-nHA* Bleach & na-HA mixed together *Control (CTR*	*6HP & 6HP-nHA:* Bleaching agent applied for 50 min/day for 7 days *CTR:* no treatment	Scanning Electron Microscopy (SEM) evaluation SEM micrographs of the enamel were obtained with magnifications of 400×, 2000× and 8000×	Not stated	*CTR:* Showed sound enamel morphology, with an aprismatic superficial enamel layer. *6HP:* Minimal integrity loss with increased enamel irregularities. There were microporosities, a wavy surface pattern, partial dissolution of the rods, and raised enamel interrods. *6HP-nHA:* Similar to CTR, but with the prismatic enamel layer exposed. High magnification revealed prismatic features similar to CTR in the superficial layer, despite an increase in rods, presenting a honeycomb structure typical of the prismatic layer.
Parreiras SO, et al. 2020 [35]	*In Vitro*	(N=4) Extracted premolars (five fragments of each tooth were obtained)	In office bleaching - 35% HP	Five groups (n=10) *Positive control:* Bleach only *Negative control*: No treatment *Nano-P®:* (na-HA & bleach)	Nano-P was applied according to manufacturer's recommendations. After, the bleaching gel was applied by three 15 min applications.	Scanning Electron Microscopy (SEM) evaluation	Not stated	The negative control group and bleached specimens had different superficial morphologies. Enamel subjected only to beaching (positive control group) showed obvious surface changes, irregularities, and demineralization Due to saturation, desensitizers accumulated on the enamel surfaces of desensitizer groups.

Author /Year	Study Design	Samples (N=)	Bleaching System	Groups (n=)	Application Regimen	Surface Morphology Change	Analysis Period	Outcome
Kutuk ZB, et al. 2018 [36]	*In Vitro*	(N=117) Anterior human teeth	In office bleaching - 38% HP	Nine groups (n=13) *Group 1*: bleaching only *Group 5*: bleaching and 30% na-HA *Group 9*: bleach and 30% na-HA mixed	*Group 1:* Three 15 min applications *Group 5:* NaHa applied for 2 min before and after Bleaching. The bleaching agent was applied in three 15-min applications. *Group 9*: Paste formed by mixing 1.5 mL bleach with 0.5 mL NaHa. The paste was applied 3 times for 15 min.	Scanning Electron Microscopy (SEM) evaluation	Before bleaching (BB) One day after bleaching (B1) 14 days after bleaching (B14)	SEM analysis revealed no detrimental effects on any of the groups 1 day or 14 days after bleaching. The enamel surfaces of the test groups showed no changes at any time.

Table 9: A summary of the studies evaluating post-bleaching sensitivity. Only groups analyzed are included in the table.

Author /Year	Study Design	Nº of patients (dropouts)	Mean Age	Bleaching System	Groups (n=)	Application Regimen	Tooth Sensitivity Assessment	Analysis Period	Outcome	
									G 3	G 4
Mohamed H, et al. 2021 [37]	*In Vivo*	28 (0 drop outs)	18 - 45 years	Two types of in office bleaching: Photo catalyzed bleaching agent (Philips ZOOM!) – 25% HP gel Chemo catalyzed bleaching agent (Philips Dash) – 30% HP gel	Four groups (n=7) *G 3*: Bleaching with ZOOM, followed by application of na-Ha (Nano p) *G 4*: Bleaching with Dash, followed by application of na-Ha (Nano p)	*G 3:* Bleach applied, LED device used for 15 min. The patients received 3 sessions, 15 min each. *G 4:* Whitening accelerator applied before whitening gel. The whitening gel was then applied for 3 sessions, 15 min each *G 3 and G 4:* After bleaching: na-HA (Nano p), was rubbed on enamel for 10 sec. The material was left for five min then removed.	Visual analogue scale (VAS) Pain intensity: 0 – none 1 – mild 2 – moderate 3 – severe	After bleaching After na- HA After 24 hours (D1) After 48 hours (D2) After 1 week (D7)	*After bleaching:* 3 – 57.1 2 – 42.9% 1 – 0% 0 – 0% *After na-HA*: 3 – 0% 2 – 42.9% 1 – 42.9% 0 –14.3% *D1:* 3 – 0% 2 – 0% 1 – 14.3% 0 – 85.7% *D2 and D7*: 3 – 0% 2 – 0% 1 – 0% 0 – 100% Before na-HA - statistically significant difference in pain severity. Immediately after na-HA; no statistically significant difference until day 7 indicating gradual pain reduction.	*Aafter bleaching:* 3 – 42% 2 – 42% 1 – 0% 0 – 14%. *After na-HA:* 3 – 0% 2 – 42.9% 1 – 42.9% 0 – 14.3% *D1*: 3 – 0% 2 – 0% 1 –14.3% 0 – 85.7% *D2 and D7:* 3 – 0% 2 – 0% 1 – 0% 0 –100% No statistically significant difference until day 1; day 2 & 7 statistically significant difference from other time periods indicating gradual pain reduction.

Author /Year	Study Design	Nº of patients (dropouts)	Mean Age	Bleaching System	Groups (n=)	Application Regimen	Tooth Sensitivity Assessment	Analysis Period	Outcome
Gümüştaş B, et al. 2021 [38]	*In Vivo*	64 (0 drop outs)	18 - 40 years	In-office bleaching - 38% HP gel activated by light source	Four groups (n=16) *Group 1:* Control (Placebo) *Group 3:* na-HA	*Group 1:* The placebo agent was applied for 4 minutes. *Group 3*: Subjects were treated with 30% na-HA gel for 4 min. After, subjects in both Group 1 and 3 were treated with hydrogen peroxide. There were three 15-minute bleaching agent applications.	Visual analogue scale (VAS) Pain intensity: 0 -none 1 -mild 2 -moderate 3 -considerable 4 -severe The VAS was based on a 100-mm scale: 0 mm - no pain 100 mm - severe pain	(T0) Before treatment (T1) 24 hours after bleaching (T7) Seven days after bleaching	*# of patients experience sensitivity* (T0) *Group 1:* 0 – 16, 1 – 0, 2 – 0, 3 – 0, 4 – 0 (T1) *Group 1:* 0 – 0, 1 – 2, 2 – 5, 3 – 6, 4 – 3 (T7) *Group 1:* 0 – 4, 1 – 7, 2 – 5, 3 – 0, 4 – 0 *Group 3:* 0 – 16, 1 – 0, 2 – 0, 3 – 0, 4 – 0 *Group 3:* 0 – 1, 1 – 9, 2 – 6, 3 – 0, 4 – 0 *Group 3:* 0 – 4, 1 – 11, 2 – 1, 3 – 0, 4 – 0 *Comparison of VAS values over time:* *Group 1:* (T0) 1.94 ± 0.85 (T1) 60.87 ± 17.17 (T7) 30.3 ± 11.39 *Group 3:* (T0) 2.00 ± 0.81 (T1) 36.06 ± 10.42 (T7) 25.19 ± 7.27 All groups had increased sensitivity after the bleaching application. After 24 h, more patients treated with na-HA had low sensitivity (none, mild, moderate) than those in control group. No groups of patients felt considerable or severe sensitivity after seven days.

2.5 Outcomes

2.5.1 Evaluation of dental enamel microhardness

Five studies included assessed the effect of na-HA on dental enamel microhardness after bleaching [31-34, 36]. According to Monterubbianesi R, et al. [31], who compared the effects of an at-home bleaching system with and without added na-HA, it was found that microhardness values (MHV) were not statistically different after 7 days in all test groups compared to baseline MHV. Kunam D, et al. [32] investigated the effects of an in-office bleaching system and discovered a significant reduction in microhardness after 14 days in the samples subjected to bleaching only compared to the group that was treated with na-HA following bleaching, which showed a significant increase in MHV. Ata MS [33] conducted a study investigating the effects of na-HA treatment on teeth following in-office bleaching treatments. This study [33] evaluated the MHV at baseline, 24h after bleaching and 24h after treatment with na-HA. It was found that enamel SMH values decreased after bleaching in all groups compared to baseline values. Post-treatment SMH values were significantly higher compared to post bleaching values, except for the control group which was only subjected to bleaching and was not statistically different. The study showed that na-HA increased the enamel SMH after bleaching, but the control group did not. Natsir N, et al. [34] investigated the effects of using na-HA on teeth after being subjected to either in-office or at-home bleaching. This study evaluated the MH after bleaching treatment, and again after the application of na-HA paste. It was found that the applications of na-HA paste after in-office bleaching resulted in a significant increase in tooth enamel microhardness compared to after bleaching. In contrast, no significant effect was observed after na-HA application to the teeth subjected to at-home bleaching. Kutuk ZB, et al. [36] investigated the effect of na-HA on teeth subjected to an in-office bleaching treatment. The study compared a bleaching only group (G1), a group which was subjected to na-HA application both before and after bleaching (G5), as well as a group with na-HA mixed together with the bleaching gel (G9). MH values were analyzed before bleaching, 1 day after the procedure, and 14 days after. A decrease in microhardness was seen in all groups 1 day after bleaching. The highest loss was observed in G1, which was bleached only, and the lowest loss was observed in G9, which contained na-HA mixed into the bleaching agent. The difference in MH loss between G9 and the other groups was significant. After 14 days, the microhardness of all groups increased in comparison to baseline.

2.5.2 Evaluation of whitening efficacy

Color change (ΔE) was analyzed in three studies included in this review. The parameters L*, a*, and b* were calculated. The L* value indicates the luminosity (values range from 0 [black] to 100 [white]), the a* value indicates the red–green axis, and the b* value indicates the yellow–blue axis [35]. Monterubbianesi R, et al. [31] evaluated the color change of teeth bleached at home at baseline, and after one week of bleaching. It was concluded that color change was not statistically different in any of the test groups.

Parreiras SO, et al. [35], who evaluated teeth bleached with an in-office bleaching agent, similarly found no significant difference between groups bleached with and without na-HA. Kutuk ZB, et al. [36] who used an in-office bleaching agent in their study, observed that the bleaching impact of all groups diminished after 14 days compared to one day after bleaching, but that modifying the bleaching gel with na-HA had no effect on color change.

2.5.3 Evaluation of surface morphology alterations

In the evaluation of surface morphology change, one study analyzed the difference between at home bleaching [31], while the other two analyzed the change using in office bleaching [35-36]. Monterubbianesi R, et al. [31] obtained SEM micrographs of the enamel with magnifications of 400×, 2000× and 8000× and analyzed the teeth before and after bleaching treatment. Differences were found between the group subjected to bleaching alone in comparison to the group with na-HA added to the bleaching agent. 6HP exhibited an uneven surface and structure due to the absence of rods and interrods. By contrast, the enamel structure of rods and interrods was preserved in 6HP-nHA.

Parreiras SO, et al. [35] obtained SEM micrographs of the enamel at a magnification of 10,000× at baseline and one week after bleaching procedures. This study found that the group which was only bleached showed surface alterations of the enamel. The group that utilized na-HA prior to bleaching achieved a surface comparable to that of the unbleached control group. In contrast to both of these studies, Kutuk et al. [36] used a 256-magnification to obtain SEM micrographs at baseline, one day after, and fourteen days after bleaching procedures. They discovered no difference in any of the groups over the course of the evaluation.

2.5.4 Evaluation of post-bleaching sensitivity

Both studies [37-38] included for the evaluation of tooth sensitivity used in office bleaching techniques. Mohamed H, et al. [37] analyzed two different bleaching techniques – a photo catalyzed and a chemocatalyzed group. Both groups were treated with nano-hydroxyapatite after bleaching. A visual analogue scale was used to measure patients' hypersensitivity 24 hours, 48 hours, and 1 week after bleaching sessions.This study found that cases of severe dental sensitivity were relieved immediately after application of na-HA. There was a statistically significant difference in the photocatalytic group immediately after application of na-HA compared to before application.

Reduction in dental sensitivity over time was evident in both tested bleaching groups. In addition, it was found that after one week, all pain scores disappeared within all tested groups. Gümüştaş B, et al. 2021[38] analyzed tooth sensitivity before bleaching, 24 hours after, and 7 days after bleaching. It was found that after 24 h, there were more patients with low sensitivity (none, mild, moderate) previously treated with na-HA before bleaching in comparison with the control groups which used a placebo gel before bleaching. However, the number of patients who felt considerable or severe sensitivity after seven days was not observed in any group [38].

3 DISCUSSION

This systematic review analyzed the effect of nano-hydroxyapatite (na-HA) as a remineralizing agent on enamel bleached with hydrogen peroxide (HP). The included articles examined the effects of bleaching with varied concentrations of HP and na-HA on dental enamel microhardness, surface morphological changes, whitening effectiveness, and post-bleaching sensitivity.

In terms of microhardness reduction, two publications [31, 34] examined the effect of na-HA on teeth subjected to at-home bleaching. When compared to baseline levels, neither of these studies found a significant decrease in microhardness. Four studies [32-34,36] analyzed the influence of na-HA on teeth that had undergone in-office bleaching. Three of these investigations [32-33,36] found that bleaching reduced microhardness values compared to baseline. Natsir N, et al. [34] did not report baseline values before bleaching, and the other three investigations [32-34] found an increase in microhardness values following na-HA exposure compared to solely bleached groups. In the instance of Kutuk ZB, et al. [36], the maximum loss of microhardness was reported in the bleaching only group, whereas the lowest loss was recorded in the group that included na-HA mixed into the bleaching agent. Anyhow, after 14 days, all groups tested demonstrated remineralization and increased microhardness. The authors maintain that this may be because specimens were stored in artificial saliva between treatments, but considering that other investigations [32-33] did the same, it is probable that the discrepancies in results are related to the differences in the sources and concentrations of na-HA.

In terms of enhancing whitening capabilities of hydrogen peroxide, all studies reporting on this outcome[31,35-36] found no significant difference in color change when combining na-HA with the bleaching treatment. The results were neither diminished nor improved. This indicates that regardless of the presence or absence of na-HA, hydrogen peroxide maintains its effectieffectivenessve in whitening teeth.

With regard to the surface morphology alterations, two studies [31,35] found that alterations were visible on the enamel surface after bleaching only despite using low or high concentrations of hydrogen peroxide. These studies [31,35] also found that the surface morphology of the groups exposed to na-HA showed similar characteristics to the enamel surface before being bleached. Kutuk ZB, et al. [36] reported no significant changes in the surface morphology of any of the groups during all periods of treatment. This finding could be due to the fact that SEM micrographs were taken at a much lower magnification in comparison to the other studies [31,35] and could therefore not provide sufficient information on the surface alterations.

Tooth sensitivity is a typical reported side effect of dental whitening. Remineralization agents may be used before or after dental bleaching to reduce tooth sensitivity. Because of the tiny particle sizes of nano-hydroxyapatite, dentinal tubules may be accessible via micro-cracks in the dentin [38]. As a consequence of the concentration of na-HA molecules, the cracks get smaller [38]. A VAS scale was used to assess tooth sensitivity after bleaching operations. Of the studies analyzing the effect of na-HA on dental bleaching induced sensitivity [37-38], a total of 92 patients were selected to evaluate the effects of na-HA. The patients were asked to score their sensitivity levels at different follow up periods. Both studies discovered that na-HA was capable of decreasing immediate post-bleaching sensitivity. Over a longer period of time, all groups, even those receiving merely bleaching, saw a progressive reduction of sensitivity, as the saliva in the natural environment of the oral cavity remineralizes the enamel. Similarly to the results of this review, Browning et al. [39]. showed that using remineralization products containing na-HA reduced post-bleaching sensitivity. Another research, conducted by Vano et al. [40]., showed that the use of na-HA reduced post-operative sensitivity.

The main limitation of this review is the heterogeneity of the included studies. Different concentrations of hydrogen peroxide and different sources of na-HA were used. In addition, only two studies met the inclusion criteria for determination of tooth sensitivity. Therefore, further studies and clinical investigations using less variable methods should be conducted.

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CONFLICT OF INTEREST

The author has not encountered any conflict of interests.

CONCLUSIONS

Based on the results and limitations of this systematic review,

1. Nano-hydroxyapatite has the potential to remineralize dental enamel and restore microhardness lost during bleaching with both low and high concentrations of hydrogen peroxide.
2. No significant change is observed on the whitening effectiveness of hydrogen peroxide when using nano-hydroxyapatite during the bleaching procedure.
3. Following hydrogen peroxide bleaching, the dental enamel microstructure was found to be altered, however, the altered enamel surface could be restored to its original state using nano-hydroxyapatite.
4. Nano-hydroxyapatite demonstrated the ability to alleviate post-operative sensitivity experience immediately after bleaching.

PRACTICAL RECOMMENDATIONS

According to the findings of this review, utilizing a remineralizing agent such as nano-hydroxyapatite in clinical practice may be beneficial for minimizing the adverse effects of bleaching procedures on teeth. However, due to the lack of consistency among the studies, further research using more standardized materials and procedures is required. While the results of this study cannot be considered conclusive, they may serve as a guide for future research on na-HA use.

REFERENCES

1. Carey CM. Tooth whitening: What we now know. Journal of Evidence Based Dental Practice. 2014;14:70–6.
2. Rodríguez-Martínez J, Valiente M, Sánchez-Martín MJ. Tooth whitening: From the established treatments to novel approaches to prevent side effects. Journal of Esthetic and Restorative Dentistry. 2019;31(5):431–40.
3. Vaez SC, Faria-e-Silva AL, Loguércio AD, Fernandes MT, Nahsan FP. Preemptive use of etodolac on tooth sensitivity after in-office bleaching: A randomized clinical trial. Journal of Applied Oral Science. 2018;26.
4. Vieira-Junior WF, Lima DA, Tabchoury CP, Ambrosano GM, Aguiar FH, Lovadino JR. Effect of Toothpaste Application Prior to Dental Bleaching on Whitening Effectiveness and Enamel Properties. Oper Dent. 2016;41:E29–38.
5. Vieira-Junior WF, Ferraz LN, Pini N, Ambrosano G, Aguiar F, Tabchoury C. Effect of Toothpaste Use Against Mineral Loss Promoted by Dental Bleaching. Oper Dent. 2018;43:190–200.
6. Rauen CA, Chidoski- Filho JC, Bittencourt BF, Gomes GM, Gomes JC, Gomes OMM. Effect of bleaching agents containing fluoride or calcium on enamel microhardness, roughness and permeability. Braz J Oral Sci. 2015;14:262–6
7. Sasaki RT, Catelan A, Bertoldo Edos S, Venâncio PC, Groppo FC, Ambrosano GM. Effect of 7.5% hydrogen peroxide containing remineralizing agents on hardness, color change, roughness and micromorphology of human enamel. Am J Dent. 2015;28:261–7.
8. Ferraz LN, Vieira-Junior WF, Ambrosano GMB, Giorgi MCC, Aguiar FHB, Lima DANL. Effect of different concentrations of nanohydroxyapatite on tooth bleaching effectiveness and enamel bond strength. Braz Dent Sci. 2018;21:17–25
9. Vieira I, Vieira-Junior W, Pauli M, Theobaldo J, Aguiar F, Lima D, et al. Effect of in-office bleaching gels with calcium or fluoride on color, roughness, and enamel microhardness. Journal of Clinical and Experimental Dentistry. 2020;
10. Pepla E, Besharat LK, Palaia G, Tenore G, Migliau G. Nano-hydroxyapatite and its applications in preventive, restorative and regenerative dentistry: a review of literature. Ann Stomatol (Roma). 2014 Jul;5(3):108-14.

11. Kensche A, Holder C, Basche S, Tahan N, Hannig C, Hannig M. Efficacy of a mouthrinse based on hydroxyapatite to reduce initial bacterial colonisation in situ. Archives of oral biology. 2017 Aug 1;80:18-26.
12. Fabritius-Vilpoux K, Enax J, Herbig M, Raabe D, Fabritius HO. Quantitative affinity parameters of synthetic hydroxyapatite and enamel surfaces in vitro. Bioinspired, Biomimetic and Nanobiomaterials. 2019 Feb 1;8(2):141-53.
13. Nobre CM, Pütz N, Hannig M. Adhesion of hydroxyapatite nanoparticles to dental materials under oral conditions. Scanning. 2020 May 5;2020.
14. Lelli M, Putignano A, Marchetti M, Foltran I, Mangani F, Procaccini M, Roveri N, Orsini G. Remineralization and repair of enamel surface by biomimetic Zn-carbonate hydroxyapatite containing toothpaste: a comparative in vivo study. Frontiers in physiology. 2014 Sep 5;5:333.
15. Enax J, Fabritius HO, Fabritius-Vilpoux K, Amaechi BT, Meyer F. Modes of action and clinical efficacy of particulate hydroxyapatite in preventive oral health care− state of the art. The Open Dentistry Journal. 2019;13:274-87.
16. Epple M, Meyer F, Enax J. A critical review of modern concepts for teeth whitening. Dentistry journal. 2019 Sep;7(3):79.
17. Steinert S, Kuchenbecker J, Meyer F, Simader B, Zwanzig K, Enax J. Whitening effects of a novel oral care gel with Biomimetic Hydroxyapatite: A 4-week observational pilot study. Biomimetics. 2020;5(4):65.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The Prisma 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;
19. Sarkis-Onofre R, Skupien JA, Cenci MS, Moraes RR, Pereira-Cenci T. The role of resin cement on bond strength of glass-fiber posts luted into Root Canals: A systematic review and meta-analysis of in vitro studies. Operative Dentistry. 2014;39(1).
20. Critical appraisal tools [Internet]. JBI. [cited 2022Apr18]. Available from: https://jbi.global/critical-appraisal-tools
21. Silva CM, de Lima Gomes YSB, Alexandrino LD, de M Alencar C, Alves EB, Faial KCF. In situ effect of nanohydroxyapatite paste in enamel teeth bleaching. The Journal of Contemporary Dental Practice. 2017;18(11):996–1003.
22. Vano M, Derchi G, Barone A, Genovesi A, Covani U. Tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: A 9-month follow-up randomized clinical trial. International Journal of Dental Hygiene. 2015;13(4):301–7.

23. Browning W.D, Cho S.D, Deschepper E.J. Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity. Journal of Esthetic and Restorative Dentistry. 2011;24(4):268–76.
24. Kaveh S, Khoroushi M, Shirban F, Doustfateme S. Effect of three nanobiomaterials on the surface roughness of bleached enamel. Contemporary Clinical Dentistry. 2015;6(4):466.
25. da Rosa Nogueira T, Alexandrino LD, de Lima Gomes Ydo S, de Melo Alencar C, Alves EB, Silva CM. An in situ Evaluation of Bioactives on the Morphology of Bleached Enamel. J Contemp Dent Pract. 2016 Mar 1;17(3):192-7.
26. Jiang T, Ma X, Wang Z, Tong H, Hu J, Wang Y. Beneficial effects of hydroxyapatite on enamel subjected to 30% hydrogen peroxide. Journal of Dentistry. 2008;36(11):907–14.
27. Prevention of bleaching induced sensitivity [Internet]. ClinicalTrials.gov. [cited 2022Apr20]. Available from: https://clinicaltrials.gov/ct2/show/NCT04855279
28. Hypersensitivity and color changes of bleached teeth using different remineralizing agents [Internet]. ClinicalTrials.gov. [cited 2022Apr20]. Available from: https://clinicaltrials.gov/ct2/show/NCT04875000
29. Daneshkazemi, A., Davari, A., Sadoughi, M. Effect of 40% Hydrogen Peroxide with and without Nano-Hydroxyapatite and Nano-Bioactive Glass on the Dentinal Tubular Occlusion: An In Vitro Study. *Journal of Mashhad Dental School*, 2019; 43(3): 271-278.
30. Ferraz LN, Vieira Júnior WF, Ambrosano GM, Giorgi MC, Aguiar FH, Lima DA. Effect of different concentrations of nanohydroxyapatite on tooth bleaching effectiveness and enamel bond strength. Brazilian Dental Science. 2018;21(1):17–25.
31. Monterubbianesi R, Tosco V, Bellezze T, Giuliani G, Özcan M, Putignano A, et al. A comparative evaluation of nanohydroxyapatite-enriched hydrogen peroxide home bleaching system on color, hardness and microstructure of dental enamel. Materials. 2021;14(11):3072.
32. Kunam D, Sampath V, Manimaran S, Sekar M. Effect of Indigenously Developed Nano-Hydroxyapatite Crystals from Chicken Egg Shell on the Surface Hardness of Bleached Human Enamel: An In Vitro Study. Contemp Clin Dent. 2019 Jul-Sep;10(3):489-93.
33. Ata MS. Influence of nano-silver fluoride, nano-hydroxyapatite and casein phosphopeptide-amorphous calcium phosphate on microhardness of bleached enamel: in-vitro study. Tanta Dent J 2019;16:25-8
34. Natsir N, Tanumihardja M, Sebon A, Hafsah Katu, Nugroh JJ, Lukman M. In situ effects of nanohydroxyapatite paste derived from chicken eggshell on tooth enamel during two bleaching regimens. International Journal of Pharmaceutical Research. 2020;12(sp1).

35. Parreiras SO, Favoreto MW, Lenz RE, Serra ME, Borges CP, Loguercio AD, et al. Effect of prior application of desensitizing agent on the teeth submitted to in-office bleaching. Brazilian Dental Journal. 2020;31(3):236–43.
36. Kutuk ZB, Ergin E, Cakir FY, Gurgan S. Effects of in-office bleaching agent combined with different desensitizing agents on enamel. Journal of Applied Oral Science. 2018;27.
37. Mohamed H, Fayed A, Elkassas D, Hassanien O. Impact of using nano-hydroxyapatite on postoperative hypersensitivity of two bleaching techniques – randomized controlled clinical trial. IOP Conference Series: Materials Science and Engineering. 2021;1046(1):012004.
38. Gümüştaş B, Dikmen B. Effectiveness of remineralization agents on the prevention of dental bleaching induced sensitivity: A randomized clinical trial. International Journal of Dental Hygiene. 2021;
39. Browning WD, Cho SD, Deschepper EJ. Effect of a nano-hydroxyapatite paste on bleaching-related tooth sensitivity. Journal of Esthetic and Restorative Dentistry. 2011;24(4):268–76.
40. Vano M, Derchi G, Barone A, Genovesi A, Covani U. Tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: A 9-month follow-up randomized clinical trial. International Journal of Dental Hygiene. 2015;13(4):301–7.

ANNEXES

Annex 1.

LIETUVOS SVEIKATOS MOKSLŲ UNIVERSITETAS

BIOETIKOS CENTRAS

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2022.04.15 Nr. BEC-OF-133

DĖL PRITARIMO TYRIMUI

LSMU Bioetikos centras, įvertinęs Jennifer Azo Torres pateiktus dokumentus, studento tiriamajam darbui tema „Evalution of effectiveness of tooth bleaching with hydrogen peroxide and nano-hydroxyapatite: a systematic scientific literature review“ pritaria*.

Dr. Elmantas Peičius

* Pastaba: šis pritarimas neatleidžia tiriamąjį mokslinį darbą vykdančių asmenų nuo prievolės laikytis Bendrojo duomenų apsaugos reglamento nuostatų ir nuo atsakomybės gauti nacionalinio arba regioninio bioetikos komiteto leidimą, jei toks leidimas būtinas pagal LR Biomedicininių tyrimų etikos įstatyme numatytus reikalavimus.