An injectable nano-delivery system for the sustained release of lidocaine

Iman K. Yazdi[1,2], Sm Khaled[1], Jeff Van Eps[1,3], Nima Taghipour[1], Jonathan Martinez[1], Joseph Fernandez-Moure[1,3], Seth Haddix[1], Bradley Weiner[4], and Ennio Tasciotti[1]

[1]Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX

[2]Department of Biomedical Engineering, University of Houston, Houston, TX

[3]Department of Surgery, The Methodist Hospital, Houston, TX

[4]Department of Orthopedic Surgery, The Methodist Hospital, Houston, TX

Introduction: Non-opioid drug therapies are lacking in their availability and efficacy to treat chronic radicular or acute incisional (post-operative) pain. Subsequent reliance on opioid drugs for analgesia has massive consequences, including: addiction, GI dysmotility and socioeconomic loss. Providing 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 prolonged local anesthetic action provide no longer than 1-2 days of blockade [1]. To overcome the short duration of action of these locally-acting drugs in pain management, it is essential to develop methods of prolonging their efficacy. Recent advances in nanotechnology make it increasingly possible to address the shortcomings associated with current therapies of pain management. We have recently developed a multifunctional nanostructured platform for localized sustained release of drug molecules [2,3]. The present study evaluates the ability of our nanoscale delivery system to provide greatly prolonged, sustained release of lidocaine compared to what is currently used as standard clinical practice.

Methods: Poly(lactic-co-glycolic acid) (PLGA) microspheres, a widely studied delivery carrier for pain medication has been modified in this study with nanostructured silica enclosure (Si) in order to prolong the release of anesthetic. Si loaded with lidocaine hydrochloride was embedded in PLGA microspheres having two different 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. For release study, the polymer solution containing the loaded PLGA-Si were injected in 48-well plates and left at 37 ºC for one minute for complete gelation of Pluronic. The pharmacokinetics of the composite was performed 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. 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.

Results: The silica 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.

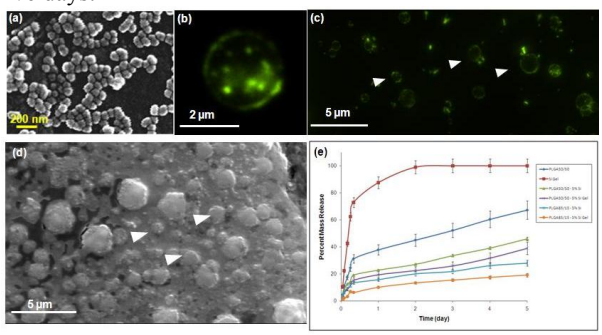

Figure 1. (a) Si; (b) PLGA-Si ; (c) Confocal micrograph of PLGA-Si in pluronic gel and (d) SEM micrograph of PLGA-Si in Pluronic gel (Arrow heads showing the existence of PLGA-Si microspheres in gel matrix); (e) Release profile of lidocaine hydrochloride from different nanocomposite formulations over five days.

Conclusions: We have tangibly demonstrated the capability to provide sustained release of the local anesthetic lidocaine via a novel nano-delivery platform. This biodegradable PLGA-Si system provides a promising new alternative for the delivery of local anesthetics in vitro, and demonstrates the potential to produce prolonged nerve blockade for the management of acute and chronic pain in vivo. This in vivo testing is currently being undertaken in our lab and has great potential implications for translational application in the clinical realm of anesthesia and surgery. Success in this realm could significantly decrease the large burden of opioid analgesics currently existing in the medical community, and society at large.

References:

[1] Dierking GW, et al. Br J Anaesth. 2012; 68(4) 344-348.

[2]Dongmei F, et al. Adv Func Mat. 2012; 22(2) 282–293.

[3] Murphy MB, et al. Eur J Pain. 2011; 5 (S2) 423–432.