Fibrin Glue Does Not Increase Drug Retention in the Spine

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Statement of Purpose: One major concern for patients undergoing spinal surgery is the pain associated with post-surgical recovery. Pain can increase the length of time a patient spends in the hospital and can decrease their mobility. Most commonly pain is managed with oral or IV analgesics. There are considerable negative side effects from use of systemic analgesics such as addiction, nausea, vomiting, respiratory depression, and death. Pain from surgery is caused by damaged tissue at the surgical site. Theodore and coworkers performed a study demonstrating that delivering analgesics directly to the damaged tissue can more effectively manage pain in patients (Hurlbert R. J Neurosurg. 1999;90(2):191-197.). That paper and other similar work show reduced pain 24 hours after surgery, but it is unknown whether the pain reduction is a function of drug presence or the psychological and physical effects of having reduced pain immediately postoperatively. In this experiment we used MRI to compare the clearance of a morphine surrogate from the spine when the surrogate was delivered as a loose powder or embedded in fibrin glue.

Methods: The MRI contrast agent Diethylenetriaminepentaacetic acid gadolinium(III) dihydrogen salt hydrate (Gd-DTPA)(Aldrich, St. Louis, MO) is used as a surrogate for morphine (both small, hydrophilic molecules). Spine surgery is performed in rats that receive either no drug (n=3), 200 µL of fibrin glue only (n=1) (Evicel® Fibrin Sealant, Ethicon, Kiryat Ono, Israel), 5.4 mg of loose Gd-DTPA powder (n=3), or 5.4 mg of Gd-DTPA embedded in 200 µL of fibrin glue (n=3).

For this experiment spine surgeries (laminectomies) are performed in 10 athymic nude rats. A 1 cm incision is made over the vertebrae of interest. The muscle is dissected away from the spinous process. Rongeurs are used to remove the spinous process of L4-L6 and expose the dura. The drug or delivery vehicle is placed over the exposed dura. The muscle, fascia, and skin are closed in separate layers using suture.

Post-surgically, the animals are scanned at 1hour, 4 hours, 1 day, 2 days, 3 days, and 7 days on a 7T MRI (Bruker Biospin, Billerica, MA, USA). To obtain T1 maps, a series of T1-weighted images are acquired with Rapid Acquisition with Relaxation Enhancement (RARE) method, at different relaxation times (TR=4000, 2500, 1500, and 743.7ms). The images are converted to concentration maps via a method outlined by Giers et al. (Giers, MB. Compu Math Methods Med. 2013;149608.). Briefly, the muscle tissue in the region of interest is segmented, the muscle tissue is thresholded to determine the location of the contrast agent, and the concentration of the contrast agent is calculated. 3D volume maps and 2D concentration maps are constructed with the use of Mimics and Matlab, respectively. The animal is euthanized at the end of 7 days.

Results: The total number of millimoles present in the muscle tissue surrounding the spine is not significantly different between the loose Gd-DTPA groups and the fibrin embedded group. In both groups contrast agent is highest at the 1 hour time point and is gone by 24 hours (figure 1). Contrast agent is visible spreading from the delivery location along the incision track (figure 2). Gd-DTPA does not disperse far from the delivery site in the muscle tissue and is not found anterior to the spine. Contrast agent enters the tissue plane between the fascia and skin though it is excluded in the concentration maps difficulty quantifying concentration in that location. The image processing technique used here does not show significant contrast agent presence in the nonsurgical controls and only minimum contrast in the surgical controls. The false positive of contrast agent in the surgical controls is likely from scar tissue.

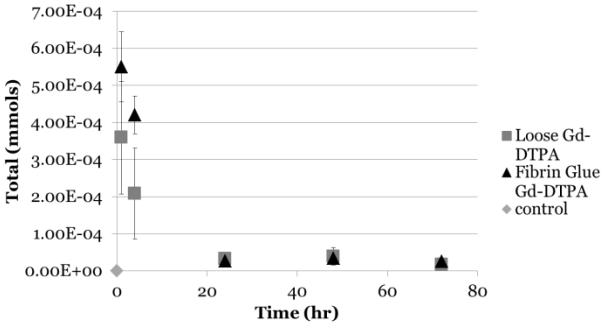

Figure 1. Total mmols of Gd-DTPA in the spine loaded as a powder or embedded in fibrin glue.

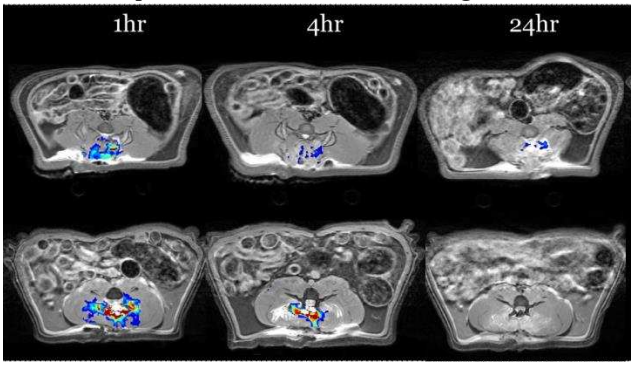

Figure 2. Coronal concentration maps of Gd-DTPA in the spine loaded as a powder (top) or embedded in fibrin glue (bottom). Most contrast is gone by 24 hours.

Conclusions: Fibrin glue does not retain morphine surrogate longer than muscle tissue. The drug remains local to the wound site or distributes under the skin. The clinical efficacy at time points greater than 24 hours after morphine injection or fibrin implantation is likely caused by reasons other than drug presence.