Post-Surgical Pain Management using Long Lasting Analgesic Release from Sol Gel Powder

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Statement of Purpose: Pain following common orthopedic surgical procedures such as joint replacement surgery can affect overall recovery. The benefits of effective post-surgical pain management are earlier mobilization and shortened hospital stay[1]. The limitations of the routinely administered opiates following surgery are nausea, urinary retention, depressed respiration as well as the possibility of dependency. In contrast, local anesthetics do not have the severity of undesirable side-effects or risk of dependency. Bupivacaine (BP) is a long-lasting local anesthetic which acts as a sensory nerve blockade and has been incorporated in release vehicles delivered locally within the surgical site[2]. These drug delivery vehicles, generally prepared with poly α-esters have shown promise in post-surgical pain management, yet acidic by-products following hydrolytic degradation of these polymers *in vivo* may have deleterious effects on surrounding tissue. Herein, we report a biocompatible implantable delivery system composed of silica based mesoporous Sol-Gel (SG) microparticles incorporated with BP for the purpose of relieving post-surgical pain with the benefit of long-lasting release without the risk of potentially harmful degradation by-products. In this study, the release of BP from SG microparticle granules on the effectiveness of pain relief in rodents following the widely used Brennan incisional model[3] is evaluated.

Methods: SG fabrication: SG granules were synthesized in a method described previously[4]. Briefly SG's were synthesized by acid catalyzed hydrolysis of the silica precursor, tetraethylorthosilicate (TEOS). With the goal of altering BP release kinetics, several formulations were synthesized by partially substituting TEOS with another silica precursor, methyltriethoxysilane (MTES) at various molar ratios (10% and 25%). The BP was incorporated at either 15% or 30% (w/w).

In vitro release: BP incorporated SG granules were incubated in Phosphate Buffered Saline (PBS) at 37°C which was collected at various time-points. The concentration of BP in the collected PBS (n=3 per time-point) was spectrophotometrically determined at 265 nm.

In vivo study: Several formulations of the sol-gels were selected based on the minimum effective dose (MED) of BP in adult rats (250±25 g) which is 10 mg/kg. Using *in vitro* release data, the formulations prepared with 15% BP would hypothetically deliver the MED within 24 hours, while the formulations with 30% BP would deliver nearly twice the MED. The control groups included: blank SGs without BP and sham surgery. Under anesthesia, the plantaris muscle in the left hindpaw of each rat (n=6 per treatment group) was longitudinally incised. Each SG sample was suspended in PBS and implanted into the incision site underneath the plantaris muscle. In the sham surgeries, PBS was pipetted into the incision site. Post-surgical pain was evaluated using the von Frey filament test. Briefly, a series of nylon filaments with force values (2-26 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 3 times per time-point and the median of the withdrawal response measurements were recorded and averaged for each treatment.

Results: The release of BP from SGs could be tailored with the addition of the silica precursor, MTES at various molar ratios (Figure 1). In formulations with 15% BP, the addition of MTES slightly reduced the release of BP; however in formulations with 30% BP, the addition of MTES increased the release of BP as a function of time.

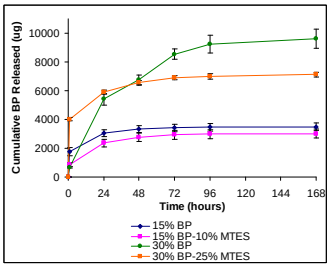

Figure 1: Cumulative release of BP from SG granules.

The post-surgical behavior response indicated that at early time-points (1-24 hours), rats implanted with 30% BP - 25% MTES displayed higher withdrawal forces (i.e. less pain sensation) compared to other formulations and control groups (Figure 2). The *in vitro* data show a burst release response, and this may account for a leveling off of the response throughout the subsequent time points. The rats implanted with 15% BP and 15% BP-10% MTES, had higher withdrawal response values (i.e. less pain sensation) from 48 hours-1 week.

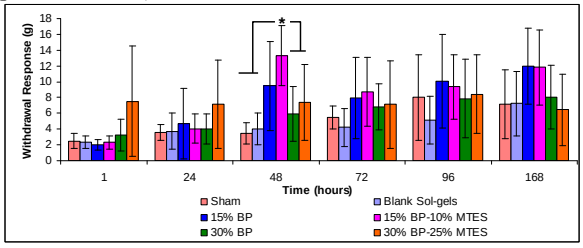

Figure 2: Withdrawal response measured using the von Frey filament test.

Conclusions: The results of this study indicate that the BP dosage and release kinetics from SG granules alleviated incisional pain for up to one week.

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References: [1]Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline 1992;
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