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Evaluate different nanoparticles into dental restorative materials: A systematic review and meta-analysis

Marzieh Rohaninasab
Assistant professor, Aesthetic and Restorative Department, Dental school, International Campus, Tehran University of Medical Sciences, Tehran, Iran

Farimah Hajebi
Post Graduate Student, Department of Restorative Dentistry, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
Corresponding author email: farimah.hajebi@yahoo.com

Sheida Hosseinian Ahangarnezhad
General Dentist, Tehran, Iran

Amirahmad Pahlavan Hoseini
Department of Prosthodontics, Islamic Azad University of Medical Sciences, Dental School, Tehran, Iran

***Abstract*---**Background and aim: The purpose of this study was to evaluate different nanoparticles in dental restorative materials. Method: Databases of PubMed, Scopus, Web of Science, EBSCO, ISI Web of Knowledge, and Embase were searched for systematic literature between 2012 to July 2022. Data analysis was performed using STATA/MP V17 software. 95% confidence interval for mean differences or Hedges' g (a measure of effect size) with fixed effect model and Inverse-variance method were calculated. Result: In the initial review, duplicate studies were eliminated and abstracts of 151 studies were reviewed, the full text of 42 studies was reviewed by two authors, and finally, 11 studies were selected. Hedges' g of changes to the bacterial activity of dental restorative materials for silver nanoparticles was –1.90 (Hedges' g -1.90 95% CI -2.52, -1.28), for calcium phosphate nanoparticles, was –0.64 (Hedges' g -0.64 95% CI -2.03, 0.94), for CaP/Ag nanoparticles was –0.44 (Hedges' g -0.44 95% CI –1.83, 0.94) and Hedges' g of changes to the bacterial activity of dental restorative materials for Titanium dioxide nanoparticles was –2.41 (Hedges' g -2.41 95% CI –3.11, -1.72). Conclusion: Based on the findings of the present study, Titanium dioxide nanoparticles showed

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the highest antibacterial effect when combined with bonding materials.

***Keywords*---**nanoparticle, dental restoratives, dental cements.

Introduction

In restorative dentistry, the first choice for the restorative procedure is the selection of resin-based materials(1). Compared to other restorative materials, resins cause more biofilm to accumulate on the teeth(2, 3). Studies have shown that the failure rate of dental restorations after ten years is very high and the failure rate of their restoration is about 50-70%(4, 5). Among the factors that affect the success rate of restoration is the colonization by caries bacteria at the restoration/tooth interface, which causes the subsequent acid attack to cause secondary caries(6, 7). In orthodontics, by placing fixed orthodontic apparatus, an increase in caries-causing bacteria is observed(8, 9). White spot lesions are the first sign of demineralization(10, 11), which is a common complication in patients undergoing orthodontics; Studies have reported the prevalence of white spot lesions to be 50%(12, 13). The use of restorative materials that minimize the accumulation of bacteria is of great importance, today many efforts have been made to develop dental restorative materials that can minimize the activity of bacteria and their mechanical properties are stable(14, 15). The findings of the studies have shown that the antibacterial properties of nanoparticles are high and they can be used in tooth restoration and thus prevent the appearance of caries again(16, 17). However, there is a knowledge gap in this field because, firstly, there is a large variety of nanoparticles and it is challenging to choose the right nanoparticles, and the methodology used is very diverse; Therefore, in the present study, it has been tried to provide sufficient evidence in this field with the consensus of the results of the studies; The purpose of this study was evaluated different nanoparticles in dental restorative materials.

Method

Search strategy

Present study is a systematic review and meta-analysis based on PRISMA guidelines(18), all articles published in international databases such as PubMed, Scopus, Science Direct, Embase between 2012 and July 2022 included. Google Scholar search engine was used. *The following keywords were used to search:* ((("Dental Atraumatic Restorative Treatment"[Mesh] OR "Dental Cements"[Mesh] OR "Dental Care"[Mesh] OR "Dental Amalgam"[Mesh] OR “Dental Alloys"[Mesh]) AND "Carcinogenicity Tests"[Mesh]) AND "Dental Bonding"[Mesh]) AND "Nanoparticles"[Mesh]. Key considerations PRISMA was the basis of the present study(19).

Selection criteria

Inclusion criteria: in-vitro studies and Experimental studies, English language, sample incubation periods of between 0 and 72 h. Case studies, case reports, reviews were excluded from the study.

Data Extraction and risk assessment

Studies data were reported by first author name, years, Nanoparticles. The quality of Systematic Review and Meta-analysis of In Vitro Studies was evaluated using the study of Sarkis-Onofre et al., 2014(20). This scale measures seven items (sample size calculation, adequate control group, use of materials according to the manufacturer's instructions, standardized sample production process, standardized antibacterial assessment, evaluation of antibacterial properties by a single operator, and adequate statistical analysis). Studies with one to three items reported were classified as having a high risk of bias, four or five items as medium risk of bias, and six or seven items as low risk of bias. If an item was reported in the article, the study was marked with a 'Y' (yes) for that specific parameter; if the item was not stated, the study was marked with an 'N' (no).

Data analysis

Data analysis was performed using STATA/MP V17 software. 95% confidence interval for mean differences or Hedges' g (measure of effect size) with fixed effect model and Inverse-variance method were calculated. To deal with potential heterogeneity, random effects were used and I^2 showed heterogeneity. I^2 values less than 50% indicate low heterogeneity and above 50% indicate moderate to high heterogeneity.

Result

The review of the existing literature using the studied keywords, 151 studies were found. In the initial review, duplicate studies were eliminated and abstracts of 138 studies were reviewed. At this stage, 96 studies did not meet the inclusion criteria, so they were excluded, and in the second stage, the full text of 42 studies was reviewed by two authors. At this stage, 31 studies were excluded from the study due to incomplete data, inconsistency of results in a study, poor studies, lack of access to full text, inconsistent data with the purpose of the study. Finally, eleven studies were selected (Fig.1).

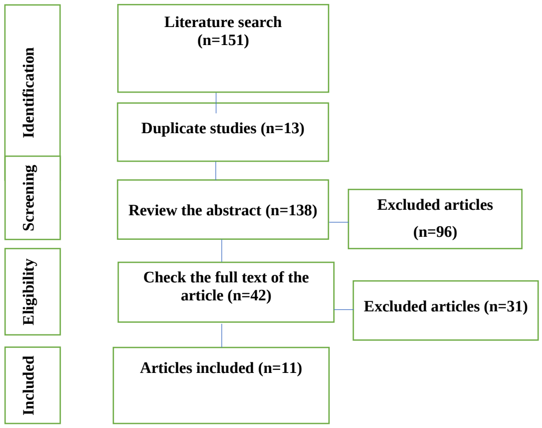

Figure 1. PRISMA flowcharts

Detailed information and required data extracted for analysis are summarized in Table 1. As for the methodological quality of the studies, nine studies were classified as at high risk of bias (low quality), and two studies showed a medium risk of bias (medium quality).

Table 1
Summary of data

n	Study. Years	Nanoparticle type	Material	Type of antibacterial test / Microorganisms /Culture broth	Risk assessment
1	Garcia et al., 2017 (16)	Zinc oxide nanoparticles	Glass ionomer cement and resin-modified glass ionomer cement	Agar diffusion test, CFU3 / S.mutans / Brain-heart infusión agar, sucrose agar.	4/7
2	Natale et al., 2017 (21)	Calcium phosphate nanoparticles silver phosphate/calcium phosphate mixed nanoparticles	Composite resin	CFU3 / S.mutans / Todd-Hewitt agar supplemented with 0.3% yeast extract.	3/7
3	Sodagar et al. (2017) (22)	Titanium dioxide nanoparticles	Orthodontic adhesive	Antibacterial propierties of eluted components, agar diffusion test, biofilm inhibition test, CFU3 / S. mutans, S.sanguinis, L.acidophilus / Brain-heart infusión agar.	3/7

4	Degrazia et al., 2016 (8)	Silver nanoparticles	Orthodontic adhesive	Growth inhibitory assay, CFU3, agar diffusion test / S.mutans / Brain-heart infusión agar.	4/7
5	Sodagar et al., 2016 (13) a	Silver/ hydroxyapatite nanoparticles	Orthodontic adhesive	Agar diffusion test, biofilm inhibition test, antibacterial properties of eluted components / S.mutans, S.sanguinis, L.acidophilus / Brain-heart infusión agar, mueller hinton agar.	3/7
6	Saffarpour et al., 2016 (23)	Zinc oxide nanoparticles	Dental adhesive	Direct contact test, CFU3 / S.mutans / Brain-heart infusión agar, blood agar.	3/7
7	Sodagar et al., 2016 (24) b	Curcumin nanoparticles	Orthodontic adhesive	Eluted component test, agar diffusion test, CFU3 / S. mutans, S. sanguinis y L. acidophilus / Trypticase soy agar.	3/7
8	das Neves et al., 2014 (7)	Silver nanoparticles	Composite resin	Direct contact test, CFU3 / S. mutans, L.acidophilus / MRS broth modified with 20% de sucrose.	3/7
9	Kasraei et al., 2014 (3)	Silver nanoparticles, zinc oxide nanoparticles	Flowable composite resin	Agar diffusion test, CFU3 / S.mutans, L.acidophilus / Brain-heart infusión agar, blood sangre.	3/7
10	Poosti et al., 2013 (25)	Titanium dioxide nanoparticles	Orthodontic adhesive	CFU3 / S.mutans / Brain-heart infusión agar.	3/7
11	Azarsina et al., 2013 (26)	Silver nanoparticles	Composite resin	Agar difussion test, CFU3 / S.mutans, L.acidophilus / Brain-heart infusión agar, blood agar.	3/7

Antibacterial activity of orthodontic adhesives
Subgroup meta-analysis

Hedges' g of changes to bacterial activity of orthodontic adhesives on *Streptococcus mutans* (*S. mutans*) was -3.27 (Hedges' g -3.27 95% CI -4.15, -2.40) with moderate heterogeneity (I^2=65.58%; P =0.02). Hedges' g of changes to bacterial activity of orthodontic adhesives on *Streptococcus sanguinis* (*S. sanguinis*) was -6.02 (Hedges' g -6.02 95% CI -7.15, -4.89) with low heterogeneity (I^2=0%; P =0.65). Hedges' g of changes to bacterial activity of orthodontic adhesives on *Lactobacillus acidophilus* (*L. acidophilus*) was –5.82 (Hedges' g -5.82 95% CI -6.95, -4.69) with high heterogeneity (I^2=92.52%; P =0.00). overall changes to bacterial activity of orthodontic adhesives were -4.72 (Hedges' g -4.72 95% CI -5.31, -4.13) with high heterogeneity (I^2=82.88%; P =0.00) (Fig.2). according to test of group differences statistically significant difference observed between the groups (p=0.00). It should be mentioned that the concentration of nanoparticles and its type are different in the studies.

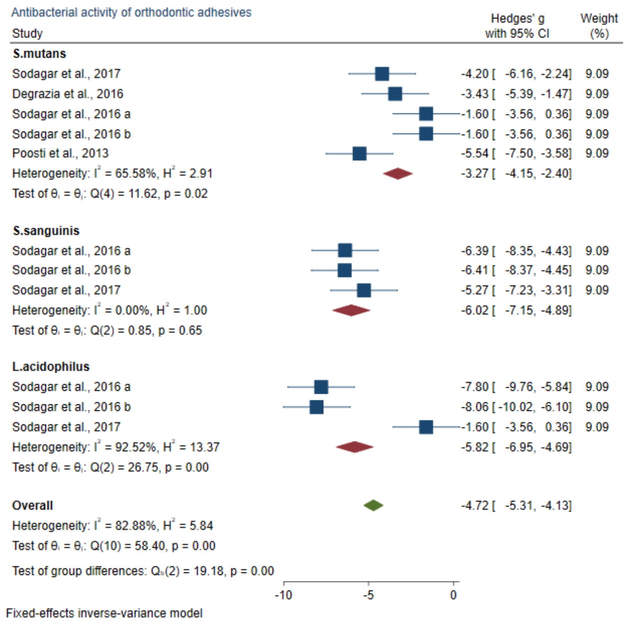

Figure 2. nanoparticles antibacterial activity of orthodontic adhesives

Antibacterial activity of resin-based materials
Subgroup meta-analysis

Hedges' g of changes to bacterial activity of resin-based materials on *Streptococcus mutans* (*S. mutans*) was –1.86 (Hedges' g -1.86 95% CI -2.66, -1.06) with high heterogeneity (I^2=74.86%; P =0.00). Hedges' g of changes to bacterial activity of resin-based materials on *Lactobacillus acidophilus* (*L. acidophilus*) was –-0.94 (Hedges' g -0.94 95% CI -2.07, -0.19) with low heterogeneity (I^2=0%; P =0.88) (Fig.3). overall changes to bacterial activity of resin-based materials were -1.55 (Hedges' g -1.55 95% CI -2.21, -0.90) with moderate heterogeneity (I^2=63.31%; P =0.01) (Fig.3). according to test of group differences no statistically significant difference observed between the groups (p=0.20). It should be mentioned that the concentration of nanoparticles and its type are different in the studies.

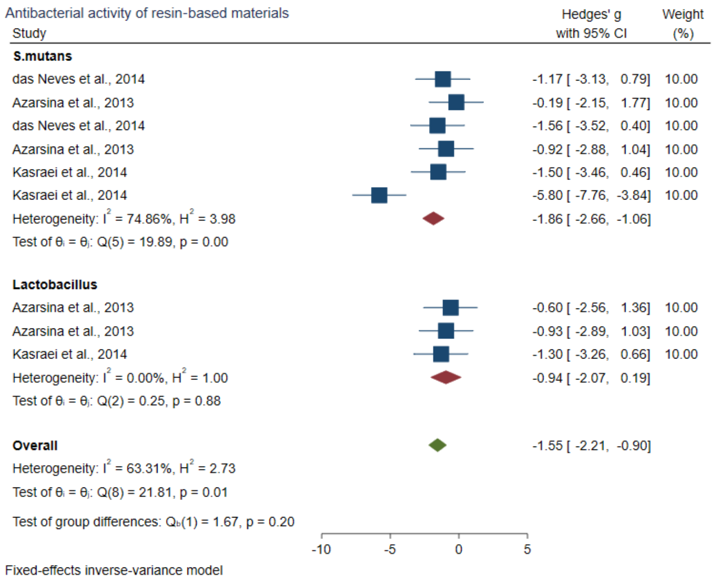

Figure 3. nanoparticles antibacterial activity of resin-based materials

Antibacterial activity of dental restorative materials
Subgroup meta-analysis

Hedges' g of changes to bacterial activity of dental restorative materials for silver nanoparticles (Ag nanoparticles) was –1.90 (Hedges' g -1.90 95% CI -2.52, -1.28) with moderate heterogeneity (I^2=61.68%; P =0.01) (Fig.4). Hedges' g of changes to bacterial activity of dental restorative materials for calcium phosphate nanoparticles (CaP nanoparticles) was –0.64 (Hedges' g -0.64 95% CI -2.03, 0.94) with low heterogeneity (I^2=0%; P =0.79) (Fig.4). Hedges' g of changes to bacterial activity of dental restorative materials for CaP/Ag nanoparticles was –0.44 (Hedges' g -0.44 95% CI –1.83, 0.94) with low heterogeneity (I^2=0%; P =0.79). Hedges' g of changes to bacterial activity of dental restorative materials for Curcumin nanoparticles was –1.98 (Hedges' g -1.98 95% CI –2.78, -1.18) with low heterogeneity (I^2=0%; P =0.87) (Fig.4).

Hedges' g of changes to bacterial activity of dental restorative materials for Titanium dioxide nanoparticles (TiO2 nanoparticles) was –2.41 (Hedges' g -2.41 95% CI –3.11, -1.72) with low heterogeneity (I^2=48.56%; P =0.06) (Fig.4). Hedges' g of changes to bacterial activity of dental restorative materials for Zinc oxide nanoparticles (ZnO nanoparticles) was –1.07 (Hedges' g -1.07 95% CI –1.72, -0.42) with moderate heterogeneity (I^2=69.62%; P =0.00) (Fig.4). Overall changes to bacterial activity of dental restorative materials were –1.68 (Hedges' g -1.68 95% CI –2.00, -1.36) with moderate heterogeneity (I^2=54.57%; P =0.00). according to test of group differences statistically significant difference observed between the groups (p=0.02) (Fig.4). bacterial activity changes are considered according to the type of nanoparticles without considering the type of bacteria and the concentration of the nanoparticles.

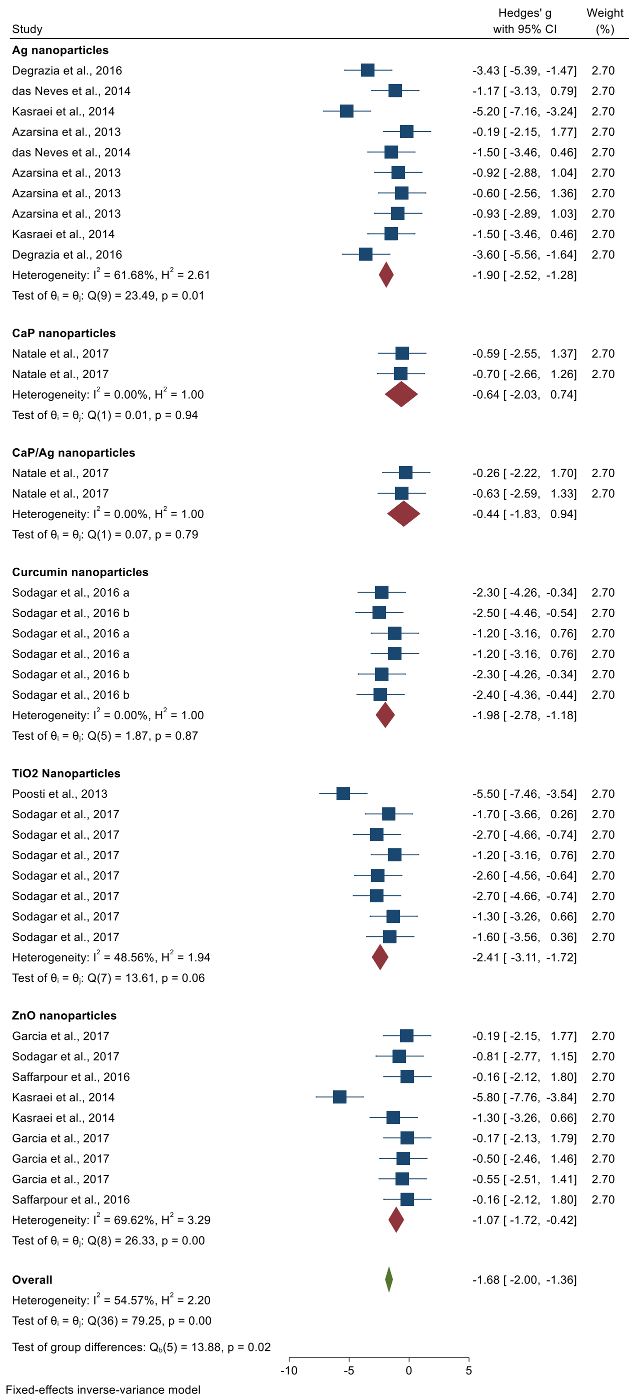

Figure 4. Antibacterial activity of dental restorative materials

Discussion

Currently, the use of nanoparticles in dental materials is of interest and they are used to improve the durability and efficiency of dental restorations. Many in-vitro studies have investigated different types of nanoparticles, their concentration and the optimal means of combining them in materials, and the focus of most studies has been to obtain a dental material resistant to bacterial colonization. The purpose of this study was to investigate the antibacterial properties of nanoparticles as dental restorative materials. In the present study, only experimental studies were included in the searches. One of the limitations of the current study was the selection of in vitro studies because these studies are not able to simulate the exact oral conditions and can lead to some biases; Also, the findings of these studies cannot be fully generalized to the clinic. However, the available studies were in vitro; Another limitation of the current study was the control group of studies, which used different restorative materials for this group, which can lead to some biases and the comparisons made are not accurate. However, all studies in the control group had used restorative materials without the incorporation of nanoparticles, which indicates that the comparisons in the same study are more accurate.

Based on the findings of the current studies, silver nanoparticles are the most commonly used nanoparticles that were measured alone or in combination with others. One of the most important and involved in the results of the studies was that most of the studies used commercial nanoparticles, which may cause the incorporation of excipients or other types of materials in the composition. Nano-diamonds have recently appeared in the field of medicine and dentistry, whose positive results have been observed in various medical fields. Also, studies have shown that Nano-diamonds can be used as bioactive or antibacterial coatings for dental implants(27, 28). Based on the available evidence, mainly the appearance of caries is related to Streptococcus mutans and Lactobacillus acidophilus, for this reason, these bacteria have been used in the experiments in most of the studies. It is suggested that future studies conduct antibacterial tests for each type of nanoparticles against different types of microorganisms. In this way, it is possible to evaluate whether one type of nanoparticles has a higher antibacterial activity against some specific microorganisms than others, and also to compare the antibacterial capacity of different nanoparticles against the same bacteria. Several reviewed studies did not find a significant relationship between nanoparticle composition and improved antibacterial capacity. Based on the findings of the study, it was observed that adding Ag nanoparticles in resin-based cement did not increase its antibacterial activity against Staphylococcus mutans (29). Also, another study showed that the inclusion of ZnO nanoparticles in glass ionomer cement does not increase the antibacterial activity against S. mutans(16).

The findings of a meta-analysis study that examined different nanoparticles added to orthodontic band materials and evaluated their antibacterial properties showed that the positive effect on antibacterial capacity is due to the incorporation of nanoparticles(22).The results of the studies showed that TiO2 nanoparticles are more effective against S. mutans and S. sanguinis colonies and CurcNP nanoparticles are more effective against L. acidophilus, although further research with a clearer protocol is needed to confirm this hypothesis(22, 24). Another study that investigated the antibacterial effect of nanoparticles integrated with resin-based materials showed that silver and zinc oxide nanoparticles have a much greater antibacterial effect on Staphylococcus mutans than Lactobacillus(3). Data obtained by Poosti et al., 2013 showed that TiO2 has a strong antibacterial effect against S. mutans(25), while Cardoso et al., 2016 showed that even at low concentrations, the strong antibacterial effect of Ag against S. mutans is observed(8). The findings of the present meta-analysis showed that nanoparticles as restorative materials lead to an increase in antibacterial activity. The selected studies had a high risk of bias, because in most of them the calculation of sample size was not reported, more studies with a more accurate cognitive methodology and a more appropriate design are needed to provide stronger evidence. Also, the concentration of nanoparticles can also affect the results of the study; Therefore, it is suggested that the concentration of nanoparticles be considered more carefully in future studies.

Because the findings of the studies that used the same nanoparticles, but the concentration of the nanoparticles were not the same, obtained different results(3, 8, 30). Although more research with more specific targets is needed to generate stronger evidence, the incorporation of nanoparticles into dental restorative materials, regardless of their composition, provides a significant increase in their antibacterial activity. One of the most important factors that must be considered is that in the oral environment, other factors can also affect the activities of bacteria, such as diet, the use of pH neutralization techniques, and since acid production is the main cause of caries. which is influenced by both phenotypic and genotypic characteristics of the oral microflora, oral conditions should always be considered(31, 32).

Conclusions

Based on the present meta-analysis, the incorporation of nanoparticles in dental bonding materials can be an effective method to reduce bacterial activity and can be considered an antibacterial method. Also, comparing dental bonding materials modified with nanoparticles with primary materials, higher antibacterial activity is observed. Based on the findings of studies, TiO2 nanoparticles showed the highest antibacterial effect when combined with bonding materials.

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