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Journal of Education Technology in Health Sciences

Journal homepage: https://www.jeths.org/

Review Article

Nanotoxicity in endodontics - the lurking hazards of nanomedicine

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ARTICLE INFO

Article history:
Received 27-11-2022
Accepted 03-01-2023
Available online 21-02-2023

Keywords:
Nanotechnology
Nanoparticles
Endodontics
Nanotoxicity

ABSTRACT

Molecular engineering has bought revolution into endodontics. Nanoparticles are particles of 1-100nm in dimension. Their small size, increased surface to volume ratio, specific surface properties and charge produces properties desirable for endodontic usage. It has been incorporated into sealers, obturating materials, restorative materials, disinfectants etc to name a few. However, there is other side to it. These micrometre-sized particles can easily cross biological barriers, and enter into various organ systems in the body causing damage at cellular level. These ultrafine particles can be "Nanotoxic".

Nanotoxicology is the study of the nature and mechanism of toxic effects of nanoscale materials/particles on living organisms and other biological systems. It deals with the quantitative assessment of the severity and frequency of Nanotoxic effects in relation to the exposure of the organisms.

As the next generation of endodontics moves towards nanotechnology, it is crucial to develop proper understanding of the processes happening when a nanoparticle comes in contact with a living system. Biocompatibility is achieved when a material interacts with the body without inducing any toxic, immunogenic, thrombogenic or carcinogenic response. Little is known about the toxicological impact of these nanoparticles.

This paper discusses the mechanism of nanotoxicity, factors affecting it, possible routes of nanotoxicity in endodontics, and its methods of assessment.

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1. Introduction

Richard feynman introduced the concept of Nanotechnology in 1959.[1] The revolutionary one nm in one billionth of a meter particle size changed the dynamics of pharmaceutical sciences.[2] Its intrinsic qualities have enhanced anti-microbial properties, drug delivery, particle stabilisation etc.

The main endodontic applications of nanoparticles are in irrigant, intracanal medicament, obturating material, sealer, photodynamic therapy, dental tissue stabilisation, regenerative endodontics, in restorative materials and as disinfectant.[3–6] (Figure 1)

Nanoparticles has its known benefits and unknown risks. These ultrafine particles which provide amazing properties, can also pose as a threat. Hence, it is imperative to study about the possible toxicity and biocompatibility of nanotechnology in depth as we broaden its application in Endodontics.

2. Nanotoxicity

Nanomedicine holds tremendous promise. It has been prognosticated to change the world of pharmacology. Nanomedicine has the ability to improve drug pharmacokinetics, biodistribution, cell- or tissue -specific targeting, and drug exposure kinetics, resulting in enhanced

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https://doi.org/10.18231/j.jeths.2022.017
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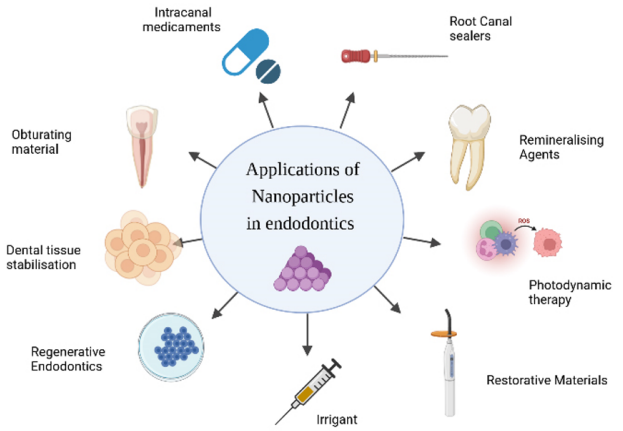

Fig. 1: Application of nanoparticles in endodontics

efficacy and improved tolerability.[2]

Nanotoxicology is the study of the nature and mechanism of toxic effects of nanoscale materials/particles on living organisms and other biological systems. It deals with the quantitative assessment of the severity and frequency of Nanotoxic effects in relation to the exposure of the organisms.[7]

Like two sides of a sword, Nanomaterials have known benefits and unknown risks. As endodontics moves towards Nano-dentistry it is imperative to carefully understand its properties and shortcomings.

3. Factors accountable for Toxicity of Nanoparticles

Nanoparticles have complex biological interaction and toxicity at nano scale. This can be due to various reasons, which include chemical composition, physicochemical properties and biological activities, and environmental conditions of synthesis, preservation, and degradation. Properties of nanoparticles accountable for its toxicity are:

1. Particle size and surface area: Size is an important factor in determining toxicity.[8] They dictate how the body responds to, distributes, and eliminates it. As the size decreases, the surface area to volume ratio increases which in turn increases its chemical and biological activity.[9] Its greater reactivity leads to increased production of reactive oxygen species (ROS), including free radicals. ROS and free radical production is one of the primary mechanisms of nanoparticle toxicity. They lead to oxidative stress, inflammation, and consequent damage to proteins, membranes, and DNA.[10] Smaller sized nanoparticles are more readily taken up by the human body and are capable of crossing physiologic barriers.
2. Surface charge: Surface charge determines its interactions with other biological entities.[11] Surface charge determines the adsorption of nanoparticles, colloidal behaviour, plasma protein binding, blood-brain barrier integrity, and transmembrane permeability.[12,13]
3. Shape/structure: Nanomaterials exist in varied shapes including fibres, rings, tubes, spheres, and planes. Elimination of spherical nanoparticles is easier and faster as compared to other shapes like rod or fibre shaped. Hence, spherical nanoparticles are relatively less toxic, while non-spherical nanoparticles have biological consequences.[14,15]
4. Solubility, and surface coatings and roughness: Surface coating impart properties like magnetic, electric, and optical and chemical reactivity. These properties alter the pharmacokinetics, distribution, accumulation, and toxicity of nanoparticles.[16–18]
5. Dosage: Dose is one of the key parameters in toxicology. Toxicology is often associated with the concept of dose and dose response.[19]

4. Mechanism of Nanotoxicity

Once nanoparticles gain entry into the body, they are capable of penetrating various skin barriers like skin, mucosa, blood brain barrier etc. As these particles gain entry to the body, they are internalised by cells through a process called trojan horse effect. Inside the cell along with lysosome the release ions, which exert toxic effects. This is called the “lysosome-enhanced Trojan horse effect”.[20]

Nanoparticles cause oxidative stress in mitochondria by the production of reactive oxygen species (ROS). This makes the cells incompetent to perform redox reactions.[21] These leads to oxidative modification of proteins, DNA damage, activate inflammatory signals which result in apoptosis, necrosis, and genotoxic effects.[22,23]

Both these process in turn result in Nanoparticle-mediated ROS-dependent autophagy and NP-mediated lysosome dependent autophagy.[23]

These nanosized particles cause activation of microglial cells which release pro-inflammatory factors. This is how it exerts inflammation, cell dysfunction, and cytotoxicity in cells.[24]

Finally, in DNA it accelerates mutagenesis by damaging and disturbing the in and out flow of substances in the cell and causing structural damage in proteins.[25]

5. Nanotoxicity in Endodontics

In endodontics nanoparticles have been used both in clinic and personal home care products like dentifrices. There are several theoretical routes of exposure for dental patients. The most obvious mechanism would be the accidental or incidental ingestion of the nano-containing dental material during or after treatment. The restorative procedures are notorious for producing aerosols during dental treatment that might present a respiratory hazard to the patient (e.g.,

aerosols generated during restoring or removing a filling). Any ingested or inhaled nanoparticle can directly reach to the cells/tissue of the body and cause systemic effects. Thus, there is a continuous exposure to nanoparticles. Hence, Nanotoxicity is a matter of concern for endodontics.

The utmost importance for a clinician is patient safety and care. While there is an obvious lack of regulatory use of nanomedicine, Juillerat-Jeanneret et al. argued these laws are fundamental and should be laid out same as that for other pharmacological agents. Occupational exposure of the practitioner.[26]

As aptly said 'Health is wealth', the occupational health of the practitioner should not be ignored. Potential exposure of the practitioner could arise from incidental ingestion or through skin contact. The major source of exposure is through aerosols of dental materials containing nanomaterials especially during procedures like drilling or filing into a repair. Although the exposure may see to be in minuscules, they might add up and cause toxic effects. Hence, the clinical practice of wearing surgical gloves, and avoiding consumption of food at workplace are simple methods to minimise this exposure. But most importantly a safe system for the usage of such ultra-fine nanoparticles should be set up for health care professionals.

While nanotechnology has ample of benefits, we need to ponder about few things. There have been few studies about nanotoxicity and almost nil literature is available in regard to nanotoxicity in dentistry. Most of the studies done are in vitro studies, hence there is a clear need for in-vivo studies. Its hazardous potential and toxicological pathology are not well understood. Lastly, use of these ultra-fine particles can be an environmental concern.

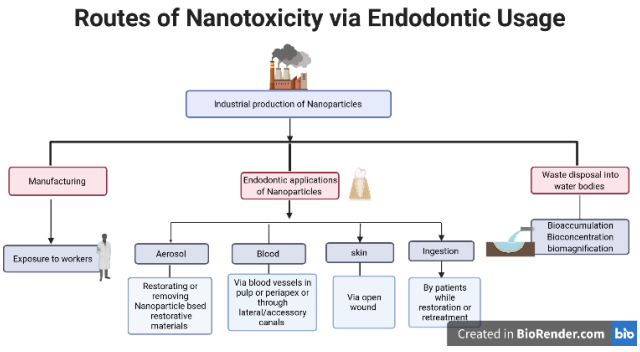

Fig. 2: Possible routes for nanotoxicity viaendodontic usage

6. Conclusion

Nano dentistry is on fast rise. Use of ultra-fine particles is a like the two sides of the sword. Since there are multiple unwanted exposure to such particles in a dental environment. We need clear data on the dosage, methods of exposure, and its toxic effects. Hence, further research is needed on workplace exposure to Nanomaterials in restorative dentistry.

7. Source of Funding

None.

8. Conflict of Interest

The authors have declared that no conflict of interest exists.

9. Acknowledgement

We would like express sincere gratitude Dr Neeta Shetty, Professor, MCODS, Mangalore, for expert guidance and valuable suggestions.

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Cite this article: Raj S. Nanotoxicity in endodontics - the lurking hazards of nanomedicine. *J Educ Technol Health Sci* 2022;9(3):68-71.