

Nanomedicine: the use of nanoparticles to treat acute traumatic spinal cord injuries

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ABSTRACT Spinal cord injuries (SCIs) are difficult to treat without using traditional invasive methods that are not always precise or efficient. Traditional methods used to treat SCIs often involve targeting a broad area in close proximity to the specific locality of the injury as opposed to direct targeting. Recent studies suggest the use of nanoparticles can be a viable way to treat SCIs. Nanoparticles are nanotechnological devices that operate on a nanometre (1×10^{-9} m) scale, varying in dimension from 1-100nm. They can be designed to target an assigned area with a high degree of specificity, thus ensuring that the affected area is treated with maximum proficiency. This article will explore the properties of silica nanoparticles, polymer nanoparticles, and chondroitinase ABC-(chABC)-releasing nanoparticles to determine whether they present a non-invasive alternative treatment for acute traumatic spinal cord injuries (tSCIs). A review of the literature suggests that the use of multifunctional silica-polymer nanoparticles can plausibly treat SCIs by maximizing the beneficial characteristics of both materials. Silica nanoparticles have a zero-order drug-releasing property which provides efficacious targeting, and when combined with polyethylene glycol (PEG) this polymer increases aqueous stability and retention of the nanoparticle, which protects the loaded drug when it crosses the blood-brain barrier to target the SCI. In addition, chABC-releasing nanoparticles show promising results in treating SCIs due to their ability to remove glycosaminoglycans (GAGs) and promote nerve regeneration, potentially decreasing the healing time of SCIs. Overall, the application of nanoparticles provides a potential non-invasive treatment method for SCIs in mice models. However, further research needs to be done to explore the potential medical applications of nanoparticles regarding human SCIs.

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INTRODUCTION

The spinal cord is the bundle of nerves connected to the brain that extends down the spinal canal (Noonan, 2012). A temporary or permanent impairment of the spinal cord is termed a spinal cord injury (SCI) (Noonan, 2012). There are two general classes of SCIs: (i) traumatic spinal cord injuries (tSCIs), which occur due to external physical impact; and (ii) non-traumatic spinal cord injuries (ntSCIs), which occur when damage is done to the spinal cord by means other than physical impact (Noonan, 2012).

In order to implement an appropriate treatment plan for an SCI, it is important to distinguish the type of SCI and its severity. The severity of SCIs can vary from acute to chronic (Beaulieu, 2018). Acute SCIs result from sudden trauma that is potentially repairable depending on the circumstances of the injury; chronic SCIs result from trauma that has happened over time (Beaulieu, 2018). SCIs often have debilitating effects on patients and can severely impact their quality of life (Infante, 2018). Damage to the spinal cord can result in tetraplegia, which indicates damage to the cervical cord, or paraplegia, which indicates damage to the thoracic, lumbar, or sacral spinal cord (Noonan, 2012). This article will solely discuss acute tSCIs to delineate the mechanism of action of each treatment regarding the site of inflicted physical injury.

Research indicates that tSCIs affected approximately 43,974 Canadians in the year 2010 (Noonan, 2012). These injuries often

have extensive recovery times, and traditional methods of treatment are invasive to the human body, prolonging recovery times (Ho et al., 2018). Traditional methods of treating SCIs such as electrical stimulation often entail stimulation of a broad area in close proximity to the specific area of treatment (Ho et al., 2018). However, this does not target the affected area with specificity. Nanoparticles have the potential to treat SCIs more effectively due to their ability to perform immaculate targeting specificity to their assigned locality without being invasive (White-Schenk et al. 2015; Ellis, 2017). Nanoparticles are nanotechnological devices that operate at 1×10^{-9} m, or one nanometre (nm) (Ellis, 2017). Nanoparticles offer a potential method of treatment for acute tSCIs by selectively degrading damaged nerve tissue in the spinal cord to promote axonal regeneration, potentially reducing patient recovery time (Prabhakar et al., 2005).

METHODS

A scoping review was performed to outline the advantageous properties of silica, polymer, and chABC-releasing nanoparticles and this review explored the characteristics of these devices as potential treatments for acute tSCIs. The articles retrieved were all written in English. Secondary research was conducted at the University of Ottawa using the PubMed database: a narrow keyword search using combinations of the search terms 'tSCIs', 'nanoparticles', and 'proteoglycans' was performed. A full description of the search strategy is presented in Table 1. The search was last updated October 13, 2020. No additional databases were used.

However, additional lecture material from Physical Activity, Work and Health Ergonomy presented at the University of Ottawa was included.

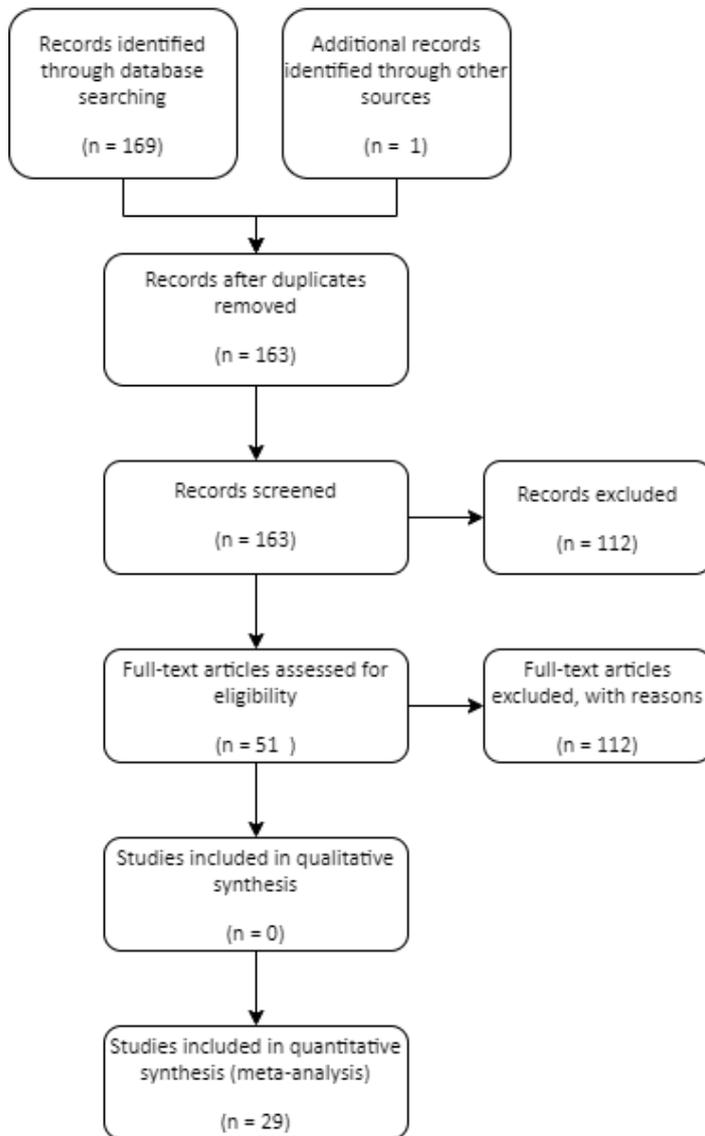


Fig. 1: PRISMA flow diagram: a total of 169 original articles were retrieved of which 29 articles were considered relevant.

Study selection

After eliminating duplicate results, title and abstract screening was performed by the author. Then, full-text screening was performed dating back to the last 15 years to retrieve relevant articles according to the inclusion criteria. Articles that explored the characteristics of silica, polymer, and chABC-releasing nanoparticles as potential treatment methods for acute tSCIs were eligible under these criteria. The characteristics of the nanoparticles were explored and the intent of this review was to explain their potential applications as a non-invasive alternative method to treat acute tSCIs. Studies that did not report on these criteria were excluded. The search sensitivity was confirmed by reviewing the articles cited in each study. The search results and selection process using the PRISMA protocol are summarized in Figure 1.

Quality assessment

The quality of the selected articles was assessed based on their

study characteristics and methodological approach. The two selection criteria narrowed the search to those that explored the properties of silica, polymer, and chABC-releasing nanoparticles; these nanoparticles were further described in terms of their potential as treatments for tSCIs. In terms of the methodological approach, articles that outlined the characteristics of the nanoparticles with regards to treating tSCIs were considered high-quality studies. Only moderate- to high-quality studies were considered in this review.

Data extraction

The author extracted data from eligible studies from their original publications and lecture material from Physical Activity, Work and Health Ergonomy which included information about the type of SCI, study design, intervention used, country of origin, and primary and secondary research. If the data did not comprehensively explore the characteristics of nanoparticles or did not explore SCIs it was excluded from the review.

RESULTS

The reviewed secondary literature indicates that nanoparticle-based strategies for the delivery of neurotrophic factors to promote functional axon regeneration in the spinal cord can occur in an effective and safe manner (Infante, 2018). Thus, nanoparticle delivery methods may be a promising alternative treatment for SCIs due to their non-invasiveness, precision, and specificity (Infante, 2018).

Research has explored the combination of polymer and silica nanoparticles as a potential treatment for SCIs by maximizing their individual chemical properties to create multifunctional silica-polymer nanoparticles with a maximized therapeutic effect.

Materials such as long-chain polymers have been used to treat SCIs in the past due to their ability to first plug the damaged membrane; then close the holes to prevent the entry of unwanted ions and molecules (White-Schenk et al. 2015). One polymer material of interest in SCI therapy is hydrophilic polyethylene glycol (PEG), a stealth polymer that is used to extend the half-life of therapeutics and prevent protein adsorption on the surface of nanoparticles during opsonization (White-Schenk et al. 2015). This reduces the likelihood of an immune response against the nanoparticle, which makes PEGs very successful in crossing the blood-brain barrier and targeting an assigned locality in the spinal cord (Rollerova et al., 2011). Silica nanoparticles are characterized as being mesoporous with a zero-order drug release, which enables efficacious drug-loading and accurate targeting of an assigned locality (White-Schenk et al. 2015). Silica nanoparticles have cytotoxic properties, however they can be used in conjunction with PEG to maximize their beneficial properties while simultaneously reducing their cytotoxic effects, improving their aqueous stability and retention to reduce toxicity in vivo and in vitro (White-Schenk et al. 2015). One study explored the chemical properties of PEG-decorated silica nanoparticles and their effect on the restoration of membrane integrity, axonal conductivity, and functional recovery in model animals (Cho, 2010). This study analyzed the in-vitro crush/contusion model of a SCI in a guinea pig, which was injected with PEG-decorated silica nanoparticles; the model showed signs of conduction recovery through the cord lesion (Cho, 2010). This suggests that the use of multifunctional nanoparticles such as silica and polymer nanoparticles may present a novel approach to

treating SCIs (Rollerova et al., 2011).

Chondroitin sulfate proteoglycans (CSPGs) are inhibitors of neural stem/progenitor cells (NSPC) whose regeneration is essential to the healing process of an SCI (Ikegami, 2005; Massey, 2006). However, the bacterial enzyme chABC has been shown to digest CSPGs and promote the migration of transplanted cells and neurite outgrowth (Ikegami, 2005). An *in vitro* study revealed that the migration of NSPC-derived cells was inhibited by CSPG, and that chABC treatment combined with NSPC transplantation into an injured spinal cord significantly induced the axonal outgrowth due to an increase of growth-associated protein-43 positive fibres at the lesion epicentre, which is important to new neuronal growth (Ikegami, 2005). This suggests that chABC-based treatment may encourage regeneration of injured spinal cords (Ikegami, 2005). Another study indicated that using chABC to degrade CSPGs in the cuneate nucleus of rats reduced the number of CSPGs present in the injured spinal cord (Massey, 2006). Another study explored the effects of increasing the rate of delivery of chABC using nanoparticles to promote axonal regeneration following injury and to protect the enzyme from rapid degradation in a rodent contusion model (Zuidema et al., 2016). Although there is limited data presented in this area of research it is plausible that chABC-releasing nanoparticles are a potential treatment method for tSCIs due to their ability to remove CSPGs and promote NSPCs which are essential to reducing the healing time of an SCI (Zuidema et al., 2016).

DISCUSSION

A novel potential treatment

An injured spinal cord does not regenerate; it undergoes expansion and demyelination, resulting in macrophage activation, which increases axon growth and motor function (Gensel & Zhang, 2015). A macrophage is a type of white blood cell that travels to sites of inflammation to remove damaged material, which is essential to axon growth because this helps to degrade the damaged axons and encourage new axonal sprouting (Gensel & Zhang, 2015). Therefore, in order to treat these areas of inflammation with a high degree of specificity, it is imperative that the treatment be very precise (Infante, 2018).

Because nanotechnology operates at nanometre scale, it operates at the molecular and atomic level (Abou et al. 2015). Nanotechnology includes a variety of technological devices such as nano-assemblers, nano-shells, and nanoparticles, which may play a role in treating SCIs (Ellis, 2017). Nanoparticles offer both precision and target specificity with regards to treating SCI-affected tissues. Nanoparticles are designed through layer-by-layer synthesis, each layer changing the characteristics of the nanoparticle, which adds functionality; this makes nanoparticles programmable (White-Schenk et al. 2015). Nanoparticles are popularly used as a drug-delivery system because they are capable of crossing the cell membrane due to their small size (Amezcuca et al., 2017). Nanoparticles are molecular units that behave as a whole unit during their mobile phase in the human body, and they can be modified with organic and inorganic substances, such as silica or polymer (Gupta, 2010).

Material format of multifunctional silica-polymer nanoparticles

Silica and polymers are used to create nanoparticles because of their unique properties, and they have been extensively tested

as potential platforms for drug-delivery to the spinal cord (R.N., 2017). Silica is an inorganic compound that is used to create nanoparticles because of its porous structure (White-Schenk et al. 2015). Polymer nanoparticles are spherical and are a potentially beneficial treatment for SCIs because they have low toxicity (Rollerova et al., 2011; Kreuter, 2014). Silica and polymeric nanoparticles are notably capable of absorbing and encapsulating drugs (White-Schenk et al. 2015).

Polymer nanoparticles release their drug load to the target area in the form of a burst, resulting in a controlled release (White-Schenk et al. 2015). Polymer nanoparticles are notably much larger than silica particles because of their extensive bonding properties, which is useful in increasing the bioavailability of an otherwise scarce substance (White-Schenk et al. 2015). This is because polymer nanoparticles can directly interact with the desired substance and release it in large quantities in an assigned locality (White-Schenk et al. 2015). Polymeric nanoparticles are usually encapsulated via self-assembly, and as they disassemble their loaded drugs are released in large amounts at a time, potentially causing adverse side effects (White-Schenk et al. 2015). However, polymer nanoparticles can cross the blood-brain barrier, which is advantageous to SCI treatment due to the local nature of such injuries (Kreuter, 2014).

Silica nanoparticles on the other hand are very porous, giving them advantageous qualities such as zero-order drug release (i.e. a constant rate of release), enabling it to minimize interaction with the tissues surrounding an assigned area of treatment; this is very beneficial because most of the loaded drug will be released in the affected area at a constant rate necessary for effective delivery (Ukmar and Planinsek, 2010; White-Schenk et al. 2015). Depending on the material format of silica nanoparticles conjugated with an appropriate polymer nanoparticle such as PEG, this multifunctional type of nanoparticle could potentially be used to treat acute spinal cord injuries through silica encapsulation, enabling the programmed nanoparticle to reach its target area and deliver the appropriate substance (Kreuter, 2014).

It is important that the successful treatment of an SCI entails stimulated and guided axon regrowth along a specific path (Zuidema et al., 2016). This ensures that the axons grow in the appropriate direction so that the healing process occurs properly (Zuidema et al., 2016). Multifunctional silica nanoparticles show promise in treating SCIs because of their ability to increase axonal sprouting through target specificity due to their zero-order drug release capability and their ability to cross the blood-brain barrier (Kreuter, 2014).

Based on the reviewed literature multifunctional silica particles are a more feasible treatment for tSCIs because controlled amounts of silica simultaneously minimize potential toxicity and ensure precise drug release in the targeted locality, while the polymer nanoparticles will ensure a safe crossing through the blood-brain barrier (Kreuter, 2014). Due to the lack of clinical research regarding the use of silica and polymer nanoparticles, it is difficult to draw conclusions on whether they can be used to effectively treat SCIs based on the minimal assessments that have been made using theoretical reasoning. Thus, the results obtained in these controlled studies cannot be directly translated to the treatment of acute tSCIs.

Potential of chABC-releasing nanoparticles

Glycosaminoglycans (GAGs) are linear acidic polysaccharides; these biomacromolecules are believed to be responsible for the inhibition of nerve regeneration following injury to the central nervous system and they constitute the side chains of CSPGs (Prabhakar et al., 2005). CSPGs are major components of the extracellular matrix responsible for nerve regeneration failure (Prabhakar et al., 2005). Research has shown that one effective strategy to promote nerve regeneration is the removal of GAG side chains from the proteoglycan core protein in CSPGs using chABC (Massey et al., 2006).

ChABC is an enzyme that is purified from the bacterium *Proteus vulgaris* (Chondroitinase ABC for Neuroscience Research, 2016). This bacterium produces two related enzymes with broad substrate specificity; this includes chondroitinase ABC I (cABC I) and chondroitinase ABC II (cABC II) (Prabhakar et al., 2005). These two enzymes depolymerize a variety of GAG substrates including chondroitin 4-sulphate, dermatan sulphate, chondroitin 6-sulphate, and hyaluronic acid (Prabhakar et al., 2005). The principle of this depolymerization methodology is to remove GAGs which inhibit nerve regeneration in the spinal cord and promote functional recovery through axon regeneration and reactivation of plasticity through chABC treatment (Massey et al., 2006). Research suggests that there is a mobile functional change directly linked to anatomical evidence of sprouting by spinal cord primary afferents after chABC treatment, potentially decreasing the healing time of an SCI (Massey et al., 2006). Thus, the application of chABC in combination with precise nanoparticles increases their efficiency in treating SCIs (Massey et al., 2006). The application of chABC-releasing nanoparticles differs from that of silica and polymer nanoparticles: although silica and polymer nanoparticles would be effective in targeting and degrading the damaged nerve tissue of the spinal cord they do not promote nerve regeneration (White-Schenk et al. 2015). chABC-releasing nanoparticles remove GAGs from the damaged nerve tissue while still promoting rapid nerve regeneration (Prabhakar et al., 2005). Theoretically, this makes chABC-releasing nanoparticles a more effective method to treat SCIs

Currently, research in North America regarding the use of nanoparticles in SCI treatment is limited to model organisms, such as mice, to test the effectiveness of chABC releasing nanoparticles (Zuidema et al. 2016; Ikegami et al. 2005). chABC-releasing nanoparticles target CSPGs which are known to inhibit axon regeneration by creating glial scars on the spinal cord (Justin et al., 2014). Glial scars inhibit repairs to brain and spinal cord damage (Justin et al., 2014).

By targeting CSPGs to promote axon growth, chABC-releasing nanoparticles present an opportunity to improve the outcome of SCI treatment (Mahajan, 2018). Ikegami et al. (2005) performed chABC treatment combined with neural stem cell (NSC) transplantation to the injured spinal cord of rats and found that this enhanced growth associated with protein-43 axons. Protein-43 is also known as neuromodulin and is associated with axonal growth (Denny, 2006). The results of this study potentially imply that the use of neural stem cell transplantation in combination with chABC-releasing treatment may encourage axon growth and potentially speed up the healing process of a SCI (Ikegami et al. (2005).

A second study carried out by Zuidema et al. (2016) inflicted external physical force on mice to induce an acute tSCI. This study involved two experiments, where: (i) controlled nanoparticles were used to treat the tSCIs of one group of mice; and (ii) chABC-releasing nanoparticles were used to treat the tSCIs in a second group of mice (Zuidema et al., 2016). Upon comparing outcomes between groups, it was observed that the treatment with chABC-releasing nanoparticles resulted in rapid and enhanced axonal sprouting in the spinal cord in comparison to the controlled nanoparticles (Zuidema et al., 2016). This study could also be used to draw the conclusion that although nanoparticles are effective in targeting their assigned tissue localities, it is possible that chABC-releasing nanoparticles are more effective in encouraging axon growth due to their CSPG-targeting properties (Zuidema et al., 2016).

It is important to keep in mind that although chABC-releasing nanoparticles seem to encourage axonal growth, their instability as a compound makes it difficult to use them in an effective SCI treatment (Raspa et al. (2019) . To overcome this, Sasaki et al. (2015) proposed modifying them through site-directed mutagenesis or viral-mediated chABC gene delivery to host cells. These modifications seem theoretically reasonable, but changes to an enzyme such as chABC could have adverse health effects on the human body, and the enzyme itself could denature if the conditions in the body are unfavorable (Mahajan, 2018; Raspa et al. 2019). chABC-releasing nanoparticles have great potential, and their applications in the human spinal cord needs to be further studied.

CONCLUSIONS

Based on the evidence available in various studies, multifunctional silica-polymer nanoparticles are a more appropriate method of treatment for SCIs because of their ability to target specific regions with a zero-order drug release while safely crossing the blood-brain barrier (Kreuter, 2014) (White-Schenk et al. 2015). Although these nanoparticles can be made porous to avoid provoking the immune system (Zuidema et al., 2016) (Ukmar and Planinsek, 2010). More research is necessary to explore these characteristics in depth and to evaluate the potential use of silica and polymer nanoparticles and their application to SCI treatments.

Similarly, the limited research on chABC-releasing nanoparticles indicates that they can ensure maximum substrate specificity to lesion sites in encouraging nerve regeneration and may reduce the time of the healing process (Prabhakar et al., 2005). However, there are many factors to take into consideration when using nanoparticles to release chondroitinase ABC such as enzyme stability, bioavailability, and material used for encapsulation. It is important to further understand the various functions of the enzyme and its effect on the human body by performing additional research that explores its characteristics and functions.

Due to the limited research with regards to nanoparticles and their applications in SCI treatments, it is imperative that extensive research is done in order to further understand the potential function of each nanoparticle. Further steps would entail the testing of safety precautions of nanoparticle release in humans, potentially testing for allergenicity. Then, clinical trials could be carried out to give a better understanding as to whether designed nanoparticles are compatible with the human body in treating SCIs.

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TABLES

Table 1 Summary of search strategy and results as of February 2019

No.	Search terms	PubMed results
1	SCI OR tSCI OR Acute OR Canada OR Nanoparticles OR Silica OR Polymer OR ChondroitinaseABC OR Proteoglycans	169