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Local delivery of mometasone furoate from an eluting endotracheal tube

Abu Ammar Aiman[a,1], Maayan Gruber[b,c], Patrick Martin[a], Ohad Stern[a], Forsan Jahshan[b], Offir Ertracht[d], Eyal Sela[b,c], Samer Srouji[c,e], Eyal Zussman[a,*]

[a] NanoEngineering Group, Faculty of Mechanical Engineering, Technion – Israel Institute of Technology, Haifa 3200003, Israel
[b] Department of Otolaryngology-Head and Neck Surgery, Galilee Medical Center, Nahariya 2210001, Israel
[c] Faculty of Medicine in the Galilee, Bar-Ilan University, Safed 1311502, Israel
[d] Eliachar Research Laboratory, Galilee Medical Center, Nahariya 2210001, Israel
[e] Institute of Oral and Maxillofacial Surgery and Oral Medicine, Galilee Medical Center, Nahariya 2210001, Israel

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ABSTRACT

Laryngeal and tracheal morbidity is a common complication of endotracheal tube (ETT)-based airway management, and manifests as local irritation, inflammation, and edema. Systemic corticosteroids are commonly administered to manage these conditions; however, their efficacy is inadequate and limited by potential severe side effects. In the present study, a steroid delivery system for local therapy was developed to generate relatively high local drug concentrations and to improve drug efficacy. ETTs were coated with electrospun poly (lactic-*co*-glycolic acid) (PLGA) nanofibers loaded with mometasone furoate (MF), creating a microscale thick layer. MF exhibited sustained release from coated ETTs over 14 days *in vitro*. An *in vivo* efficacy study in rats demonstrated the therapeutic benefit of MF-coated ETTs over bare ETTs, as measured by reduced laryngeal mucosal thickness and submucosal laryngeal edema. The fiber coating remained intact during tube intubation and extubation, demonstrating good adhesion to the tubes even after 24 h in aqueous solution at 37 °C. These findings demonstrate the potential of drug-loaded ETTs to revolutionize the standard of care for endotracheal intubation.

1. Introduction

Endotracheal intubation is a widely used technique to support ventilation in the operating room and intensive care units. Pressure exerted by endotracheal tubes (ETT) typically deployed in airway management, can result in laryngeal and tracheal morbidity. Among the complications are sore throat, cough, hoarseness, dyspnea and post-extubation stridor, due to local irritation and inflammation [1]. Post-extubation upper airway obstruction is another possible complication of both pediatric and adult mechanical ventilation [2].

The common clinical approach to prevent post-extubation complications and the need for reintubation, is the use of multiple steroid intravenous doses over hours to days, prior to elective extubation [3–6]. Mainly high-risk groups may benefit from this intervention [7,8]. Re-intubation following laryngeal injury, increased length of stay for additional monitoring and associated treatment, likely contribute to hundreds of millions of dollars in healthcare costs each year [9,10]. On average, patients who are re-intubated in an intensive care unit setup, require five additional days of mechanical ventilation, at a cost of thousands of dollars per day.

Recently, a meta-analysis of 18 randomised controlled trials indicated that prophylactic administration of corticosteroids is effective in decreasing the frequency and harshness of postoperative sore throat and hoarseness, as well as the incidence of laryngeal edema and re-intubation [11]. A reasonable surrogate option for the traditional systemic steroid administration is a localized drug delivery [12,13], which allows for its direct administration at the inflammation site, high local concentrations, controlled release over an extended period of time, loading of water-insoluble drugs, and reduced incidence of adverse events [14,15].

Electrospinning is a useful technique for producing nanofibers made of biomaterials such as polymers, polysaccharides, and proteins [16–19]. Electrospun nanofibers have several remarkable characteristics that are advantageous in pharmaceutical applications, such as nano-scale diameters, unique physical and mechanical properties, large surface area to volume ratio, which improves the solubility of the drug. In addition, they can be used as drug reservoir, as well as modulate the drug release profile [20,21]. Biodegradable polyesters, such as polylactic acid (PLA), polyglycolic acid (PGA), poly (lactic-*co*-glycolic) acid (PLGA), and polycaprolactone (PCL) have been electrospun for drug

* Corresponding author.
E-mail address: meeyal@technion.ac.il (E. Zussman).
[1] Current address: Department of Pharmaceutical Engineering, Azrieli College of Engineering, Jerusalem 9103501, Israel.

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delivery applications and controlled drug release [22]. Among these, PLGA is used extensively, due to its biodegradability, biocompatibility, and mechanical properties, and had been cleared for such use by the FDA [23,24]. Moreover, PLGA provides a wide range of degradation rates depending on its composition (the ratio between glycolic and lactic acid) and molecular weight [25–28]. The application of PLGA nanoparticles in upper and lower airways has been proven to be safe and did not induce significant changes in the inflammation markers analyzed [29,30].

Mometasone furoate (MF) is a synthetic 17-heterocyclic glucocorticoid, with potent anti-inflammatory activity, and has been shown to effectively treat skin disorders, asthma, allergic rhinitis and rhinosinusitis. Moreover, MF is well-tolerated, due to its low systemic absorption and relatively high binding affinity to the glucocorticoid receptor [31–33]. MF has a lipophilic nature [34], and has also been shown to be a potent inhibitor of the *in vitro* production of three inflammatory cytokines, interleukin-1, interleukin-6, and TNF-alpha [35].

The present study aimed to develop steroid-eluting ETTs to locally release MF to the laryngeal and tracheal lumen. Using electrospinning techniques, ETTs were coated with polymeric PLGA nanofibers loaded with MF. The fibers were characterized in terms of morphology, mechanical properties and adhesion to the ETT. Lastly, the anti-inflammatory and therapeutic effects of the fibers over time, were studied.

2. Materials and methods

2.1. Materials

Mometasone furoate (MF) (≥ 98%), PLGA (85:15) Lactel® B6001-1, sodium dodecyl sulfate (SDS), and phosphate buffered saline (PBS) were purchased from Sigma-Aldrich (Rehovot, Israel). The solvents tetrahydrofuran (THF), dimethylformamide (DMF), methanol (MeOH), and ethanol (EtOH) were obtained from Bio-Lab Ltd. (Jerusalem, Israel). Acetone was purchased from Gadot Biochemical Industries Ltd. (Haifa, Israel). Closed-suction system for endotracheal tubes (ETT), KimVent® for neonates/pediatrics, were used as an ETT and was purchased from Kimberly-Clark LLC (Roswell, Georgia, USA) and from Halyard Health (Alpharetta, USA). The inner diameter of the tubes was 1 mm, the outer diameter was 1.6 mm.

2.2. Preparation of MF-loaded polymeric nanofibers

Electrospinning of drug-loaded fiber mats was performed using a rotating mandrel [36]. PLGA was dissolved in THF/DMF (4:1) at a concentration of 20%, MF was added at a drug/polymer ratio of either 1:20 (MF1) or 3:20 (MF3). ETTs were cut to a length of 30 mm and assembled on a 1.2 mm-diameter stainless steel wire, which served as the grounded collector. A syringe pump (Harvard Apparatus, Holliston, USA) was used to pump the spin dope through a 25 G needle, at a flow rate of 0.3 mL/h. The distance to the collector was 8 cm, and the applied voltage was 9 kV, resulting in an electrical field of 1.125 kV/cm. Each tube was coated for 12 min. The radial velocity of the mandrel resulted in a tangential velocity of the tube of 0.047 m/s. The process was carried out under ambient conditions, with a measured humidity of ~45%.

2.3. Morphology, size and orientation of fibers

A scanning electron microscope (SEM) "Phenom" (FEI Company, Hillsboro, Oregon, USA) was used to observe the morphologies and sizes of the fibers. For this purpose, fiber-coated ETTs were cut to a length of 0.5 cm and gold sputtered. The distribution of fiber diameters and orientation was assessed from SEM micrographs, using ImageJ software (National Institutes of Health, Bethesda, MD, USA). For each group of samples, the diameters of at least 80 fibers were measured.

2.4. Degradation of fiber mats

Degradation of fiber mats was monitored after placing them (10 mm × 5 mm) in 0.01 M PBS (pH = 7.4) and storing them in a rotary incubator at 37 °C and 50 rpm (n = 3 per type, per time point). At predefined time intervals (0 h, 2 h, and 24 h) samples were taken out of the medium and imaged with SEM.

2.5. Dimensional stability of fiber mats

To monitor dimensional changes of fiber mats under physiological conditions electrospun MF3-loaded mats were cut into 10 mm × 5 mm samples (n = 3 per type, per time point) and incubated in 0.01 M PBS solution (pH = 7.4), at 37 °C, for 1 min, 2 h or 24 h. Length, width and thickness of the specimens were measured after each period of incubation.

2.6. Tensile testing

Tensile tests of aligned fibers mats were carried out in displacement-controlled mode, using a horizontal tensile machine equipped with a temperature-controlled water bath and 1 mN resolution load cell (Model 31/1435-03, Sensotec, Columbus, OH). Fiber mats made of MF3 in 4:1 THF/DMF were cut into 20 mm × 2 mm samples, with an average thickness of 179 ± 4 μm (n = 4 per type, per time point). The length between the clamps was set to 10 mm and the strain rate was 0.05 s^{-1}. Tensile strength of fiber mats was measured under dry conditions, as well as following incubation in 0.01 M PBS (pH = 7.4, 37 °C in a rotary incubator (50 rpm)) for 0 h, 2 h or 24 h.

2.7. Adhesion of fiber mats to ETT

Adhesion strength between the fiber coating and the ETT was measured using the aforementioned horizontal tensile machine, under the same settings. Samples were prepared by placing two ETTs (25 mm) adjacently on the mandrel. Electrospinning directly on the mandrel, as described above, resulted in coating 20 mm of the ETTs (each tube section was covered along 10 mm). Coating of the specimen was carried out using MF3 in THF/DMF (4:1). A scheme of the specimen's dimensions is shown in Fig. 1 and Fig. S1 (see supporting information). The adhesion of the fibers to the ETT was measured, and the force *vs.* strain was registered until slipping of the coating. The adhesion force was measured on both dry and wet conditions. Wet samples testing was performed in a bath filled with 0.01 M PBS (pH = 7.4), at 37 °C.

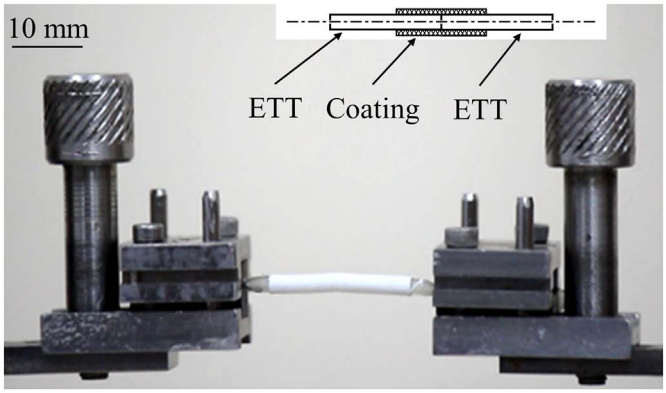

Fig. 1. Image of the adhesion testing setup. Two adjunct ETTs (25 mm) were coated by a layer of electrospun fibers (MF3). The uncoated end of each tube was clamped (see the figure inset).