Polymer - Xerogel Composites for Controlled Release Wound Dressings: a Rat Incisional Pain Model Study

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Statement of Purpose: Previous studies demonstrated that the controlled release kinetics from composite wound dressings comprising drug-loaded xerogels in a polymer film can be tailored by adjusting various material parameters of both the xerogels and the polymers. Specifically, zero-order release was obtained [1]. Building on these data, we pursue the treatment of chronic pain in severe trauma and we focus on the constant, controlled local delivery of anesthetics. Herein we describe the *in vitro* release kinetic data and we report on *in vivo* pain control using the rat incisional pain model.

Methods: Silica xerogels containing bupivacaine (BP) were prepared at room temperature via a one step acid catalyzed sol-gel process [2]. The BP content of silica xerogels was 16.7 and 28.6 wt% for R15-200 and R15-400 respectively. For the xerogels, R is the ratio of water to tetraethoxysilane (TEOS) at which the sols are prepared. The nomenclature is, for example, R15-200, meaning the xerogel is prepared at R =15 and it contains 200 mg bupivacaine/g silica. The dried xerogel samples were then crushed into granules and sieved by nylon meshes to obtain granules in the range 20-105 μm. Tyrosine-PEG-derived poly(ether carbonate) copolymers were synthesized using a previously reported procedure [3] and were used as the matrix for the composites. Composites containing 75% (w/w) BP-loaded xerogels were prepared by solution blending followed by vacuum drying and compression molding. The composite films used for implantation were cut into 7x2x0.7mm strips.

In vitro study: for the *in vitro* release kinetics, composite specimens of approximately 30 mg were immersed in 6 ml phosphate buffered saline (PBS) at 37°C and 100 rpm in a water bath shaker. The buffer was exchanged periodically and the drug release was followed for seven days. The bupivacaine concentrations were assayed by HPLC.

In vivo study: The rat model of (hindpaw) incisional pain described by Brennan et al. [4] was used for studying tactile hypersensitivity. Male Sprague Dawley rats (250-300 g, Ace Laboratories) were acclimated in individual Plexiglas observation boxes. The floor of each box consisted of smooth wire mesh so that a series of von Frey monofilaments could be presented perpendicular to the plantar surface of both hindpaws immediately before isoflurane inhalation and surgery. Two experimental groups (n=5) received composites containing different bupivacaine doses (R15-200 75% and R15-400 75%). Two control groups (n=5) underwent either sham surgery or surgery with implantation of pure polymer films without bupivacaine. Tactile sensitivity was evaluated at 0.5, 1, 1.5, 2, 6, 24, 48, 72 and 120hr and paw withdrawal pain thresholds were calculated by the method of Chaplan et al [5]. Various blood samples for the determination of the bupivacaine concentration were obtained from the tail vein at 2, 6, 24, 48 and 72 hr after surgery. The blood samples were stored at -80°C before HPLC measurement.

Results: The *in vitro* results show that bupivacaine was continuously released from the composite in a controlled manner for 7 days. With increasing drug payload, higher concentrations of bupivacaine were released within the first 24 hours.

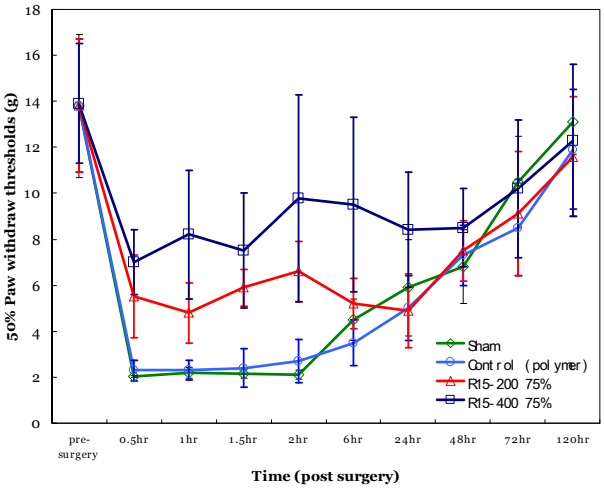

Figure 1 Attenuation of mechanical hypersensitivity in rats receiving bupivacaine loaded composites relative to sham and control groups

Both sham and control groups showed a similar pain response after surgery. Both groups showed a sharp drop in withdrawal pain threshold after incision. The incision produced a significant decrease in pain threshold from the pre-surgery value for 72 hours. Composite films containing bupivacaine provided statistically significant pain reduction up to 24 hours after incision and insertion of R15-200 75% and R15-400 75% films (Figure 1). The data also demonstrates that the magnitude of the antiallodynic effect produced by different composites in the incisional wound is dose dependent.

Conclusions: The in vitro and in vivo studies have shown that polymer-xerogel composite wound dressing is a promising controlled release carrier for the acute and chronic pain management.

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