Original Article

On-demand antibiotic-eluting microchip for implanted spinal screws

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ABSTRACT

Objective: Surgical instrumentation of the spine is susceptible to infection. Intravenous antibiotics is a current mainstay of treating infection; however penetrating the bacterial biofilm and directly targeting the source of the infection is challenging.

Methods: Using multiple reservoirs of discrete drug doses, microchips represent a new technology capable of on-demand drug release over long periods of time.

Results: A novel solution of integrating vancomycin-eluting microchips into pedicle screws in order directly target and treat spinal infections is proposed.

Conclusion: This drug-releasing implant has the potential to provide the particular benefit to high-infection-risk patients in order to avoid reoperation.

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1. Introduction

Lumbar spine fusion is one of the most common completed in the United States.³³ The surgery is used to treat degenerative disc disease; spinal stenosis; instability; fractures; and deformity (such as scoliosis, lordosis, or kyphosis). The goal of lumbar spine fusion surgery is to alleviate pain, numbness, paresthesia, and/or weakness due to inappropriate vertebral segment movement. Fusion surgery aims to permanently connect two or more vertebrae in your spine to eliminate this movement. Each of the various surgical approaches includes adding a bone graft to elicit physiologic bony ingrowth and reduce motion by fusing adjacent vertebral segments together. Rods, screws, and metal plates are used to hold the vertebrae together as one solid unit (Figs. 1 and 2).

Spinal instrumentation is correlated with a 2–20% infection rate.³⁸ The most common cause of infection is due to *Staphylococcus aureus*.³⁹ Many infections present days to months post-operatively.^{40,41} The intravenous of the antibiotic vancomycin is a current mainstay of treatment.⁴² However such a systemic approach has trouble penetrating the bacterial biofilm on the implant and directly targeting the source of the infection.⁴³ Failure to treat the infection with IV antibiotics leads to additional surgical intervention—debridement, removal of hardware—which is associated with worse outcomes long-term, increased morbidity,

increased healthcare costs, increased hospital stays, and decreased patient satisfaction.³⁸ If detected and treated at earliest onset, patients may be spared reoperation to remove their infected hardware.⁴⁴

2. Deficiencies in current capabilities

Local administration of vancomycin powder at the end of surgical cases has been shown protective against postoperative spine infections.⁴⁵ However the administration of powder is only effective before biofilm formation has occurred. Many cases of spine infection occur days to months after surgery.⁴⁰ These infections can be harder to treat because the pathogenic bacteria protected underneath the biofilm, hiding in the crevices of the implant. Targeting the bacteria from within the implant could provide a novel strategy to overcoming the challenge of the biofilm.

In order to determine the optimal drug delivery system, we must consider the different options available with respect to their ability of achieving stable release rates, drug concentrations, and at a specific site of action.¹ Traditional routes of administration, such as oral capsules or intravenous infusion, encounter problems in maintaining drug concentrations within the therapeutic window, wherein the drug is above a threshold for efficacy but not toxic to the patient. Thus, the design of delivery systems initially focused on attaining a sustained release of drug over a time interval. Much of this work focused on polymers and their material properties that allow for steady-state diffusion of drug out of the polymer or degradation of the polymer itself over time.^{2,3} In addition to

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Fig. 1. Spine fusion.^{34–36}

Fig. 2. Pedicle screw system.³⁷

sustained release, pulsatile delivery at variable time intervals is necessary for compounds, such as insulin or hormones of the anterior pituitary, for physiological functions that follow either circadian rhythm or a time structure.^{4,5}

With advancement in technology, implantable controlled-release systems for drug delivery have emerged as a promising new class of drug formulation to translate pharmacological effect into clinical practice. Implantable drug delivery systems (IDDS) are currently grouped into three classifications: biodegradable/non-biodegradable implants, implantable pump systems, and the newest atypical class of implants.⁶ Biodegradable and nonbiodegradable implants are available as reservoir and matrix systems, which exhibit release kinetics based on system and surrounding parameters.⁷ However, these formulations are not suitable for drugs that are unstable in-vivo and need to be hermetically sealed, especially since new protein-based drugs become unstable upon water penetration. Some controlled-release microfluidic pumps, valves, and channels have been developed that utilize moving parts such as a pneumatic piston or electroosmotic pumping.^{8,9} However, limitations of drug instability, complexity of fabrication, and breakdown of moving parts hinder clinical translation of microfluidics.¹⁰

As a result, the field of microfabrication demands the need for a new class of controlled-release delivery system of intelligent, programmable microelectronics. Microchips are capable of complex release patterns, simultaneously constant and pulsatile, increased accuracy, and isolation of the drug from the outside environment.¹¹ With the goal of treating spine infections as early as possible to prevent removal of hardware reoperations, this paper describes a novel approach to overcome biofilm impedance of antibiotics by integrating an on-demand vancomycin-eluting microchip for implanted spinal screws.

Clinically, the vancomycin-eluting pedicle screw will be of greatest value to the patients for whom such an implant could be

indicated—those at greatest risk of infection after lumbar spine fusion. Those patient populations include: increased age, male sex, those on steroid therapy, diabetics, smokers, high American Society of Anesthesiology score, obese, malnourished, presence of comorbidities, and previous surgery.³⁸

3. Engineering objective

A want is a closed-loop system that both monitors (e.g., by detecting changes in local pH changes) and then dispenses the correct dosage of the correct antibiotic.

The needs include: externally-controlled, on-demand release of drug targeted specifically to local bacteria. Allows provider to reliably and precisely administer doses of vancomycin. In order to do so, the clinician must get confirmation of delivery.

On the patient side, implanting a device that is made for antibacterial purposes raises awareness about the possibility of infection. Patients more aware of potential infection risk and likely to present earlier to their doctor to have the device begin targeted treatment.

A way to target the nidus of bacterial infection in patients undergoing spine lumbar spine fusion to reduce postoperative spinal infection rates. Broadly speaking, the microchip will be slotted into a pedicle screw (red arrow in Fig. 3).

Microchips have recently been described in the literature, as different research groups are beginning to investigate uses. The novelty of my implanted device is its application—nobody has suggested integration into existing implants; all other applications suggest a standalone implantable microchip.

The core engineering challenge is on controlled release and therefore the design of the microchip itself. Microreservoir release is achieved by applying a voltage between the thin, metallic (e.g., copper or gold) anode membrane and a cathode to electrochemically dissolve the reservoir cover. This electrical potential can be activated wirelessly, external to the body, or secondary to metabolic changes in the host. The control circuitry can be integrated into the microchips. This circuitry includes a timer, demultiplexer, microprocessor, and input source (e.g., biosensor).¹¹ Such controlled drug delivery can release drugs over months, on a pre-set or as needed schedule [24,25] (Figs. 4 and 5).

As previously tested, the microchip will be powered via a microbattery with a 1 V potential,²⁷ capable of 5 mA current.⁴⁷ The

Fig. 3. Pedicle screw with microchip slot and opening (arrow).⁴⁶

Fig. 4. Microchip device schematic.²³

microchip will have wireless capability to transmit information to a specific provider computer in order to confirm delivery of drug dosage. This will be achieved via the Medical Implant Communication Services wireless band, which has been set aside for the FDA by the FCC.

4. Materials

Building on the previous studies, initial in-vitro release studies determined whether microchip technology could achieve controlled-release of a chosen therapeutic agent, with regular pulses of drug expulsion into the experimental system (Fig. 6).⁵ Various molecular masses of PLGA copolymer (PLGA 4.4, 11, 28, or 64) were chosen as the reservoir membrane material of choice, with a 50:50 ratio of lactic acid and glycolic acid.⁵ As seen with ³H-heparin release below, a consistent step-wise release of the drug was observed—correlating to each of the microchip reservoir membranes degrading and opening.⁵ Similar results were achieved with ¹⁴C-dextran, ¹²⁵I HGH, and a combination of dextran and heparin.

Fig. 5. A microchip.²⁴

Fig. 6. Each symbol represents the testing of a single device. Each device was loaded with four drug reservoirs. For all drugs utilized, "the release times of the chemicals from the reservoirs increased as the molecular mass of the reservoir membrane polymers was increased."⁵

Fig. 7. Microchip fabrication steps.²³

Figure 6-2 Make a longitudinal incision over the spinous processes, extending from the spinous process above to the spinous process below the level of pathology. A line drawn across the highest point of the iliac crest is in the L4-5 interspace.

Figure 6-3 Deepen the incision through the fat and fascia in line with the skin incision until the spinous process itself is reached. Detach the paraspinal muscles subperiosteally.

Figure 6-4 (A) Dissect the paraspinal muscles from the spinous process and lamina to the facet joint. Remove the paraspinal muscles subperiosteally as one unit from the bone. (B) Continue dissecting laterally, stripping the joint capsule from the descending and ascending facets. Note the branches of the lumbar vessels that bleed during stripping of the muscles.

Figure 6-5 (A) Remove the ligamentum flavum by cutting its attachment to the superior or leading edge of the inferior lamina. (B) Immediately beneath the ligamentum flavum and epidural fat is the blue-white dura. Identify the nerve root. Note the overlying epidural veins.

spinal canal, retracting the dura and its nerve root medially (Figs. 6-5 through 6-8).

Fig. 8. Posterior approach to lumbar spine.

These findings provided evidence that controllable and pulsatile drug release from microchips was achievable in-vitro, catalyzing in-vivo experimental models. A 2007 study investigated the canine pharmacokinetic profiles of leuprolide—a polypeptide therapeutic indicated for prostate cancer and endometriosis treatment—when delivered in vivo via microchip reservoirs compared to subcutaneous injection.¹³ The authors concluded that the pharmacokinetics of the two delivery methods were indeed comparable, yet the microchip method offered greater control over serum drug concentration.¹³

Understanding the components of microchips is best done in the context of how microchips are fabricated (Fig. 7). Microchips are fabricated using the same well-developed technology as used for microelectronic integrated circuits and microelectromechanical systems (MEMS),¹⁷ processes used to manufacture micro devices such as pressure sensors, accelerometers, flow sensors, ink-jet printer heads, and micro mirrors for projection.¹⁸ To allow for accurate control of surface microarchitecture, microchips are created using repetitive thin-film deposition, photolithography, and etching (removing).¹⁹

Leveraging MEMS fabrication technology, the process begins with depositing an insulating or dielectric material on a both sides of a substrate surface.²⁰ The substrate provides structural support to the device. Substrates have been made from ceramics, semiconductors, degradable polyethylene glycol, and most commonly with silicon.^{21,22} Then using photolithography the insulating material is photomasked to a light-sensitive chemical resist onto the substrate, to pattern the desired geometric shape, serving as an etching mask. Various etching processes are used to generate the desired reservoir topography on one side of the insulator and substrate. On the yet-interrupted surface, an anode is created by laying electrode over the reservoir opening. The insulating material functions as the cathode. At the base of the to-be reservoir, the insulating material is removed and the reservoirs are filled with the drug solution of choice. Reservoir filling can be accomplished using injection/inkjet printing or spin coating methods. Wafer bonding—a method of hermetically encapsulating MEMS—is then used to cover and seal the reservoir.²³

Implanted microchips enable on-demand drug release.^{5,12,13} Solid silicon microchips consist of hundreds of reservoirs filled with up to 1 ml drugs in an aseptic solid, liquid, or gel filing.^{14,15} The multireservoir microchips are hermetically sealed to avoid degradation and subsequently covered by an anode membrane which can be ablated electrothermally to release the reservoir contents.¹⁶ As previously described, a compression welding process was developed to provide a long-term hermetic seal.²⁵

5. Foreseeable developmental challenges

Hermetically sealing each reservoir near room temperature will be critical to prevent degradation of the vancomycin antibiotic. Reliable protection and exposure of drug contents is required—in other words, accidental release or failing-to-elute microchips will not be acceptable.

There are two manufacturing considerations. First, the pedicle screw needs a slot for the microchip. Second, the microchip needs to be prepared for installation into the slot. Creating the implant and then carving out a slot will be easier than building an implant around the microchip. Moreover, by inserting the microchip into the slot, there is no interference with the drug release (vs. if the implant completely surrounds the chip).

Being an antibiotic, vancomycin has different size, properties, and characteristics than previously studied drugs (which are smaller). Therefore the device must be calibrated by testing in vitro first, testing different concentrations of the drug, to find out the

optimal amount to be released—ensuring reliable quality assurance.

6. Intellectual property evaluation

A survey of recent microchip developments, notable patents, and clinically-relevant applications can inform the position of microchips in medicine today, as well as motivate areas of further study. In 1998, the U.S. Patent “Microchip drug delivery devices” was awarded to Santini, Cima, and Langer, which first outlined the parameters of a multi-reservoir microchip system with an active release system.²⁶ In 1999, Santini, Cima, and Langer debuted the first electrochemically activated drug delivery microchip.²⁷ In their device, release from individually dosed reservoirs is activated by applying an electric potential between the cathode and the anode—a thin gold membrane covering the specific reservoir to be deployed.²⁷ An extensive number of further advancements, notably including (but not limited to) refined fabrication methods,²⁸ microchip flexibility for ophthalmic use and improved versatility²² methods of operation²⁹ and details of wireless data and power transfer³⁰ have since been discovered and patented by the group.

The prior art search for an on-demand vancomycin-eluting microchip for implanted spinal screws demonstrates microchips have recently been described in the literature, as different research groups are beginning to investigate uses. The novelty, non-obviousness, and therefore the defensible claims is the application of a microchip as a component of a larger implant—nobody has suggested integration into existing implants; all other applications suggest a standalone implantable microchip. A pending patent has been filed.

7. Surgical approach

Because the microchip will be housed in the screw head, it will be in contact with vertebral bone and overlaying skeletal muscle. The pedicle screw will be implanted using the following, well-established⁴⁸ posterior approach of the lumbar spine (Fig. 8).

8. Potential adverse tissue interactions

Screws are typically made of titanium, which have shown to be corroded by human osteoclasts. The released metal ions are taken up by the osteoclasts and immune cells leading to different metal sensitivity reactions and enhanced activation of osteoclasts.⁴⁹ PLGA degradation in clinical studies of microchips have been biocompatible without any adverse effects.²⁵ The placement of the microchip in the head of the screw allows for removal of the microchip alone without having to remove the entire screw construct. Access to the microchip inside the screw head slot can be surgically accessed using the same posterior approach to the lumbar spine as illustrated in Fig. 8.

Conflict of interest

The authors have relevant pending intellectual property.

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