Review Article

Role of Nanotechnology in Dentistry: Systematic Review

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ABSTRACT

Aim: This systematic review aimed to provide an overview of role of nanotechnology in dentistry and to evaluate its applicability in prevention and treatment of oral diseases. **Materials and Methods:** A systematic literature search was conducted in 2 electronic databases – PMC and Cochrane. The search was restricted to the articles published during the last 5 years. First-level screening was done to select articles for the review on the basis of title and abstract. Then, full texts of selected articles were studied, and relevant articles were selected to be included in this review. Articles selected were critically appraised to evaluate their quality. **Results:** Literature search revealed 837 articles in PMC, 15 in Clinical trial register of US National library, and 43 in Cochrane. Additional 6 articles were identified by hand search. Eleven clinical trials were included in this review. **Conclusion:** Advancement in nanotechnology has greatly influenced dental disease prevention and therapy significantly.

Keywords: *Dentistry, nanomaterials, nanotechnology*

Introduction

The first definition of "nanotechnology" was given by Norio Taniguchi (Tokyo Science University) in a 1974 paper. According to him, "nanotechnology" mainly consists of the processing of separation, consolidation, and deformation of materials by one atom or one molecule.[1]

Nanomaterials are synthetic or natural materials with components <100 nm in at least one dimension, including clusters of atoms, grains <100 nm in size, fibers that are <100 nm diameter, films <100 nm in thickness, nanoholes, and composites that are a combination of these.[2,3] Nanomaterials due to their small size have a much-increased surface area per unit mass compared to bigger particles. All properties, including electrical, optical and magnetic ones, are altered.[4] Many nanomaterials have been used as nanomedicines in past few decades. The concept of "nanomedicine" was given by Freitas in 1993 and was defined as observing, controlling, and treating the biological systems of the human body at the molecular level using nanostructures and nanodevices.[5]

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Nanotechnology offers a broad range of innovations and improvement in prevention, diagnostics, and treatment of oral diseases. Many review articles addressing the potential of nanotechnology in dentistry has been published till now; however, the literature is void of systematic reviews discussing the applications of nanotechnology in the field of dentistry. In this systematic review, we will focus on role of nanotechnology in dentistry.

Materials and Methods

Study identification and selection

Data extraction was done according to a Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A systematic literature search was conducted in PMC, Cochrane, and Clinical trials.gov. The electronic search was done from April 30, 2019 to June 13, 2019. The keywords used in the search of the selected electronic databases were nanotechnology, nanotechnology in dentistry. The search was restricted to the articles published during the last 5 years. An additional hand search was also performed. Duplicate articles were removed. First-level screening was done to select articles for the review on the basis of title and abstract. Then, full texts of selected articles were studied and relevant articles were selected to be included in this review. Articles selected were critically appraised to evaluate their quality.

Inclusion and exclusion criteria

The full text of all studies of possible relevance was obtained for assessment against the following inclusion criteria:

1. Randomized clinical trials published in English language in the last 5 years.

The applied exclusion criteria for studies were as follows:

- Not related to dentistry or maxillofacial fields
- Articles published before July 2014
- Editorials
- Letter to editor
- Review articles
- Case reports
- Phase 1 clinical trial
- Observational studies.

Data extraction

The review author and a research assistant assessed all selected randomized controlled trials to assess risk of bias and extract data using a data extraction form.

Risk of bias assessment

Articles selected on the basis of inclusion exclusion criteria were critically appraised to evaluate their quality according to the guidelines provided in Cochrane handbook. Assessment of risk of bias for individual study was done under the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding participants), detection bias (blinding outcome assessors), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting).

Studies were categorized into three categories

1. Good quality: Low risk for all domains
2. Fair quality: 1 criterion not met or 2 criteria unclear but unlikely to affect the outcome of study
3. Poor quality:
   a. 1 criterion not met or 2 criteria unclear and likely to affect the outcome of study
   b. Two or more criteria listed as high risk of bias.

All good and fair quality studies were included for qualitative synthesis.

Results

Study identification and selection

The initial electronic and hand search retrieved 895 citations. Additional hand search identified 6 clinical trials. In first screening 193 articles were selected on the basis of title and abstract. Finally 14 clinical trials were selected but 11 were included in the study as full texts of 1 clinical trial were not found and results of 2 studies were not posted. Total 37 review articles, 1 editorial, 18 animal studies, and 1 letter to editor were excluded. Other *in vitro* and *ex vivo* studies were also excluded [Chart 1].

Data extraction

All the included studies were randomized clinical trials, conducted in Italy, Egypt, Australia, Brazil, Iran, and 3 studies were conducted in India. In one study, trial site was not mentioned. Sample size estimation was done in 9 studies. In 2 studies, power analysis was not mentioned. Data were recorded under the following headings: study title, study author, aim of study, sample population, and results. Information is presented in Table 1.

Risk of bias assessment

Risk of bias assessment was done according to the method described in Cochrane hand book.

Six studies were categorized as good-quality studies with low risk of bias. Five studies were categorized as fair quality studies with unclear risk of bias unlikely to affect the outcome of study. No study was categorized as poor study. Information is presented in Table 2.

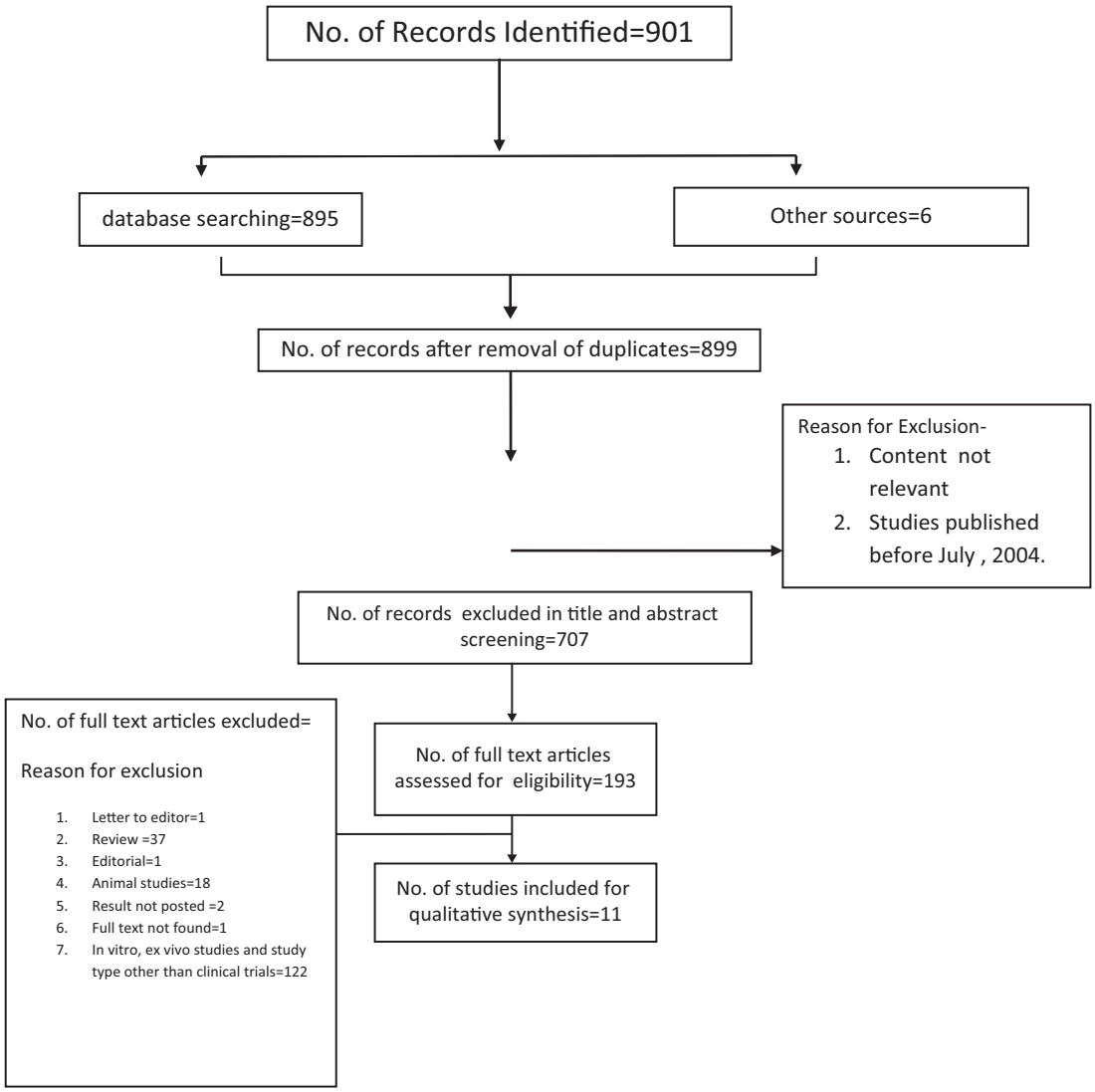

Chart 1: Flow chart for study selection process

Discussion

The studies included in this review evaluated a range of different interventions, and due to heterogeneity, it is not possible to analyze the data quantitatively. However, the results of all clinical trials are summarized to provide overview on role of nanotechnology. According to the included studies, nanotechnology is effective in the management of the following conditions:

1. Treatment of dental hypersensitivity experimental toothpaste was able to reduce dentin hypersensitivity (DHS) over short duration time period.[6,10] According to Amaechi *et al*., 20% nano hydroxyapatite (nHAP) dental cream is an effective method to promote the relief of DHS symptoms when applied daily[13]
2. Dental remineralization – 10% nHAP solution effectively increases microhardness of the enamel of permanent teeth following soft drink exposure. This randomized double blind clinical trial was conducted in Iran on 20 teeth of 10 individuals of 18–21 years of age[14]
3. Cariostatic – A randomized clinical trial done on 159 lesions in 50 children of 6–10 years concluded that annual application of 5% nanosilver fluoride is equal to 38% silver diammine fluoride in preventing the progression of dental caries in primary molars without causing any staining of dentinal tissues[15]
4. Anti-biofilm – Nano sodium fluoride showed bactericidal effect against *Streptococcus mutans* biofilm when tested in 12 children of 7–8 years in a crossover clinical trial. Therefore, it can be used

Table 1: Summary of studies

Serial number	Author	Title study	Aim of study	Number of individuals	Results
1	Vano *et al*., July 2014[6]	Effectiveness of nHAP toothpaste in reducing DHS: A double-blind RCT	To compare the efficacy in reducing DHS of a dentifrice containing nHAP with a fluoride dentifrice and a placebo	105 individuals of 20–70 years of age range	nHAP toothpastes showed remineralising effects comparable to those of fluoride containing toothpaste
2	Santos *et al*., 2014[7]	A new "Silver bullet" to treat caries in children-NSF: A RCT	To investigate the effectiveness of a new anti-caries agent, NSF, applied once a year to arrest caries in children	130 teeth in 60 children of 6–7 years of age	NSF was demonstrated to be effective in arresting caries when applied once a year. The agent had advantage of not staining the dental tissue black
3	Pandit *et al*., 2015[8]	The use of nanocrystalline and 2 other forms of calcium sulfate in the treatment of infrabony defect: A clinical and radiographic study	To evaluate the efficacy of 3 forms of calcium sulfate i.e., Nanogen (nCS) (+), BoneGen (+) and Dentogen (+) in treatment of infrabony defects and to compare their efficacy as bone grafting substitutes	45 sites in 16 individuals (age range 20–64 years)	Both nanogen and bonegen were found effective in the treatment of infrabony periodontal defect
4	Hegazy *et al*., 2016[9]	Peri-implant outcomes with laser versus nanosurface treatment of early loaded implant-retaining mandibular overdenture	To compare peri-implant changes seen with two early loading protocols for modifying surface Treatment of dental implants-one modifying the collar portion (Laser-Lok implant) and the other modifying the implant surface (nanosurface treated implant)	36 individuals, age range 47–78 years	Both laser collar and nanosurface-treated dental implants found to be reliable with good stability
5	Wang *et al*., 2016[10]	Treatment of DHS using nHAP pastes: A RCT	to compare the effect of nHAP pastes indicated for professional (Desensibilise Nano-P) with or without experimental home-care application to Pro-Argin (new technology), and fluoride varnish (already established treatment) on DHS relief after 1 and 3 months of treatment	28 individuals	The tested formulation was effective in reducing DHS over duration of 3 months
6	Freire *et al*., 2017[11]	AgNPs: The new Allies against *S. mutans* biofilm: A pilot clinical trial and microbiological assay	To evaluate the antimicrobial properties of a new formulation containing AgNPs, named NSF, to inhibit *S. mutans* biofilm formation on children's dental enamel	12 individuals of 7–8 years of age	NSF treated enamel had lower values of *S. mutans* viability and therefore can be used for clinical control and prevention of dental biofilm formation

Table 1: Continued

Serial number	Author	Title study	Aim of study	Number of individuals	Results
7.	Priyadarshini *et al*., 2017[12]	One year comparative evaluation of Ketac Nano with RMGIC and giomer in noncarious cervical lesions: A RCT	To evaluate the clinical performance of Ketac Nano (Ketac™ N100), RMGIC (Fuji Filling™ LC), and Giomer (Beautifil® II) in NCCLs	120 restorations in 20 individuals	Ketac nano RMGIC restoration were better retained NCCLs while superior color match and surface finish were observed with Giomer restoration. Marginal discoloration was high with Ketac nano
8	Amaechi *et al*., 2018[13]	Clinical efficacy in relieving dental hypersensitivity of nHAP containing cream: A RCT	To compare the effectiveness of Apadent Pro (Sangi) nHAP dental cream to relieve DHS with a positive control cream containing 20% pure silica	56 individuals (18–80 years of age)	20% nHAP dental cream is an effective method to promote the relief if dental hypersensitivity symptoms when applied daily
9	Yaberi and Haghgoo 2018[14]	A comparative study of the effect of nHAP and egg shell on erosive lesion of the enamel of permanent teeth following soft drink exposure: A RCT	To compare the effects of nHAP or ES extract on the microhardness of healthy third molar tooth enamel following soft drink exposure	20 permanent 3rd molars in 10 individuals	nHAP and ES have the potential to remineralise erosive lesions
10	Tirupathi *et al*., 2019[15]	Comparative cariostatic efficacy of novel NSF varnish with 38% SDF varnish a double-blind randomized clinical trial	To evaluate the clinical cariostatic efficacy of a concocted 5% NSSF dental varnish with 38% SDF in preventing the progression of dentinal caries of primary molars	159 lesions in 50 children (6–10 years)	Annual application of 5% NSSF dental varnish with 38% SDF in preventing the dentinal caries of primary molars
11	Fernando *et al*., 2019[16]	Self-assembly of dental surface nanofilaments and remineralisation by SnF_2 and CPP-ACP nanocomplexes	To demonstrate that SnF_2 and CPP-ACP interact to form a nanofilament coating on the tooth surface and that together they are superior in their ability to promote dental remineralisation	8 healthy controls, age ranges from 18 to 60 years	The combination of CPP-ACP and SnF_2 in oral care products may significantly improve their efficiency in prevention and treatment of dental caries, erosion and hypersensitivity

RCT=Randomized controlled trial, *S. mutans*=*Streptococcus mutans*, CPP-ACP=Casein phosphopeptide-stabilized amorphous calcium phosphate, HA=Hydroxyapatite, nHAP=Nano-HA, NSF=Nano silver fluoride, NCCLs=Noncarious cervical lesions, DHS=Dentin hypersensitivity, ES=eggshell, SDF=Silver diammine fluoride, NSSF=Nano-silver incorporated sodium fluoride, RMSIC=Resin-modified glass ionomer cement, nCS=Nanocalcium sulfate, AgNPs=Silver nanoparticles

for clinical control and prevention of dental biofilm formation[11]

5. Infrabony periodontal defect – Randomized clinical trial done on 16 individuals of 20–64 years of age concluded that Nanogen and BoneGen TR can be considered for treatment of infra-bony periodontal defects. The faster degradation of Dentogen may negatively affect its bone regeneration potential[8]
6. Nanosurface-treated implant – The results show that the differences between laser collar and nanosurface-treated implants were statistically not significant with regard to the criteria of probing depth, Modified Bleeding Index, and mobility of the dental implants at different observation periods of the study. The amount of bone loss observed was consistent with peri-implant tissue stability

Table 2: Risk of bias in included studies

Serial number	Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall risk of bias
1	Vano *et al.*, July 2014[6]	Done	Done	Done	Done	No drop outs	Done	Low risk
2	Santos *et al.*, 2014[7]	Done	Done	Done	Done	Sample size adjusted for estimated drop out	Done	Low risk
3	Pandit *et al.*, 2015[8]	Done	Not mentioned	Done	Done	No drop out	Done	Unclear risk of selection bias
4	Hegazy *et al.*, 2016[9]	Done	Not mentioned	Not mentioned	Not done	Sample size adjusted for estimated drop out	Done	Study is at risk of performance and detection bias but unlikely to affect as all outcomes are objective outcomes
5	Wang *et al.*, 2016[10]	Done	Not mentioned	Done	Done	Sample size adjusted for estimated drop out	Done	Unclear risk of selection bias as allocation bias is not mentioned
6	Freire *et al.*, 2017[11]	Done	Done	Done	Done	Not mentioned	Done	Unclear risk of attrition bias
7	Priyadarshini *et al.*, 2017[12]	Done	Done	Not mentioned	Done	Sample size adjusted for estimated drop out	Done	Low risk
8	Amaechi *et al.*, 2018[13]	Done	Done	Done	Done	Sample size adjusted for estimated drop out	Done	Low risk
9	Yaberi and Haghgoo 2018[14]	Done	Not mentioned	Done	Done	Not mentioned	Done	Unclear risk of selection bias and attrition bias
10	Tirupathi *et al.*, 2019[15]	Done	Done	Done	Done	Sample size adjusted for estimated drop out	Done	Low risk
11	Fernando *et al.*, 2019[16]	Done	Done	Done	Done	Sample size adjusted for estimated drop out	Done	Low risk

observed at 12 months. The bone loss did not cause any implant mobility[9]

7. The combination of casein phosphopeptide-stabilized amorphous calcium phosphate and SnF_2 in oral care products may significantly improve their efficacy in prevention and treatment of dental caries, erosion, and hypersensitivity[16]

Due to lack of clinical trials, it was not possible to assess effectiveness of various interventions; therefore, a broad overview on all the aspects of dentistry influenced by nanotechnology has been presented here. Nanobiomaterials combined with other medical methods may have a key role in the near future.[17] Many studies have been done on this topic till now. According to Narang and Narang, oral health can be maintained using nanodentistry; the risk and toxicity associated with the use of such nanotherapeutics need more extensive investigation and understanding. Other reviews suggested that before applying nanotechnology in clinical settings, cost needs to be considered.[18,19]

Conclusion

It can be concluded that advancement in nanotechnology has greatly influenced prevention and management of dental diseases. The use of nanotechnology in treating dental diseases has been extended to treat DHS, remineralization of dental tissues, surface treatment of dental implants, prevention of biofilm formation, and prevention of progression of dental caries. Nanotechnology is undoubtedly likely to improve dental preventions and treatments but as it is still in development phase and its use in clinical settings is limited by concern of safety and cost-effectiveness, more clinical trials are required to reach to unbiased conclusion.

Future recommendation

More multicentric clinical trials with larger sample size would be required. Issues such as cost-effectiveness and toxicity associated with the use of nanoparticles need to be considered.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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