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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.

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 boney ingrowth and reduce motion by fusing adjacent vertebral segments together. Rods, screws, and metal plates are used to hole 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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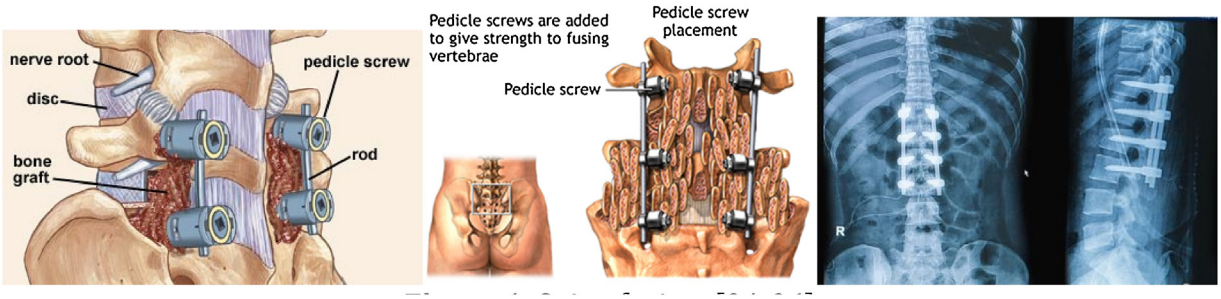

Fig. 1. Spine fusion.[34–36]

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]