Nanomed Res J 7(4):312-319, Autumn 2022

REVIEW PAPER

Therapeutic utility of nanomaterial in oral and maxillofacial tissue regeneration

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ARTICLE INFO

Article History:
Received 30 Aug 2022
Accepted 15 Oct 2022
Published 01 Nov 2022

Keywords:
Nanomaterials
Nanoparticles
Tissue
Oral
Maxillofacial

ABSTRACT

Oral and craniomaxillofacial diseases contain conditions affecting both the soft and hard tissues of face and also dentalarches. Exploiting the bioactive nanomaterials (NMs) in clinical utility has been extensively evolved. The NMs offer incredible progress in the averting and cure of oral and maxillofacial conditions. In the current review, we offer a glimpse into recent development in NMs used to oral and maxillofacial tissue regeneration and disorders therapy, with particular focus on the promoting the quality of oral and maxillofacial healthcare. NMs include polymers, liposomes, particles, micelles, capsules, and scaffolds in nano-size offer worthy oral health. They recognize and cure diseases, restore tissue failing, and enhance the restoration of the physical activity of the tissue by representing the construction of natural tissue. We also delivered an efficient, and the important knowledge gaps for upcoming investigation.

How to cite this article
Mahmoudi H. Therapeutic utility of nanomaterial in oral and maxillofacial tissue regeneration. Nanomed Res J, 2022; 7(4): 312-319. DOI: 10.22034/nmrj.2022.04.001

INTRODUCTION

Oral and craniomaxillofacial conditions include disorders in soft and hard tissues of the facial, face as well as dentalarches [1, 2]. These conditions are typically produced through physical, chemical as well as microbiological causes concomitant with systemic diseases [3]. During these conditions, we show the oral infectious disorders like caries and periodontitis, deficits in craniofacial tissue stimulated by tumors, cysts, trauma and deformities. Besides, central nervous system related disease, salivary gland disorders, and temporomandibular joint (TMJ) disorders are usually found [4].

Because of the particular prerequisite for tissue recovery and upgrading in clinical benefits in this context, the utilizing of a diversity of bio-safe materials is of paramount importance. For example, autogenous bone grafts is described as the most critical therapeutic modality for enabling maxillofacial bone restoration due to their unique attributes ranging from the remarkable biocompatibility [5, 6]. On the other hand, other types of the materials such as amalgam alloys, composites, metals, cements, heat-cured polymethyl methacrylate as well as particle fillers have recently been exploited in dental clinical practice [5, 7]. Regardless of the verified biocompatibility and suitable esthetics, such conventional ingredients have several restrictions including the establishment of scar, fatigue, eliciting infections disease, and irritations in skin. These drawbacks highlight the importance of developing novel alternative materials [8].

Therapeutic utility of nanomaterials (NMs) to support recovery of the oral and cranio-maxillofacial tissue have currently rapidly evolved and resulted in pronounced development in circumventing the challenges of the this context [9]. NMs are usually called as natural, incidental, or synthetic materials encompassing the particles, agglomerates, or aggregates [10]. It is required that these materials be in an unbound formal with at least 50% total particle size spreading between 1 and 100 nm. As

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result of their mechanical possessions as well as nanometric size, nanomaterials simply enter dental and bone tissue, influences the chemistry as well as the topography of bone area [11]. They also have anti-bacterial competencies. The NMs including the polymers, liposomes, particles, micelles, capsules, and scaffolds in nano-size offer worthy oral health [12]. They recognize and cure diseases, restore tissue failing, and enhance the restoration of the physical activity of the tissue by representing the construction of natural tissue.

Despite the NMs utility has motivated the progress of clinical dentistry and cranio-maxillofacial disease therapy, special focus of their side effects is urgently required. The nanometric size of NMs enables the penetration of the biological hurdles, exerting undesired cytotoxicity, and eliciting immunological reactions to host cells [13, 14]. Further, the topography of surface influence nanoparticle (NP) cellular uptake. Now, NMs application has driven an alteration in medical sciences and delivers valuable opportunity in healthcare. Notwithstanding, the comprehensive acts and potent poisonous influences of NMs once they are applied in oral and maxillofacial section are vague [15].

Herein, we will confer the proof of the uses of NMs in association with most current progress in oral and craniofacial tissue recovery prospect.

OVERVIEW OF NANOMATERIAL'S

NMs are usually categorized into various types including the carbon-based NMs, polymeric NMs, metal oxide NPs, metal NPs as well as quantum dots [16]. The NMs are produced in the environment due to the natural and anthropogenic sources. These sources involve both of the either incidental or nanotechnological sources [17]. The carbon-based NMs natural sources contain combustion and other extremely energetic procedures like volcanic eruptions, lightning along with sandstorms as well as wildfires [18]. By considering the anthropogenic sources, it has been noted that combustion is the key origin of carbon-based NMs, shadowed through the friction procedures and mining. This course tracked by nanotechnology that intentionally makes NMs. Indeed, the carbon-based NMs contain amorphous carbon NPs as well as various carbon allotropes [19]. They possess the specific features of sp2- and sp3-hybridized carbon bonds with physiognomies of their physics and chemistry at the non-size. In this group, the most investigated mixes are pristine fullerenes. The pristine fullerenes in fact are the unsaturated unfunctionalized carbon molecules containing at least 20 carbon atoms settled as a hollow polyhedron [19].

The NMs are fabricated elements with very minor dimensions to deliver the inimitable physical and chemical possessions that found in the nanoscale [20]. Due to the particular size, the physical and chemical possessions of NM vary from those of their larger-scale components. Thus, the NMs serves unpredictable role which currently not understood in some cases. For instance, proofs signify that NMs can cross via skin and blood–brain barriers (BB) and drive an unwanted impact on host cell [21]. Growing evidence imply that NMs can be modified and applied as new chemicals with regular principles. However, the diversity of consumer yields and food flavors in the bazaar include NMs [22]. These yields are classically unrevealed and unproved for their influences on human as well as environmental health.

MAXILLOFACIAL TRAUMA MANAGEMENT

Facial damages, especially, soft tissue damages and facial bones' fractures are typically occurred by the motor vehicle crashes, falls, violent attacks, and recreational activities-associated crashes [23, 24]. Although these damages in some case happen as restricted lesions, they are more usually related to a diversity of severe damages. It has recently been clarified that in the 50- 80 % of case, head injuries are shown in combination with the facial fracture, associated with the fracture situation [25]. Of course, the intracranial damages befall usually in the bones of the upper face and maxilla fractures [26]. While, they are less commonly related to the mandible injuries. Regardless of the combination with head injuries, cervical spine damages are shown concomitant with facial damages. For attenuating the morbidity and mortality rate, it should be noted that the initial detection of the serious head trauma and attendant damages residues a significant portion of the first valuation and treatment strategy of sternly damaged patients [27]. Appreciating the reason, harshness, and diversity of facial trauma as well as the attendant damages can aid in the developing of the early clinical cure and delineation of the correct period to apply oral surgeon [28]. In developed countries, the participants with continued multiple damages advantage from an initial multidisciplinary supervision in a developed trauma center. Regardless of the clear marks and indications the great amount of associated intracranial damages highlights the necessity to monitor all trauma patients suffering from the facial fracture for brain damages. Accordingly, the conventionally application of a head as well as full-body CT scan for all harshly damaged patients is suggested to guarantee that no attendant damages are ignored [29]. But, the necessity for instant maxillofacial operation was little, though it appears essential that cure of sternly damaged patients must be restricted to major trauma centers. Because, tight collaboration between trauma-, neuro-, and maxillofacial surgeons are required [30].

NANOMATERIAL APPLICATIONS IN ORAL AND MAXILLOFACIAL TISSUE REGENERATION

Hard tissue regeneration

Among nanomaterials, the carbon nanotubes have attracted increasing attention and are suggested as an effective therapeutic modality for bone regeneration. This positive effect are mainly because the carbon nanotubes' significant mechanical, electrical features as well as biocompatibility. Based on the literature, a graphene and single-walled carbon nanotube (G/SWCNT) hybrids could improve the osteoblast generation from dirat stem cells. Also, it suppressed the adipogenesis potently through up-regulating p38 signaling pathway and conversely negative regulation of extracellular signal-regulated kinase (ERK) 1/2 axis [31]. Besides, a sandwich-like scaffold including the nano-calcium sulfate disc plus the platelet-rich plasma (PRP) fibrin gel containing the bone morphogenetic protein-2 (BMP-2)-overexpressing stem cells is capable of inducing the bone recovery in calvarial defects in rodent models [32]. Likewise, poly(ε-caprolactone) (PCL) and chitosan/polyethylene oxide (CTS/PEO) scaffold as well as a 3D printing poly (lactic-coglycolic acid) (PLGA)/β-tricalcium phosphate (β-TCP) scaffold were found that could provoke bone regeneration in vivo [33]. These finding make them an ideal therapeutic modality to restore bone defects.

Likewise, other reports have showed that ultralight 3D hybrid nanofiber aerogels including the electrospun PLGA-collagen-gelatin including the of heptaglutamate E7 domain specific BMP-2 peptides could be developed to potently ameliorate the cranial bone damages [34]. Histo- pathological analysis demonstrated that intervention resulted in greater bone volume and bone formation area in animal models [34]. Further, alendronate (ALN) based nanofiber injected into critical-sized alveolar bone defects in rat maxillae [35]. Observation showed that the intervention markedly promoted new bone formation in injection area. Thereby, applying the mineralized nanofiber sections was found that have efficient utility in eliciting the bone restoration [35].

Finally, the electrospun nanofibrous material is another types of the NM, which strongly been investigated in craniofacial bone tissue recovery. Electrospun nanofibrous could raise the stem cell mediated osteogenesis and mineralization. Insertion of this scaffold also is a less aggressive plan. These materials act as a barrier to soft tissue and promote the expansion and development of the new bone formation [36]. Meanwhile, studies have supposed that fabricated nano/microfibrous silk fibroin (SF)/PCL composite scaffold could induce two main event in vivo. Firstly, it could promote stem cell proliferation, viability, and infiltration,, and secondly improve the new bone establishment in a calvarial defect rabbit model [37].

Oral soft tissue regeneration

Recent reports have clarified the important role of NMs in the regeneration of the oral soft tissue such as dental pulp (DP), periodontal soft and salivary gland [38, 39]. Regeneration aptitude is significant for dental pulp tissue to uphold the survival, though an important difficulty of DP tissue regeneration is the root apex revascularization [40]. As DP-Derived stem cells can restore the activity of the pulp and vasculature in the tooth, increasing investigations have focused on the effects of the NMs on DP-Derived stem cells [41, 42]. Nanotechnologies enhance the delivery of active biomolecules and other factors and provide the extracellular structure [43, 44]. For example, a diversity of recently evolved materials such as ultrasmall superparamagnetic iron oxide (USPIO)-labeled SF/HA materials, nanoparticle-gelatin with lower rate of the stifness, nanofibrous microsphere containing the growth factor have shown a marked capability to enhance the proliferation of the DP-Derived stem cells, improve their migration as we as attenuate their apoptosis [45, 46]. As well, some hydrogels like antibiotics and nitric oxide (NO) secreting biomimetic nanomatrix gel exhibited both anti-microbial activity and tooth revascularization inducing influences [47, 48]. Thus, these multi-functionalized NMs can be a putative plan to provide the complex dental tissue recovery. Besides that, guide cell homing has recently been suggested as the one of the most critical clinical approach in DP recovery [49, 50]. Studies have shown that chemotaxis-stimulated cell homing would promote pulp-like tissue in native tooth [51]. Accordingly, this strategy is a pronounced direction by nano-scaffolds and nano-drug deliver plans, directing stem cell efficient homing to augment DP regeneration [52, 53]. Furthermore, to restore the structure and activity of periodontal ligament, several NM are cited as alternative and have been widely evaluated. Meanwhile, electrospun nanofibrous constructed by electrospinning polymer nanofibrous membrane, gelatin PLGA, and PLLA has been recommended [54]. On the other hand, hydrophobically modified glycol chitosan (HGC)-based nano adjusted secretion system for sequential secretion of trichloroacetic acid (TCA) and epidermal growth factor (EGF) was found that could ameliorate oral soft tissue defects [39].

Cartilage tissue regeneration

NMs applied in this context are substantially emphasized on offering an alternative option by improving the surface area, porosity and mimicking the native extracellular millieu. Cartilage in oral and cranio-maxillofacial sections comprises the temporomandibular joint (TMJ) cartilage, auricular cartilage as well as nasal cartilage regeneration [55, 56].

Nanofibers are comprehensively used to reconstruct cartilage deficits and presented remarkable therapeutic benefits in vivo. Presently stated functional nanofibers comprise polycaprolactone (PCL) fibrous scaffolds, PCL-poly(ethylene glycol) (PEG)-PCL scaffold, and a new biomimetic and bioactive electrospun cartilage, laden with continued growth factor transport microspheres [57]. Meanwhile, the graphene oxide (GO) is a collection of material exploited in cartilage regeneration mainly as result of its privilege in mechanical power, surface zone, electrical/chemical modification possessions [58]. For instance, expert developed a hybrid scaffold containing the methacrylated chondroitin sulfate, PEG methyl ether-ε-caprolactone-acryloyl chloride, and GO for supporting the cartilage defects recovery in rabbits [59]. It offers an appropriate porosity, pore size, conductivity, and compression modulus like the normal cartilage ECM.

Nasal cartilage and auricular cartilage serve a central role in upholding the exterior and activity [60]. Unlike the articular cartilage of the TMJ, both of the nasal and auricular cartilages have their detailed form and roles. Consequently, it puts forward advanced necessities for the utilizing biomaterials in cartilage tissue recovery. A 3D printing means plus a diversity of NMs has been modified in this context lately. For example, researchers have generated an exact bionic ear usingthe 3D printing of a chondrocyte-loaded alginate hydrogel matrix plus an electrically conductive Ag NPs infused inductive coil antenna [61]. Other scientists have prepared the electrospun gelatin and PCL membranes including the chondrocytes for enhancing the auricular cartilage restoration [62]. For better adjusting the 3D organization of ear, an ear-shaped titanium alloy mold is currently applied as a template. For improved reconstruction of the defect ear form, researchers invented a bilayer bacterial nanocellulose (BNC) scaffold using a dense nanocellulose layer in association with the microporous composite layer [63]. This material provided a porous building appropriate to cell ingrowth and shape the cartilage.

Besides nanofibers and GO, other NMs including the human neutrophil-derived microparticles and other novel nanoparticles, which contain the aspirin-triggered resolvin D1 or a lipoxin A4 analog may attenuate inflammation in the TMJ [64]. In addition, 15-Deoxy-Delta-12,14-prostaglandin J2 (15d-PGJ2) in PLGA, PLG, or poly(lactic-co-glycolic acid) nanocapsules offer suitable material to convey the antinociceptive and anti-inflammatory components to cure temporomandibular Disorder (TMD) [65].

Nerve tissue regeneration

Nanotechnology provides novel viewpoints in the context of the innovative medicine, particularly for restoration and repair of permanently injured or diseased nerve tissues because of the lack of efficient self-repair process in the peripheral and central nervous systems (PNS and CNS, respectively) of the body [66].

Between PNS injuries, the progressive nerve looseness or detrriorating diseases may arise from the acute trauma. The nerves affected in the detailed section are facial, inferior alveolar, mental, lingual, incisal along with the nasopalatine, greater palatine as well as the infraorbital nerves [67]. Among them, the most frequently complicated is the mandibular nerve. Damage to the branches of the mandibular division of the trigeminal nerve is a recurrent problem in implant surgery and as well as in the bone grafting process [68]. Furthermore, the inferior alveolar and lingual nerves damages

Table 1. The main types of nanomaterials applied in oral and cranio-maxillofacial tissue regeneration

Tissue	Nanomaterial	Morphology	Reference
Bone	HA, RGD modified HA/PLGA, HA-matrix	Nanoparticle	[74]
Dental	nHA	Nanoparticle	[75]
Bone	PLGA films	Nanoplate	[74]
Cartilage	CSMA/PECA/GO	Nanofiber	[76]
Cartilage	TGF-β1/scaffold	Nanofiber	[77]
Bone	PCL nanofibers HA/PLGA	Nanofiber	[78]
Cartilage	15d-PGJ2 in PLGA	Nanocapsule	[65]
Dental	Silica and nHA	Nanoparticle	[79]
Bone	BMP-2 peptide Mineralized nanofiber segment	Nanofiber	[80]
Nerve	Electrospun SF	Nanofiber	[81]
Dental	Biopolymer blend PCL/gelatin	Nanofiber	[82]
Dental	HA bioceramics	Nanorod	[83]
Bone	Electrospun PLLA	Nanoyarn	[84]
Dental	Antibiotics and nitric oxide-secreted scaffold	Nanomatrix gel	[85]

may be linked to third molar surgery. A trigeminal nerve injury can be result from the tumors, cystic and iatrogenic lesions, infections, tooth extraction, endodontic therapy-mediated canals overfilling, flap elevation as well as the apical surgery, orthognathic, nerve transposition, and pre-prosthetic surgery [69].

Surgical processes for restoring damaged peripherical nerves are specified in axonotmesis and neurotmesis cases based on the Seddon classification [70]. They include the direct end-to-end reconnection in association with the nerve grafts in larger nerve defects. Autografting shows various significant controversies, containing the restricted obtainability of donor graft and mismatch in size [71]. Besides, the further surgery trauma at donor regions and related functional lack of a donor nerve are unwanted opposing outcomes. Accordingly, the allografts and xenografts are suggested as the alternatives to autologous nerve grafts. Nonetheless, immunological responses and infection transmission may be found in recipients [72]. Another well-known plan includes the application of processed human decellularized allograft yield.

Guided nerve regeneration is a talented policy to encourage axon recovery. In this process, the placement of a material to attach the injury gap to direct the axonal sprouting and recovery across a nerve gap from nerves proximal to distal portions [73].

An overview of recent studies based on the NMs application in oral and cranio-maxillofacial tissue regeneration has been provided in Table 1.

CONCLUSION

Nanotechnology has attracted increasing attention in dental therapy for a confident time with notable achievement. Certainly, NMs deal countless capacity in cranio-maxillofacial bone and teeth renewal, and oral disorder management, particularly in caries deterrence, osseointegration of dental implants as well as in prosthodontics material development. Nonetheless, the possible helpful possessions must continuously be weighed against the opposing impacts. Drawbacks of applying the NMs based appliances nanodentistry must always be taken into contemplation beforehand presenting in the market because the oral cavity is a distinguishing micro-environment where the communication of "targeted" and "non-targeted" organ with NM are current. Parameters like pH, plaque biofilm in combination with the buffer system in the saliva also usually moderate the performances of these NMs in the oral cavity. In addition, these nano fillings are typically worn out sue to the bite filling, erosion, and dissolving, thereby may disrupt the tooth surface, gingiva and mucosa. Also, NMs generated from oral cavity may be swallowed and cross the gastrointestinal tract, leading to the systemic side effects.

CONFLICT OF INTEREST

There is no conflict of interest.

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