

## Effect of injectable nanostructured lidocaine hydrogel in a rat model of surgical incisional pain

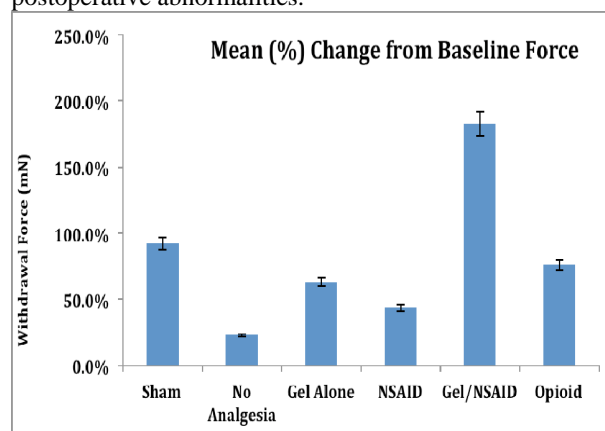
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**Statement of Purpose:** Nanostructured materials have the potential to significantly impact the healthcare industry by improving therapeutic efficacy of conventional drugs, or the clinical outcome of surgical implants. Encapsulation of drug molecules in a modified-sustained release form could lead to a slower uptake of the drug by systemic circulation and increase its pharmacokinetic effects. For example, the local administration of anesthetics has been widely used to control post surgical or procedural pain. Due to the cardiovascular and neural toxicity of frequently administered local anesthetics, a few new liposomal formulations have been recently approved for human use by FDA. We developed a multifunctional nanocomposite to answer the clinical needs by raising the efficiency and longevity of local anesthetic delivery for surgical pain management while avoiding the burst release of the drug. After extensive characterization and optimization of our formulation *in vitro*, we hypothesized that our nanocomposite formulation could provide equivalent or superior postoperative analgesia to standard treatments in a surgical incisional model of pain in rats.

**Methods:** Nanostructured lidocaine hydrogel was prepared by loading lidocaine hydrochloride in two stages: first into silica nanoparticles (SN) and second during encapsulation of SN into a poly(lactic co-glycolic acid) (PLGA) 85/15 by solid-oil-water emulsion technique. The resulting PLGA-SN microparticles were collected, washed and lyophilized for storage. Prior to use, loaded PLGA-SN was resuspended into 20% F-127 pluronic gel to create a thermo-responsive injectable formulation. Both lyophilized PLGA-SN and the final hydrogel were characterized by SEM. The *in vitro* release of lidocaine hydrochloride at 37°C was evaluated by HPLC daily for 7 days. Thermo-responsive gelification and degradation were tested at 37°C. We performed a seven day study in 36 Lewis rats to evaluate analgesic efficacy compared to standard clinical therapies in the Brennan model of hindpaw incisional pain. In these animals we measured: cumulative weight-bearing index (CBI), NINDS behavioral scoring system, and hyperalgesia from von Frey filament mechanical stimulus testing. The experimental groups included: Sham (S), No Analgesia (-C), daily non-steroidal anti-inflammatory drug or NSAID (+C), Hydrogel Alone (E), Opioid (+C2), and Hydrogel + NSAID (E2). The release kinetic was characterized *in vivo* using fluorescently-labeled gels by confocal microscopy, and *in vivo* degradation of the hydrogel was evaluated by histology and ICP-AES.

**Results:** We demonstrated that incorporation of nanostructured silica is necessary to minimize the initial burst release and to achieve sustained release of lidocaine

for over 7 days *in vitro*. The morphology, surface and size of the PLGA-SN did not vary significantly compared to control PLGA when it was incorporated with SN and loaded with lidocaine. *In vitro* degradation of nanostructured lidocaine hydrogel incubated in PBS buffer showed a slower degradation as a function of the percent weight compared to control group. Histological analysis demonstrated few intact nanostructured hydrogel PLGA microparticles after 7 days, and Si levels in key organs were non-toxic by ICP-AES analysis. Group E rats required significantly greater force stimulus to generate a painful withdrawal response than -C rats ( $p < 0.01$ ) and equivalent force to +C rats, while group E2 rats required equivalent force to daily opioids (+C2). When compared to preoperative baseline withdrawal forces (to account for inherent intra-animal variability), both group E and E2 rats demonstrated significantly less hyperalgesia (less decrease from baseline withdrawal force) compared to controls ( $p < 0.05$ ). Upon NINDS behavioral assessment, significantly fewer group E rats showed abnormal (painful) postoperative behavior compared to control group, and like sham rats, group E2 rats showed no postoperative abnormalities.



**Figure 1. Mean change (%) from baseline withdrawal threshold force over 7 day testing period.**

**Conclusions:** Our data demonstrated that our experimental nanostructured lidocaine hydrogel possessed superior analgesic power to existing drugs and extended controlled over the release of anesthetics both *in vitro* and *in vivo* by. Our characterization data confirm that the nanostructured lidocaine hydrogel could reduce drug-associated adverse effects and enhance the pharmacological activity of the free drug. Finally the possibility to lyophilize and store for long period of time the gel and/or its individual components, makes the nanostructured lidocaine hydrogel an ideal candidate for the translation to the clinic.