Intrathecal magnetic drug targeting using gold-coated magnetite nanoparticles in a human spine model

Aim: We aimed to magnetically guide and locally confine nanoparticles in desired locations within the spinal canal to achieve effective drug administration for improved treatment of chronic pain, cancers, anesthesia and spasticity.

Materials & methods: We developed a physiologically and anatomically consistent in vitro human spine model to test the feasibility of intrathecal magnetic drug targeting. Gold-coated magnetite nanoparticles were infused into the model and targeted to specific regions using external magnetic fields. Experiments and simulations aiming to determine the effect of key parameters, such as magnet strength, duration of magnetic field exposure, magnet location and ferrous implants, on the collection efficiency of superparamagnetic nanoparticles in targeted regions were performed.

Results: An 89.1% increase in nanoparticle collection efficiency within the target region was achieved using intrathecal magnetic drug targeting when compared with the control. Nanoparticle collection efficiency at the target region increased with time and reached a steady value within 15 min. Ferrous epidural implants generated sufficiently high-gradient magnetic fields, even when magnets were placed at a distance equal to the space between a patient’s epidermis and spinal canal.

Conclusion: Our experiments indicate that intrathecal magnetic drug targeting is a promising technique for concentrating and localizing drugs at targeted sites within the spinal canal for treating diseases affecting the CNS.

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Intrathecal (it.) drug delivery has been a standard treatment for different CNS disorders, such as leptomeningeal metastases and spasticity, where the required concentration reaches the target region, and has been widely used for pain management. However, the diffusion into the spinal cord and ventricle is incomplete and is not sufficient for widespread targeting of the CNS. To overcome this, we have developed a novel therapeutic delivery technique to selectively deliver drugs into the target region of interest without affecting other regions of the body. Using a human spine model, we have shown that intrathecally injected drugs can be localized to specific regions within the spinal canal, thereby allowing for targeted treatment of diseases affecting the brain and spinal cord.

For chronic pain, cancers, anesthesia and spasticity, there is a need for effective drug delivery methods. Typically, drugs are administered systemically, which can lead to excessive risk to the rest of the body. In the case of intrathecal drug delivery to the spinal cord, the drugs need to be targeted to specific regions to elicit an analgesic effect. In the case of morphine administration, the drug molecules need to transport across the pia mater and then diffuse through the spinal cord tissue in order to reach the dorsal horns. In the case of chemotherapy for cancer, the drug nanoparticles need to be delivered to the tumor to elicit a therapeutic effect. To achieve this, we have developed a novel therapeutic delivery technique to selectively deliver drugs into the target region of interest without affecting other regions of the body.

We have recently shown that pulsatile CSF motion causes intense mixing of intrathecally injected drugs at the tumoral region. Even though CSF flow within the spinal canal has a small Reynolds number, there is still fluid exchange because the fluid laminae are intertwined due to CSF pulsations. In this paper, we present a novel approach of using magnetically guided nanoparticles, which are capable of being functionalized with different types of drugs, for localizing and concentrating the particles at specific locations in an in vitro model of the human spine.

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that superparamagnetic gold-coated magnetite (Fe$_3$O$_4$) nanoparticles can be preferentially confined within an area of interest by guiding the particles with an external magnetic field. We have also provided computational results that aided in determining the optimal magnetic field for efficient drug targeting (i.e., MDT). If this novel technique can be successfully utilized with the required drug conjugated to the nanoparticles, the drugs can be locally delivered within the spinal canal at high concentrations, minimizing unwanted side effects of the drug away from the target region.

Our approach builds on the methods of MDT. MDT is a type of active drug-targeting method in which drug-functionalized magnetic nanoparticles (MNP) are injected into the body and then localized to the target region by use of an external magnetic field. The drug will then desorb from the MNP and begin its therapeutic mechanism of action. The most notable benefits of MDT reside in local drug action and minimization of systemic side effects. Until now, MDT methods have been mainly used to target drugs delivered systemically through blood vessels and have shown great promise [13–22]. The novelty of our approach lies in applying the methods of MDT within the CSF-filled spinal canal, not in blood vessels, in order to achieve a localized therapeutic effect using much smaller drug doses and substantially reducing systemic toxicity for novel treatments of CNS diseases.

This paper is organized as follows: nanoparticle synthesis is presented first, followed by a description of our in vitro human spine model and experimental setup. The ‘Results’ section presents the MNP characterization and the outcomes from experiments in order to determine MNP collection efficiency (CE) as a function of magnetic field strength, duration of magnetic field exposure, and distance to the target area. The experimental results are then presented. The nanoparticle MNP experimental setup is presented, with details regarding the experimental procedures. To systematically study the spatial distribution of the MNP in the presence of static magnetic fields within the space, and to investigate the possibility of localizing and concentrating the nanoparticles at different regions within the human spine model. In this section, we describe: the materials and methods used for nanoparticle synthesis; our in vitro human spine model; the simulations used to determine optimal magnetic fields; and our experimental procedure to determine MNP synthesis of gold-coated Fe$_3$O$_4$ nanoparticles. The nanoparticles utilized for all of our experiments had a Fe$_3$O$_4$ core with diameter varying between 8 and 12 nm, as shown in Figure 1A. Fe$_3$O$_4$ cores within this diameter range are beneficial because they display the property of superparamagnetism, which means they exhibit net magnetization only in the presence of an external magnetic field. Superparamagnetism allows the nanoparticles to transport freely throughout the spine model until they are in the presence of the externally applied magnetic field, which then acts to trap the nanoparticles at that defined location. Once the applied magnetic field is removed, these superparamagnetic nanoparticles lose their previously induced magnetization and disperse in the fluid. The nanoparticle cores were synthesized by a coprecipitation technique, described in Mandal et al. and various other articles, using ferrous and ferric salts to form Fe$_3$O$_4$ [22]. These superparamagnetic Fe$_3$O$_4$ cores were then coated with a gold layer of varying thickness between 8 and 15 nm by a surface adsorption technique. The overall hydrodynamic diameter of the particles was found to be between 20 and 25 nm, as shown in Figure 1B. The gold coating on the Fe$_3$O$_4$ core is used to form a maghemite by forming an inverted biocompatible protective coating; and it also formed an excellent platform for conjugating drugs to the nanoparticle surface, since gold has a natural affinity for thiol bonds [23]. These particles were suspended in a Triton X-100 (Fisher Scientific, PA, USA) surfactant solution in order to introduce micelles and help prevent agglomeration. The nanoparticles were characterized by using transmission electron microscopy (TEM), energy-dispersive x-ray spectroscopy (EDS) and superconducting quantum interference device (SQUID) magnetometry. More details regarding the nanoparticles can be found in the in vitro model of the human spine in the Experimental Section.