Implant-Assisted Intrathecal Magnetic Drug Targeting to Aid in Therapeutic Nanoparticle Localization for Potential Treatment of Central Nervous System Disorders

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There is an ongoing struggle to develop efficient drug delivery and targeting methods for treatment of disease within the central nervous system. One technique known as intrathecal drug delivery, involves direct drug infusion into the spinal canal and has become standard practice for treating many central nervous system diseases due to the reduced systemic toxicity from the drug bypassing the blood-brain barrier. Although intrathecal drug delivery boasts the advantage of reduced systemic toxicity compared to oral and intravenous drug delivery techniques, current intrathecal delivery protocols lack a means of sufficient drug targeting at specific locations of interest within the central nervous system. We previously proposed the method of intrathecal magnetic drug targeting in order to overcome the limited targeting capabilities of standard intrathecal drug delivery protocols, while simultaneously reducing the systemic toxicity and the amount of drug required to produce a therapeutic effect. Building off of our previous work, this paper presents the concept of implant-assisted intrathecal magnetic drug targeting. Ferritic stainless steel implants were incorporated within the subarachnoid space of our in vitro human spine model, and the targeting magnet was placed at a physiological distance away from the model and implant to mimic the distance between the epidermis and spinal canal. Computer simulations were performed to optimize implant design for generating high gradient magnetic fields and to study how these fields affect the targeting efficiency of gold-coated magnetite nanoparticles. Experiments aiming to determine the effects of different magnetically-susceptible implants placed within an external magnetic field on the targeting efficiency of gold-coated magnetite nanoparticles were then performed on our in vitro human spine model. Our results indicate that implant-assisted intrathecal magnetic drug targeting is an excellent supplementary technique to further enhance the targeting capabilities of our previously established method of intrathecal magnetic drug targeting.


INTRODUCTION

Intrathecal (IT) drug delivery is a technique which involves the direct infusion of therapeutic molecules into the cerebrospinal fluid (CSF)-filled space within the spinal canal. IT delivery is advantageous because the drugs bypass the blood-brain barrier, which serves to limit the access of different types of molecules and systemically administered drugs to the central nervous system (CNS). Furthermore, drugs experience a longer half-life within the CSF since they encounter minimal protein binding and are not exposed to the same enzymatic activities which systemically administered drugs face within the blood.¹ Current implications for IT drug delivery include leptomeningeal metastases,²–⁴ spasticity,⁵ pain management,⁶ and spinal anesthesia.⁷,⁸ For example, clinical studies on pain management show that IT delivery provides ideal pain control with fewer side effects, while using only a small fraction of the dose required when the drug is administered orally or intravenously.⁹,¹⁰ The IT delivery of neurotrophic factors has also been deemed a promising treatment for neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Huntington’s disease, and Parkinson’s disease.¹¹–¹³

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Upon IT drug administration, the drugs are transported within the spinal canal mainly by the pulsatile motion of the CSF, but also by molecular diffusion.12,14

For many CNS diseases like leptomeningeal metastases, the effected tissue is located in specific regions of the spinal canal; therefore, a method to target these regions is warranted. We previously proposed the method of intrathecal magnetic drug targeting (IT-MDT) in order to concentrate high doses of drug-functionalized magnetic nanoparticles (MNPs) at desired locations within the spinal canal.15 The basic idea behind IT-MDT is to guide intrathecally injected, drug-functionalized MNPs using an external magnetic field to diseased regions within the spinal canal. IT-MDT offers advantages over standard IT drug delivery protocols by providing a way to achieve a localized therapeutic effect using much smaller drug doses and substantially reducing systemic toxicity. Our previous results indicated that external magnetic fields can capture the intrathecally delivered nanoparticles within a targeted region of the spinal canal despite the convective transport and enhanced mixing effects caused by the pulsatile motion of the CSF and the presence of the spinal nerve roots and trabeculae. Large collection efficiencies of MNPs were achieved using our method of IT-MDT with concentration levels nearly nine-times that of control experiments when no magnetic field was present.15

Our previous IT-MDT research used rare earth permanent magnets placed within the epidural space of our human spine model. However, for situations in which the in vivo implantation of a permanent magnet within the epidural space is not practical, a different method of IT-MDT is necessary. One way to magnetically target intrathecally injected MNPs would be by using a magnet non-invasively on the surface of a patient’s back. This method would require the use of a rather large magnet in order for the magnetic field to penetrate through the tissue and into the spinal canal at a distance of 4 cm away from the skin. Due to the magnetic field strength decreasing strongly with distance, the magnetic field within the spinal canal at a physiological distance of 4 cm away from the skin would be a more homogeneous and lower gradient field. We know from the equation for magnetic force on a magnetic particle that a spatially varying magnetic field \( \frac{\partial H}{\partial x} \neq 0 \) is required to create a magnetic force on the particle. As shown in the first relation of Eq. (1), the first relation of Eq. (1) results from performing the chain rule on the first relation, and states that the magnetic force on a particle is along the gradient of the magnetic field intensity squared \( \left( \nabla \| \bar{H} \|^2 \right) \).

Here \( \bar{H} \) is the magnetic field intensity \( [\text{A/m}] \), \( \chi \) is the magnetic susceptibility \( [\text{unitless}] \), \( \mu_0 = 4\pi \times 10^{-7} \, [\text{N/A}^2] \) is the permeability of vacuum, and \( a \) is the radius of the particle \([\text{m}]\). From Eq. (1) it is evident that a high gradient magnetic field is desirable for IT-MDT and that by simply placing a larger magnet on the surface of a patient’s back may not be the best method for achieving the highest possible magnetic nanoparticle collection efficiency within the targeted treatment region.

In order to create a high gradient magnetic field within the target region of the spinal canal, we used a magnetically susceptible implant. Numerous studies of implant-assisted magnetic drug targeting (IA-IT-MDT) have been performed and show great promise for use within tissue vasculature.16–22 The ferromagnetic implant is magnetized upon exposure to the long range, low gradient magnetic field, which results in the creation of a localized high gradient magnetic field around the implant. In this paper we build upon our previous IT-MDT research by using different implants, including an in vitro human spine model and experimental setup. To our knowledge, this is the first study of its kind for subarachnoid space of our in vitro human spine model.

This paper is organized as follows. We begin by briefly discussing the synthesis of our gold-coated magnetite nanoparticles, as well as the description of our in vitro human spine model and experimental setup. We close the materials and methods section with a description of our experimental procedure used to determine the MNP collection efficiency. We then present the results from our IA-IT-MDT experiments which were performed to determine the MNP collection efficiency within each spinal zone. The paper closes with a discussion of our experimental results and the conclusions section.

MATERIALS AND METHODS

In all of our experiments, we used different designs of ferromagnetic implants and an externally placed magnet to create a high gradient magnetic field to successfully target superparamagnetic gold-coated magnetite nanoparticles at a specific location within an in vitro model of the human spine. The main aim of these experiments was to study the effect of a magnetically susceptible implant within the subarachnoid space of our spine model on the collection efficiency of intrathecally injected MNPs, and to determine if this method of IA-IT-MDT would be useful for potential future clinical trials. In this section, we explain (i) the materials and methods used for nanoparticle synthesis, (ii) our in vitro human spine model and ferromagnetic implants, and