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Sustained relief of pain from osteosynthesis surgery of rib fracture by using biodegradable lidocaine-eluting nanofibrous membranes

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Abstract

Various effective methods are available for perioperative pain control in osteosynthesis surgery, but they are seldom applied intraoperatively. The aim of this study was to evaluate a biodegradable poly([d,l]-lactide-co-glycolide) (PLGA)/lidocaine nanofibrous membrane for perioperative pain control in rib fracture surgery. Scanning electron microscopy showed high porosity of the membrane, and an ex vivo high-performance liquid chromatography study revealed an excellent release profile for both burst and controlled release of lidocaine within 30 days. Additionally, the PLGA/lidocaine nanofibrous membrane was applied in an experimental rabbit rib osteotomy model. Implantation of the membrane around the osteotomized rib during osteosynthesis surgery resulted in a significant increase in weight gain, food and water consumption, and daily activity compared to the study group without the membrane. In addition, all osteotomized ribs were united. Thus, application of the PLGA/lidocaine nanofibrous membrane may be effective for sustained relief of pain in oeteosynthesis surgery.
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Key words: Nanobiomaterial; PLGA nanofibrous membrane; Lidocaine; Perioperative pain control; Rib fracture

Severe, intolerable pain always follows surgical intervention. Particularly, orthopedic surgeries are considered "the most painful surgeries" because of the perioperative pain associated with them.[1-3] Parental narcotic administration after surgical procedures plays an important role in perioperative pain management. However, the side effects of opioids such as nausea, vomiting, constipation, drowsiness, and tolerance necessitate a reduction in the usage of opioid narcotics.[4] Therefore, multiple modalities in perioperative pain management were adapted for better postoperative quality and earlier functional recovery.

There are many routes for perioperative pain management, and oral pills are the most common route. In addition to oral analgesic medications, there are other new treatments for perioperative pain prevention to improve functional recovery after total joint arthroplasty in knee and hip joints, such as intravenous administration of long-acting non-steroid-anti-inflammatory drug one hour preoperatively,[5] peripheral nerve block postoperatively,[6,7] and intraoperative local anesthetic treatment.[8-10] Among these treatments, the injection of local anesthetics at the surgical site was considered as an effective method for pain prevention through sustained release of analgesic medication and progressive infiltration around local tissue in a contented cavity.[9-11] However, side effects, such as cardiovascular intoxication and neurological response, from soaking the tissue with largely local anesthetics within the joints are catastrophic. In addition, local anesthetics were found to have been completely depleted 48 hours after the procedure.[12-14] Therefore, it is necessary to investigate whether local anesthetics with a carrier for sustainability and controllability can achieve better clinical safety and pain control.

Clinical applications of the biodegradable material in drug delivery and nanomedicine are of great interest. Biodegradable material as a medication carrier shows the biggest advantage of controlled release of the medication, which represents safety. In addition, the carrier can be degraded into nontoxic materials in

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nature in an expected time span. Various types of medications can be carried by biodegradable materials, such as antibiotics,[8,15-18] immunosuppressants,[19] bone growth factors,[1,20] and local analgesics.[3,21-24] At the same time, nanomedicine for enhancing osteogenesis is undergoing development. Upon trauma, the periosteal of the fractured bone may be damaged. The application of nanofiber on the fractured bone may serve as a scaffold for osteogenesis.[25]

In this preliminary study, our hypothesis was to provide a novel method for perioperative pain prevention. We proposed a method of local application of analgesic medication with sustained drug release for pain prevention after orthopedic surgery through an innovative lidocaine-biodegradable material composite. Biodegradable lidocaine-eluting Poly(lactic-co-glycolic acid) (PLGA) nanofibrous membrane wrapped around the osteotomized rib in rabbits with fixation of biodegradable PCL cable-tie fixator was investigated. In addition, a new method of pain assessment of the rabbits was introduced in this experimental study.

Methods

Fabrication of nanofiber membranes

A commercially available PLGA material (Resomer RG 503; Boehringer Ingelheim, Ingelheim, Germany) that consists of lactide-to-glycolide ratio of 50:50 and a molecular weight of 33,000 Da was used. Lidocaine hydrochloride (1%) (Sigma-Aldrich, Saint Louis, MO, USA) was used as the analgesic and the solvent 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was also obtained from Sigma-Aldrich company (Saint Louis, MO, USA) in this experiment.

In the current study, the electrospinning setup was composed of a syringe and needle with a 0.42 mm internal diameter, a ground electrode, an aluminum sheet, and a high-voltage supply. The high-voltage supply which generated positive DC voltages and currents up to 35 kV and 4.16 mA/125 W, respectively, was connected to the needle. For the preparation of the PLGA/lidocaine nanofibrous membrane, the PLGA and lidocaine of various polymer-to-lidocaine weight ratios (9/1, 7/3, 5/5 in mg/mg, respectively) were dissolved in 1 mL of HFIP. The solution was then delivered and electrospun by a syringe pump at a volumetric flow rate of 3.0 mL/h to obtain a 0.110 mm-thick membrane. The distance from the needle tip to the ground electrode was 12 cm, and a 17 kV positive voltage was applied to the polymer solution. All electrospinning experiments were carried out at a room temperature of 27 °C and relative humidity of 73%. All manufactured nanofibrous membranes were placed in a vacuum oven at 40 °C for 72 h to evaporate the solvents.

SEM analysis

The morphology of the electrospun PLGA/lidocaine nanofibrous membrane, which was coated with gold, was analyzed with a S-3000 N scanning electron microscope (SEM, Hitachi, Tokyo, Japan). The average diameter and diameter distribution were determined by analyzing SEM images using a commercial image analysis program (Optimas, v 5.22, Silver Spring, MD, USA).

Fabrication of the biodegradable cable-tie fixator

A biodegradable poly(ε-caprolactone) (PCL) implant specifically for a fractured rib was designed and fabricated in our laboratory. Details regarding the fabrication process of the biodegradable cable-tie fixator can be found in the reference.[26]

Standard curve establishment for the PLGA/lidocaine nanofibrous membrane

An *in vitro* elution method was adopted to determine the release characteristics of lidocaine from the PLGA/lidocaine nanofibrous membrane. The PLGA/lidocaine nanofibrous membrane was immersed in a dissolution medium composed of phosphate buffer (0.15 mol/L, pH 7.4). Firstly, samples with controlled area (2 cm by 3 cm) and weight (216 to 220 mg) were cut from the electrospun membranes and were incubated in 1 mL of phosphate buffered saline at 37 °C for 24 h. Then the dissolution medium was isolated, collected and analyzed at 24-h intervals. The phosphate buffer (1 mL) was replaced every 24 h until the sample was fully dissolved. In the elusion study, the lidocaine concentrations in the buffer were determined by high-performance liquid chromatography (HPLC) using a Hitachi L-2200 Multisolvent Delivery System. A SYMMETRY C8, 3.9 cm × 150 mm HPLC column (Waters) was used to isolate lidocaine. The mobile phase contained acetonitrile (Mallinckrodt, USA) (85/15, v/v) and 0.01 mol heptanesulfonic acid (Fisher Scientific UK Ltd.). The absorbance was monitored at 280 nm and the flow rate was 1.4 mL/min. All samples were assayed in triplicate and sample dilutions were performed to bring the unknown concentrations into the range of the assay standard curve. A calibration curve was prepared for each set of measurements (correlation coefficient >0.99). The elution product could be specifically identified and quantified with high sensitivity using the HPLC system.

Rabbit rib fracture model: Surgical procedure and animal care

Twenty-four 3-month-old New Zealand white rabbits weighing between 2200 and 2500 g were used in this study. The rabbits were divided randomly into three groups: control group (n = 6), PCL cable-tie fixation group (PCL group, n = 6), and fixation with PCL cable-tie fixator and PLGA/lidocaine nanofibrous membrane group (PCL-PLGA/lidocaine group, n = 6).

The osteotomy model of the New Zealand white rabbit rib was designed and performed in the same laboratory. The 6th rib of the right chest wall was selected as the target rib for the fracture model. Before the surgical procedure, the animal was restrained manually and oxygen was delivered through a facemask for 5 min at 4 L/min. Following pre-oxygenation, inhalation isoflurane was delivered through the facemask until the animal was anesthetized. Isoflurane inhalation was maintained throughout the surgical procedure. The rabbit was placed in the decubitus position, with the surgical field upward. The skin was prepared and disinfected according to the standard antiseptic procedure. A 2.5 cm skin incision was made, directly above the target rib, and the soft tissue and muscular layer of the

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