Post-Surgical Neuropathic Pain Management Using Bupivacaine Loaded Sol-gels

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Statement of Purpose:

Post-surgical pain caused by neuropathic injury is an unintended consequence of orthopedic surgery [1]. Traditional pain management options rely on the administration of opiates such as morphine which have harmful side-effects like nausea, urinary retention, depressed respiration as well as the possibility of dependency. Local anesthetics used as analgesia administered at the area of injury does not have long-lasting action. Therefore, methods for developing long-lasting analgesia for chronic pain relief must be investigated. We have developed a sol-gel, drug delivery platform for the delivery of small and large molecular weight therapeutics such as antibiotics, growth factors and anesthetics. The fabrication process of sol-gels can be modified to tailor the release of the therapeutic over time[2].

In this study, sol-gels were fabricated into porous microparticles for the controlled release of the local anesthetic, Bupivacaine (BP). The release of BP from the formulation of the sol-gel microparticles used in this study showed controlled release kinetics for up to one week. We hypothesized that the BP incorporated sol-gel microparticles implanted at the site of neuropathic injury would alleviate chronic pain over time. To test this hypothesis, we evaluated the post-surgical pain behavior in response to implanted BP loaded sol-gels using a common surgical model for neuropathic injury.

Methods:

Sol-gel fabrication: Sol-gel granules were synthesized in a method described previously[3]. Briefly sol-gels were synthesized by acid catalyzed hydrolysis of the silica precursor, tetraethylorthosilicate (TEOS). The BP was incorporated at 30% (w/w) to correspond to twice the minimum effective dose (MED) in rats.

Sciatic Nerve Injury Ligation: Male adult Sprague-Dawley rats (c.a. 250 g) were anesthetized with 2% Isoflurane. The rats were placed in a prone position where the hair was clipped and sterilized with Betadine. An incision on the right plane was made through the skin, and into the muscle to expose the sciatic nerve. The sciatic nerve was identified and palpitated with a jeweler's forceps to produce a twitching of the hindpaw. The nerve was partially ligated with 8-0 silk monofilament sutures and the muscle and skin incisions were sutured with Vicryl 4-0 sutures. The sol-gels were implanted adjacent to the partially ligated nerve. Controls consisted of sham surgery and BP injection. In sham surgery, PBS was injected adjacent to the partially ligated nerve. For the injection control, 0.5cc of 0.5% BP was injected adjacent to the partially ligated nerve. Following surgery, the pain response was evaluated using the von Frey filament test[4]. Briefly, a series of nylon filaments with force values (2-60 grams) was sequentially applied to the area adjacent to the incision. The applied force that generated withdrawal of the hindpaw in response to the filament was recorded as the withdrawal response. Each rat was tested at the maximum of 3 times per time-point and the median of the withdrawal response measurements were recorded and averaged for each treatment.

Results: The von Frey filament test results shown in Figure 1 that at 1 hour, the rats that received the Bupivacaine injection had the highest withdrawal response (greatest pain attenuation). However, by 24 hours, withdrawal response of this group decreased. At 1 hour, the withdrawal response was lowest in rats that received the blank sol-gels. By 168 hours (one week), withdrawal response was highest (greatest pain attenuation) in rats that were implanted with the BP sol-gels compared to other groups including sham operated, BP injected and blank sol-gel control groups.

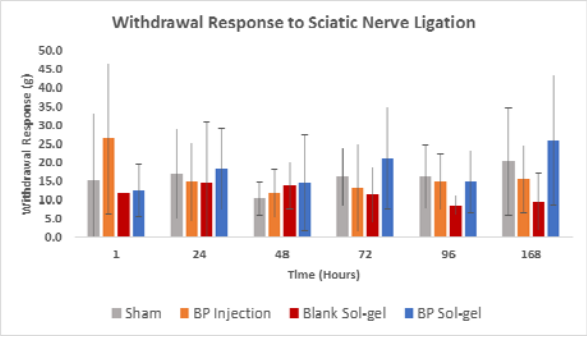

Figure 1: Withdrawal response to sciatic nerve ligation over time.

Discussion and conclusions: Previous findings characterized the release of BP from sol-gels over time [5]. The goal of this study was to determine whether novel formulations in sol-gel synthesis would yield extended BP release that would relieve chronic pain. Conventional treatment of BP injection is short-lived as indicated by these results, and must be given continually to relieve pain. However, the formulation of the BP in the sol-gel microparticles prepared in this study was sufficient to relieve pain incurred by neuropathic injury as long as 7 days post injury. These finding support long term delivery from BP- sol gel formulations as a possible treatment for chronic pain management.

References:

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