Antibacterial Nanoparticles Endodontics: A Narrative Review

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Abstract

Introduction: A major challenge in root canal treatment is the inability of the current cleaning and shaping procedures to eliminate bacterial biofilms surviving within the anatomic complexities and uninstrumented portions of the root canal system. **Methods:** Nanoparticles with their enhanced and unique physicochemical properties, such as ultrasmall sizes, large surface area/mass ratio, and increased chemical reactivity, have led research toward new prospects of treating and preventing dental infections. This article presents a comprehensive review on the scientific knowledge that is available on the application of antibacterial nanoparticles in endodontics. **Results:** The application of nanoparticles in the form of solutions for irrigation, medication, and as an additive within sealers/restorative materials has been evaluated to primarily improve the antibiofilm efficacy in root canal and restorative treatments. In addition, antibiotic or photosensitizer functionalized nanoparticles have been proposed recently to provide more potent antibacterial efficacy. **Conclusions:** The increasing interest in this field warrants sound research based on scientific and clinical collaborations to emphasize the near future potential of nanoparticles in clinical endodontics. *(J Endod 2016;■ :1–10)*

Key Words

Antibacterial, chitosan, functionalized, nanoparticles, silver

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Significance

Nanoparticles with their enhanced and unique physicochemical properties hold new prospects for the treatment and prevention of dental infections. The near future potential of nanoparticles in clinical endodontics warrants sound research based on scientific and clinical collaborations.

Nanomaterial denotes a natural, incidental, or manufactured material containing particles in an unbound state or as an aggregate or agglomerate in which 50% or more of the particles in number, size, distribution, or 1 or more external dimensions is in the size range of 1–100 nm (1). Nanomaterials offer unique physicochemical properties, such as ultrasmall sizes, large surface area/mass ratio, and increased chemical reactivity, compared with their bulk counterparts (2, 3). The increased surface to volume ratio and increased number of atoms that are present near the surface compared with micro-/macrostructures are suggested to contribute to the distinctly different properties of nanomaterials. These advantages may be exploited to design highly specific materials and devices to interact with at the subcellular and molecular level of the human body in order to achieve maximal therapeutic efficacy with minimal side effects (4, 5).

Nanotechnology has progressed rapidly in science and technology, creating a myriad of biomedical applications such as drug delivery, tissue regeneration, antimicrobial application, gene transfection, and imaging (2, 3, 5, 6). The term *nanodentistry* implies the application of nanomaterials and dental nanorobots toward diagnosis and treatment, with the goal of improving comprehensive oral health. The scope of such strategies includes a wide variety of oral health–related issues such as treatment of dentin hypersensitivity, biofilm elimination, diagnosis and treatment of oral cancers, bone replacement materials, and so on. In the field of endodontics, the development of nanomaterials is focused on steps that would improve antimicrobial efficacy, mechanical integrity of previously diseased dentin matrix, and tissue regeneration. Currently, newer technologies are being tested in endodontics, mainly toward overcoming the microbial challenge (7, 8).

Based on the composition, nanoparticles are generally classified as either naturally occurring or synthetic (Table 1). They are further categorized as organic or inorganic in nature. Based on the shape, they are classified as particles, spheres, tubes, rods, plates, and so on. Functionalized nanoparticles are those that have a core of 1 material and additional molecules or proteins bonded on its surface or encapsulated within. Depending on the specific applications, nanoparticles can be functionalized with peptides, drugs, photosensitizers, and so on (9, 10). The core nanoparticles can be used as a convenient surface for molecular assembly and may be composed of inorganic or organic materials. An additional layer of linker molecules is required to proceed with functionalization wherein the linker molecules have reactive groups at both ends that bind various moieties like biocompatibles (dextran), antibodies, fluorophores, and so on onto the core nanoparticle.

This review aimed to provide comprehensive information on the scientific knowledge that is available for the use of nanotechnology toward antibacterial applications in endodontics.

Antibacterial Nanoparticles

Bacterial biofilms are considered the major cause of both primary and secondary root canal infection (11, 12). Conventionally, chemical antimicrobials are used topically

TABLE 1. Nanoparticles Available Based on the Composition

Inorganic	Metallic	Polymeric	Quantum dots	Functionalized with
Zinc oxide	Gold	Alginate	Cadmium sulfide	Drugs
Iron oxide	Silver	Chitosan	Cadmium selenide	Photosensitizers
Titanium dioxide	Iron			Antibodies
Cerium oxide	Copper			Proteins
Aluminum oxide bioactive glass	Magnesium			

within the root canals in combination with mechanical instrumentation to achieve effective microbial reduction before filling the root canal with an inert filling material (7, 8, 13). The current level of evidence showed that despite the advancements in treatment strategies the rate of treatment failure has not decreased below 18%–26% for the past 4 to 5 decades (14–16). This could be mainly attributed to the inability or limitations of current technologies to deal with the disease process as a whole (17). Other than this, the conservative management of infections involving topical or systemic antibiotics has been shown to be ineffective because of several challenging factors (Table 2) (19, 20). Furthermore, the use of antibiotics is highly debatable, as "In the ongoing war against antibiotics, the bacteria seem to be winning, and the drug pipeline is verging on empty" (21).

Because of the shortcomings of current antibiofilm strategies in root canal treatment, advanced disinfection strategies are being developed and tested. We review newer antibacterial nanoparticles that have been introduced at the laboratory levels with significant potential for eliminating endodontic biofilms.

Chitosan Nanoparticles

Chitosan (poly[1,4-β-D-glucopyranosamine]), a deacetylated derivative of chitin, is the second most abundant natural biopolymer. Nanoparticles of chitosan could be synthesized or assembled using different methods depending on the end application or the physical characteristics required in the nanoparticles (22). Chitosan has received significant interest in biomedicine (22–24) because of its versatility in various forms such as powder (micro- and nanoparticles), capsules, films, scaffolds, hydrogels, beads, and bandages (22). Chitosan has a structure similar to extracellular matrix components and is therefore used to reinforce the collagen constructs (25). This hydrophilic polymer with a large number of hydroxyl and free amino groups can be subjected to numerous chemical modifications and grafting, resulting in functionalization, which is discussed in a separate section (26–28). Nanoparticles of chitosan have been developed mainly for antibacterial and drug/gene delivery applications.

Chitosan has excellent antibacterial, antiviral, and antifungal properties (29). In case of bacteria, gram-positive bacteria were more susceptible than gram-negative ones. The minimum inhibitory concentrations ranged from 18–5000 ppm depending on the organism, pH, degree of deacetylation (DD), molecular weight, chemical modifications, and presence of lipids and proteins (29, 30). DD is known to influence the antibacterial activity. With higher DD, the number of amine groups increases per glucosamine unit, and, thus, chitosan showed higher antibacterial efficacy (31). Chitosan nanoparticles (CS-NPs) by virtue of their charge and size are expected to possess enhanced antibacterial activity.

TABLE 2. Limitations of Current Topical or Systemic Antimicrobial Treatment Strategies to Manage Infectious Diseases

Cause and treatment	Challenges/limitations
Microbial factors	
Antibiotic-resistant mutant strains	Methicillin-resistant *Staphylococcus aureus* Vancomycin-resistant enterococci
Antibiotic-resistant mechanisms	Exchange of genetic materials Deficiency of specific porin channels Promotion of active drug efflux Thickening of the peptidoglycan layer of the outer wall
Structure and organization of microbes	Variation in the outer wall in different classes of bacteria and fungi Formation of biofilms Protozoal existence as tropic feeding stage of resting cystic stage
Antibiotic misuse	Excessive or inappropriate prescription Failure to complete treatment regimen Widespread use of antibiotics in livestock feedstuff

Data from Cunha BA. Antibiotic resistance. Control strategies. Crit Care Clin 1998;14:309–27 (18); Finegold SM. Intestinal microbial changes and disease as a result of antimicrobial use. Pediatr Infect Dis 1986;5:S88–90 (19); and Cookson BD. The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. J Antimicrob Chemother 1998;41:11–8 (20).

Mechanism of Action

The proposed mechanism of action is contact-mediated killing that involves the electrostatic attraction of positively charged chitosan with negatively charged bacterial cell membranes (Fig. 1). This might lead to altered cell wall permeability, eventually resulting in the rupture of cells and leakage of the proteinaceous and other intracellular components (29, 32). Under transmission electron microscopy, the bacterial cells were noted to be completely enveloped in the chitosan, forming an impermeable layer (33). This could result in the prevention of transport of essential solutes leading to cell death. In case of fungi, chitosan was hypothesized to enter the cell and reach the nucleus, bind with DNA, and inhibit RNA and protein synthesis.

Current Applications

For the first time, Kishen et al (34) looked into the efficacy of various cationic nanoparticles to improve root canal disinfection. Dentin treated with nanoparticles resulted in significantly reduced adherence of *Enterococcus faecalis*. The antibacterial efficacy of CS-NPs and zinc oxide in disinfecting and disrupting *E. faecalis* (ATCC and OG1RF) biofilms was evaluated later on (35). These nanoparticles eliminated biofilms on a concentration- and time-dependent manner and also retained their antibacterial properties after aging for 90 days (35). CS-NPs can be delivered within the anatomic complexities and dentinal tubules of an infected root canal to enhance root canal disinfection (36). Biofilm bacteria are known to express efflux pumps as a resistance mechanism to antimicrobials (37). When tested along with known efflux pump inhibitors, the antibacterial efficacy of CS-NPs was not affected against bacterial biofilms compared with cationic photosensitizers (38). Another challenge in using antibacterial agents inside the root canal space is the neutralizing effect of different tissue inhibitors (39). Similarly, tissue inhibitors such as pulp and serum albumin inhibited the antibacterial effect of CS-NPs significantly (40), whereas dentin, the dentin matrix, and lipopolysaccharides did not affect the efficacy of CS-NPs. In another *in vitro* study, CS-NPs were used in combination with different brands of chlorhexidine to eliminate *E. faecalis* with potential application toward tissue regeneration using membrane barriers in periapical surgery (41). The addition