An injectable nanodelivery system for prolonged, controlled release of the local anesthetic lidocaine

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ABSTRACT SUMMARY
We developed a hybrid material consisting of Silica nanoparticles (Si) and poly(lactic-co-glycolic acid) (PLGA) microparticles, as a delivery system to provide substantially prolonged, controlled release of analgesic. The medication was delivered via a Pluronic gel. Our novel nano-delivery platform allows high efficiency of loading and it has demonstrated the capability to provide sustained release of the local anesthetic lidocaine for significantly longer than any currently available therapy. Our biodegradable nano-delivery system can provide a promising new alternative for the delivery of locally acting drugs, and demonstrates the potential to produce prolonged nerve blockade for the management of both acute and chronic pain in vivo.

INTRODUCTION
Existing non-opioid analgesic therapies have limited ability to treat chronic radicular or acute incisional (post-operative) pain, or abrogate the need for opioid supplementation. Subsequent reliance on opioids for analgesia carries with it a wide side effect profile, including: nausea/vomiting, GI dysmotility, respiratory depression, addiction and socioeconomic loss. Provision of adequate non-opioid anesthesia in these clinical situations hinges upon prolonged nerve blockade resulting from the long-term bioavailability of anesthetics. Aside from infusions via an indwelling catheter, most currently available approaches for such prolonged local action provide no longer than 1-2 days of blockade [1]. To fully harness the potential of these locally acting drugs, it is essential to develop novel methods of prolonging their efficacy; and recent advances in nanotechnology make it increasingly possible to address the glaring shortcomings of current pain management therapies. Our lab has successfully developed a nanostructured platform capable of sustained release of localized drug molecules [2,3]. The present study evaluates the ability of our nanoscale delivery system to provide substantially prolonged, controlled release of lidocaine compared to what is currently used in standard clinical practice.

EXPERIMENTAL METHODS
PLGA microspheres, a widely studied copolymer in tissue engineering and used previously as a drug delivery carrier, has been modified in this study with Si in order to prolong the release of anesthetic. Si loaded with lidocaine hydrochloride was embedded in PLGA microspheres in two separate formulations (50/50 and 85/15) using solid-oil-water emulsion technique. PLGA microspheres containing 5 wt% of Si (PLGA-Si 5%) were mixed in an aqueous solution of 20% Pluronic F-127 at 4 ºC. To study drug release, the polymer solution containing the loaded PLGA-Si were injected into 48-well plates and incubated at 37 ºC for one minute for complete gelation of Pluronic. The pharmacokinetics of the composite was assessed using phosphate buffet saline (PBS) as a release media under mild agitation at 37 ºC. Samples of the release were collected at 6, 12 and 24 h, 2, 4, and 7 day time points and the amount of lidocaine in PBS samples was quantified using HPLC technique. As controls, lidocaine-loaded pristine PLGA and Si were used separately as well as embedded in the gel in this study.

Following characterization of our novel platform and successful demonstration of our ability to control its release of lidocaine over one week’s time, its efficacy was assessed in vivo using an accepted incisional pain model on the hindpaw of Lewis rats.4 Rats were divided into four cohorts: 1) sham (anesthesia only, no operation), 2) operation + no postoperative analgesia, 3) operation + full analgesia by protocol (preoperative and daily postoperative analgesics, and immediate-release lidocaine splash block at operation) and 4) experimental PLGA-Si hydrogel. For each animal undergoing an operation, preoperative NSAID analgesics were given, general inhalational anesthesia induced, and a 1-2 cm incision was made through the skin/fascia of the left hindpaw, exposing the plantaris muscle. The muscle was incised longitudinally, and the skin apposed with nonabsorbable suture. Daily pain levels in the subjects were subsequently assessed objectively via hindpaw withdrawal response to mechanical stimulation using calibrated (to specified applied
force) Semmes-Weinstein Von Frey microfilaments. Three sites on the paw of interest were stimulated sequentially with the filaments, progressing from smallest correlating force to highest (absolute threshold = 588.9mN force) until withdrawal is elicited, and the lowest threshold causing withdrawal at the three sites was averaged daily postoperatively. Additional observational scoring was done by assessing the degree (or lack of) weight-bearing via the degree of hindpaw blanching (full blanching = weight-bearing not limited by pain, touching without blanching or holding paw from ground = pain limited behavior). Final surrogates for pain assessed daily include: spontaneous activity level, hair piloerection, presence/absence of porphyrin staining, or postoperative weight loss (greater than 5% loss is significant).

RESULTS AND DISCUSSION

The Si nanoparticles were characterized by SEM as shown in Figure 1a. Fluorescently labeled silica nanoparticles integrated in the PLGA microspheres and the composite microspheres embedded in pluronic gel were evaluated using fluorescent microscopy as shown in Figure 1b and c. The gel matrix containing the composite microspheres was also analyzed by SEM (Figure 1d). The release profile of lidocaine hydrochloride from control PLGA microspheres and Si embedded in the gel showed faster release compared to PLGA-Si composite microspheres integrated in the gel. Control PLGA(85/15 and 50/50 comonomer ratio)-gel and Si-gel demonstrated 25-40 and 100% release of lidocaine respectively within two days, while the PLGA50/50-Si and PLGA 85/15-Si embedded in the gel released 10-20% of total drug content within the same time frame. Moreover, higher comonomer ratio (lactic to glycolic) of PLGA used in the preparation of composite microspheres delayed the release amount by approximately 10% over five days.

Significant differences were observed amongst cohorts during in vivo testing. When mechanically tested, rats treated with the PLGA-Si/Lidocaine gel withdrew from filament forces roughly 2-3 times higher (170-330% greater, corresponding to 50-127mN) than those receiving no analgesia, and forces equal to or greater than those rats receiving full anesthesia per protocol. Only fifty percent of rats in the experimental hydrogel group lost > 5% of preoperative weight, versus 100% of rats without analgesia. None of the experimental group consistently showed pain-limiting behavior on weight bearing (blanching), while all rats devoid of analgesia displayed limiting behavior during postoperative days 2-4. All other significant surrogate behavior for pain in the experimental hydrogel group mimicked that of rats treated with a full analgesia protocol (positive control).

CONCLUSION

We have demonstrated the capability to provide sustained release of the local anesthetic lidocaine via a novel nano-delivery platform for significantly longer than any currently available therapy. This biodegradable PLGA-Si system provides a promising new alternative for the delivery of locally acting drugs, and demonstrates the potential to produce prolonged nerve blockade for the management of both acute and chronic pain in vivo. Data provided from our in vivo testing shows great promise for translational applications of this platform across many specialties in the clinical realm, including anesthesia and surgery. Success in this clinical realm could have drastic economic implications while significantly decreasing the large burden of opioid analgesics currently existing in the medical community, and society at large.

REFERENCES