Original Article

Lidocaine-eluting endotracheal tube effectively attenuates intubation related airway response

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Background: Lidocaine (LDC) is a local anesthetic widely used to relieve intubation-related airway responses. However, low drug concentration and short effective duration of LDC is inadequate to provide a satisfactory anesthetic effect on the surface of the airway. The present study sought to develop a LDC-delivery endotracheal tube (ETT) to achieve high local drug concentration and sustained drug release with the aim of attenuating an intubation-related airway response.

Methods: ETTs and polyvinyl chloride (PVC) discs were coated with different molecular weight (MW) poly lactic-co-glycolic acid (PLGA: 50/50; MW: 3,000, 6,000, and 10,000) loaded with LDC by airbrush spray. The morphology of LDC-eluting coatings was analyzed using scanning electron microscopy. *In vitro* drug release was determined by ultraviolet spectrophotometer. An *in vivo* study was performed to investigate the differences in plasma LDC concentration, intubation tolerance, and tracheal tissue injury in rabbits undergoing intubation of blank, LDC-spray, or LDC-coated ETTs.

Results: Approximate 5 mg/cm^2 coatings (containing 2.5 mg/cm^2 LDC) were deposited onto the PVC discs and ETTs. While even distribution and smooth surfaces were generated in PLGA3000 + LDC and PLGA6000 + LDC coatings, PLGA10000 + LDC formed uneven and gullied coatings. Burst release within the first 4 h and sustained release for at least 5 days was achieved *in vitro* in PLGA + LDC coatings and the *in vivo* study demonstrated higher plasma LDC concentration and longer drug release duration in LDC-coated ETTs compared with LDC-spray. LDC-coated ETTs significantly improved intubation tolerance in rabbits, as measured by less general anesthetic consumption and longer tube tolerance duration in contrast to blank ETTs with or without LDC spray. Histology assessment showed less mucosal edema area in the PLGA3000 + LDC and PLGA6000 + LDC groups compared to the control, LDC-spray, and PLGA10000 + LDC groups. Among the different MW PLGAs, PLGA6000 presented optimal morphological characteristics, drug release, and anesthetic effect.

Conclusions: ETTs coated with PLGA + LDC effectively attenuate an intubation-related airway response

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via increasing local drug concentration and extending drug action duration, which demonstrates a potential therapeutic benefit for patients undergoing intubation.

Keywords: Lidocaine; endotracheal tube (ETT); local anesthesia; drug release; poly lactic-co-glycolic acid (PLGA)

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Introduction

Endotracheal intubation is a widely used medical technique to maintain an open airway, prevent suffocation, and facilitate ventilation in the operating room and intensive care unit. During the ongoing epidemic of coronavirus disease 2019 (COVID-19), many critically ill patients with COVID-19 survived acute respiratory failure due to the use of endotracheal intubation and mechanical ventilation (1,2). However, endotracheal intubation-related mechanical stimulation is clinically common and associated with various airway complications, such as severe coughing, laryngeal injury and postoperative sore throat (POST) (3-5). The intubation-induced airway response is prone to increase the risk of adverse cardiovascular events including arrhythmias, hypertension, myocardial ischemia, and intracranial pressure elevation (4,6,7). Further, for patients experiencing major procedures or craniocerebral operations, dramatic hemodynamic fluctuations due to the intolerance of endotracheal intubation may result in life-threatening complications such as incision bleeding and cerebrovascular accidents (8).

Common clinical approaches to attenuate intubation-induced airway and hemodynamic responses include short-acting opioids, anti-arrhythmia agents, and intravenous or topical anesthetic agents (9,10). Among these, topical lidocaine (LDC) has been applied for decades by means of intratracheal spray, oxygen atomization, intracuff filling, or gel lubrication due to the advantage of its simple operation, direct absorption, and rapid anesthetic effect (3,9-14). However, the topical use of LDC does not provide a long-term anesthetic effect due to the relatively low doses used and short effective anesthetic duration (1 to 2 h, or less) (3,7,9,15). To conquer these limitations, a reasonable option is to use a sustained drug release technique to locally deliver anesthetic agent, which allows for an extended effective duration, a higher local drug concentration, and lower adverse effects. Recent studies showed that the sustained release of corticosteroids or antimicrobials from surface coatings, including electrospinning, hydrogel, and dip coatings, on endotracheal tubes (ETTs) is feasible and effective in reducing inflammatory reactions and preventing ventilator-related infection (16-18). Therefore, surface coating techniques may also be applicable to local LDC delivery for enhancing the local anesthetic effect.

Drug-eluting stents have become one of the most successful implantable biomedical devices over the last two decades and have greatly transformed the field of interventional cardiology (19,20). DES are comprised of a polymer coating that controls the release of an anti-antiproliferative drug, and one of the most used polymer biomaterials is poly lactic-co-glycolic acid (PLGA), which can be fully degraded and metabolized *in vivo*. As an FDA approved polymer, PLGA has been extensively applied in controlled drug release techniques, due to its biocompatibility, biodegradability, a wide range of degradation rates, and tunable mechanical properties. The PLGA-based drug delivery systems, including nanoparticles and coatings, have been proven to be effective and safe in the airway and some are available on the market (21,22).

Herein, we developed a simple LDC-eluting coating technique for ETT to locally deliver LDC on the tracheal surface and eventually attenuate an intubation-related airway response (*Figure 1A*,*B*). Specifically, inspired by DES techniques, LDC was loaded on the surface of a tracheal tube *via* PLGA airbrush spray coatings (*Figure 1C*). Compared to other reported ETT coating techniques, the evaporation of spray coating is faster, which reduces the impact on the substrate from dip coatings where the tube needs to be immersed in solvent (18), and can easily prepare a thin, uniform, and transparent coating. At the same time, hydrogel (17) and electrospinning (16) ETT coatings are thicker (0.17–0.2 mm), which may limit their application in small diameter ETTs, such as size 2.5: inner diameter =2.5 mm, and outer diameter =3.3 mm.

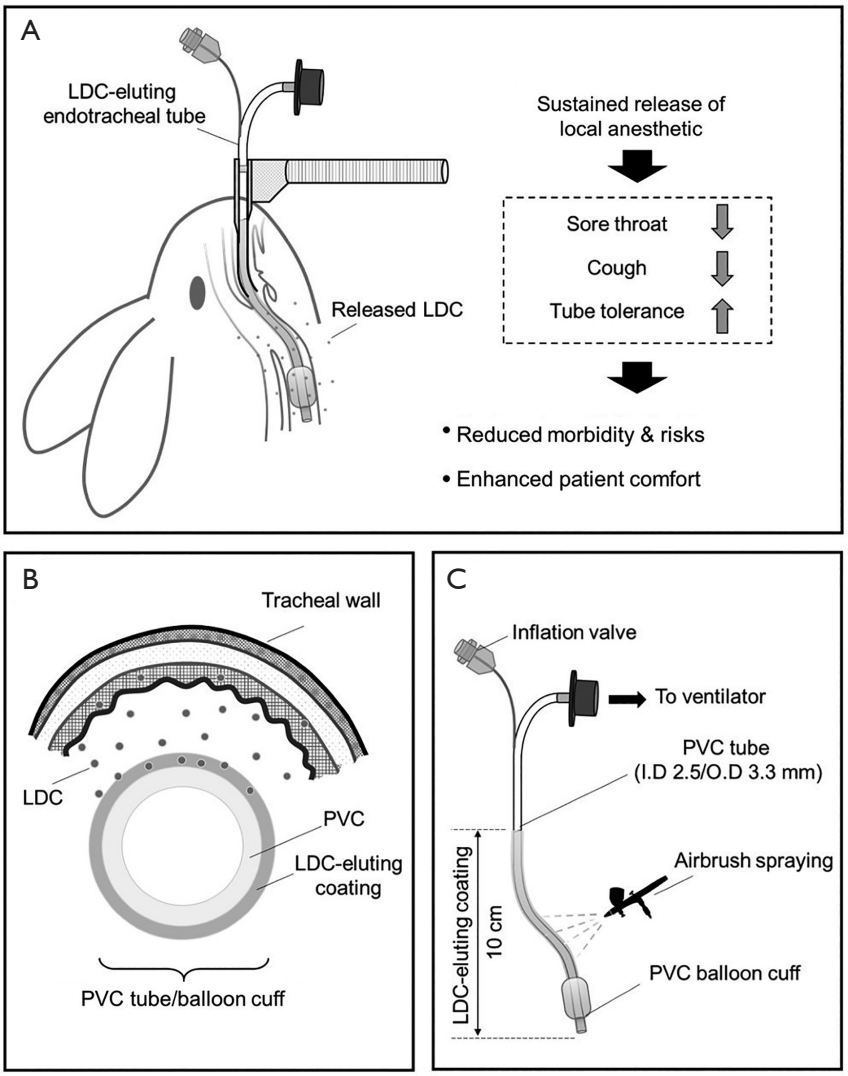

Figure 1 Schematic of LDL-eluting endotracheal tube. (A) schematic illustration for LDC-eluting endotracheal intubation in a rabbit model; (B) cross-section of sustained release of LDC from LDC-eluting coating to tracheal wall; (C) structure and fabrication of LDC-eluting ETT. LDC, lidocaine; ETT, endotracheal tube.

As the PLGA degradation rate and drug release are related to its molecular weight (MW) (22,23), we selected three low MW PLGA (50:50; MW: 3,000, 6,000, and 10,000) to assess the influence of MW on drug release. The plasma LDC concentration at different time intervals, the anesthesia efficacy of LDC-eluting coating, and the tracheal tissue damage were then evaluated in a rabbit intubation model. We present the following article in accordance with the ARRIVE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-1930).

Methods

Materials

Lidocaine powder (≥99% purity) and PLGA (50:50, MW: 3,000, 6,000, 10,000) were purchased from Aladdin (Shanghai, China), and the Daigang Bio-technology Co., Ltd. (Jinan, Shandong, China), respectively, and dichloromethane (DCM) was purchased from Chron Chemicals Co., Ltd (Chengdu, Sichuan, China). ETTs that fit the trachea of a rabbit (size 2.5: inner diameter =2.5 mm,

outer diameter =3.3 mm) were purchased from the Henan Tuoren Kingtaek Medical Device Co., Ltd (Xinxiang, Henan, China), and medical grade polyvinyl chloride (PVC, widely used polymers for fabricating ETTs) was purchased from the Dongguan Sunyo Plastic Co., Ltd., (Dongguan, Guangdong, China) and cut into discs (diameter =14 mm).

Preparation of LDC-eluting coatings

LDC-eluting coatings were performed using an airbrush paint sprayer (U Star R-102 + 201, China). Both PLGA (50:50, MW: 3,000, 6,000, 10,000) and LDC were dissolved in DCM at a concentration of 10 wt% and the PLGA control was 10 wt% PLGA in DCM alone. The PVC discs were carefully cleaned using an ultrasonic cleaning method with ethanol and deionized water in sequence (three times for 5 min) and dried by nitrogen blowing. PLGA/LDC solutions, PLGA solutions, or DCM were sprayed onto both sides of the cleaned PVC discs and ETTs (10 cm from the top, *Figure 1C*), with a fixed 15 cm distance from the tube surface and varying time. The discs and tubes were rotated during the spraying process and the coatings were dried by nitrogen blowing and vacuumed before use. For preparing LDC-eluting ETTs, an additional layer of coating was applied to ensure the desired dose if the weight of the first layer was insufficient.

Characterization of LDC-eluting coatings

The coating thickness was measured by a digital micrometer (Sanliang 211, Dongguan, Guangdong, China) and the coating weight was measured by electronic scales (BT125D, Satorius, Germany). The water contact angle of each coating at room temperature was measured using a Drop Shape Analysis System (DSA100, GmbH Hamburg, Germany) and five μL of deionized water was used as the probing liquid (n≥6). The chemical composition of the LDC-eluting coating was analyzed by the reflection absorption-Fourier transform infrared spectroscopy (RA-FTIR, Nicolet model 5700 instrument, USA) of Au substrates deposited with LDC, polymers, and LDC-eluting coatings.

Morphology of LDC-eluting coatings

Samples were photographed by digital camera, then the morphology of LDC-eluting coatings on ETTs was analyzed by scanning electron microscopy (SEM, Quanta 200 and Inspect F50, FEI, Netherlands) after being washed with deionized water and dried by nitrogen blowing.

In vitro drug release from LDC-eluting coatings

The *in vitro* LDC release study was performed by incubating LDC-coated PVC discs in 20 mL PBS buffer (pH 7.4), at 37 ℃. At appropriate intervals, the supernatants of the samples were collected and centrifuged (6,000 rpm, 15 min, at room temperature) to remove insoluble substance. The amount of released LDC was measured by UV-Vis at 263 nm (n≥3) and the standard curve was made by LDC solutions measured in the same way. Coatings without LDC were used as blank.

Experimental animals

This study was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee and animals were treated in accordance with the Guide for the Care and Use of Laboratory Animal of the US National Institutes of Health (NIH). Twelve-week-old, healthy female or male New Zealand White (NZW) rabbits (Dasuo experimental animal center, Chengdu, China) weighing ~2.5 kg were used. Rabbits weighing less than 2.2 kg or over 2.8 kg, or in a state of pregnancy were excluded. Rabbits were acclimatized for a period of 7 days prior to the procedure with adequate food supply. Ultraviolet disinfection was applied on all tubes with coatings before intubation. Animal experiment was performed according to a protocol prepared before the study.

Measurement of physiological variables

Prior to anesthesia induction, oxygen was provided by face mask at 3 L/min for 5 min, an over-the-needle catheter (24 G) was placed percutaneously into a marginal ear vein, and a T-connection was attached. A further over-the-needle catheter (20 G) was placed percutaneously into the central auricular artery and connected to a T-connection (*Figure 2A* and *A-i*). The 20 G in the auricular artery was connected to a calibrated pressure transducer (zeroed level with the thoracic inlet) to obtain arterial systolic and diastolic blood pressure (SBP and DBP). After intravenous access was achieved, animals were anesthetized by intravenous propofol (bolus intravenous injection 10 mg/kg for anesthesia induction and continuous infusion 0.5 mg/kg·min for anesthesia maintenance). Physiological

variables including heart rate, respiratory rate, SBP, DBP, arterial oxygen saturation (SaO_2), and end tidal CO_2 concentration ($EtCO_2$) were monitored and recorded every 5 min after intubation.

Endotracheal intubation

Rabbits were randomly assigned to one of five groups to undergo endotracheal intubation and the operator was blinded to the type of ETTs (animal number in each group is over 5 to ensure the statistical significance): (I) control (n≥5), intubated with blank PVC tracheal tube; (II) LDC spay (n≥5), intubated with blank PVC tracheal tube after spraying 0.5 mL 2% LDC (total 10mg) at the site of laryngeal; (III) PLGA3000 + LDC-eluting (n≥5); (IV) PLGA6000 + LDC-eluting (n≥5); (V) PLGA10000 + LDC-eluting (n≥5). Rabbits from group (III) to (V) were intubated with LDC-eluting ETTs coated with corresponding PLGA MW, with the insertion depth of ETTs determined by measurement from the incisors to the thoracic inlet. After anesthesia induction, trans-oral endotracheal intubation was performed in the following way (*Figure 2A* and *A-i*): a guide wire (0.035-inch, 60 cm, Braun Medical, Germany) was introduced into the tracheal tube lumen and remained protruded 50 mm from the tip of the tube. With the guidance of pediatric laryngoscopy, the guide wire was placed into the trachea and the tube advanced over the wire. As the tube was properly placed, the guide wire was retrieved and the tube fixed with tape. An anesthesia circuit was connected to verify the placement of the ETT and ensure ventilation for both sides of the lungs by observing $EtCO_2$. Anesthesia was maintained with propofol according to the above-mentioned dose, and a supplemental bolus of propofol (7–10 mg each time) was intravenously injected when animals showed signs of severe cough or significant limb movements. Supplemental propofol was repeatedly administered if necessary. Intubation was successfully performed in all rabbits within an average of 4±2 min from anesthesia induction and ventilatory support was obtained from the animal ventilator (Dräger, Germany) during general anesthesia (respiratory rate: 49±7 per min).

Plasma LDC concentration measurement

Over the course of 5 h following intubation, a 1.0-mL blood sample was collected at each one-hour interval *via* an over-the-needle catheter to measure the plasma LDC concentration. Plasma was separated by centrifugation at 2,000 g for 15 min at 4 ℃ and stored at –80 ℃. The determination of LDC was performed with minor modifications using HPLC-MS/MS (Agilent 1260-6460, USA), and ropivacaine water solution (100 ng/mL) was used as an internal standard solution (IS). Plasma (5 μL) was diluted with 45 μL deionized water and 5 μL IS, then mixed with 150 μL acetonitrile and vortexed for 30 s, and a supernatant sample (100 μL) was isolated by centrifugation at 3,000 rpm for 10 min at 4 ℃.

Liquid chromatography analyses of LDC and the internal standards were performed on an Agilent Hillc C18 column (3.0×100 mm, 3.5 μm, Agilent, USA). The mobile phase consisted of 0.1% formic acid water solution: acetonitrile, 50:50 (v/v). An aliquot of a 1 μL supernatant sample was injected at a flow rate of 0.3 mL/min to give a total chromatographic run time of 6 min, and the column temperature was 30 ℃. Multiple-reaction monitoring (MRM) used the transitions of the protonated molecules at m/z 235.1 to m/z 86.1 for LDC, and the standard curve was made by LDC water solutions (R^2>0.9976).

Efficacy and safety evaluation of LDC-eluting ETT

During the 5 h period of anesthesia, supplemental propofol was administered by the above-mentioned protocol to ensure sufficient anesthesia and the total consumption of supplemental propofol within 5 h was recorded. After anesthesia, propofol infusion was stopped and the rabbits were allowed to gradually awaken. With the ETTs remaining in place, the rabbits were observed for signs of tube intolerance such as cough, head shaking, or pulling the tube, and upon occurrence, the tube was removed and the duration from being awake to tube removal was recorded. Among the groups, the variability in tube tolerance would result in different propofol consumption and a different duration for the tube to remain. Therefore, we set up two parameters to evaluate the efficacy of LDC-eluting ETTs: (I) the total consumption of supplemental propofol within 5 h; (II) post-anesthesia tube tolerance duration, which was defined as the duration from being awake to tube removal.

Subsequently, rabbits were either euthanized for histology assessment or followed-up for 7 days for safety evaluation to determine whether dyskinesia, ataxia, restlessness, and/or death occurred.

Histology assessment for tissue damage

After 5 h of intubation, animals were euthanized by an

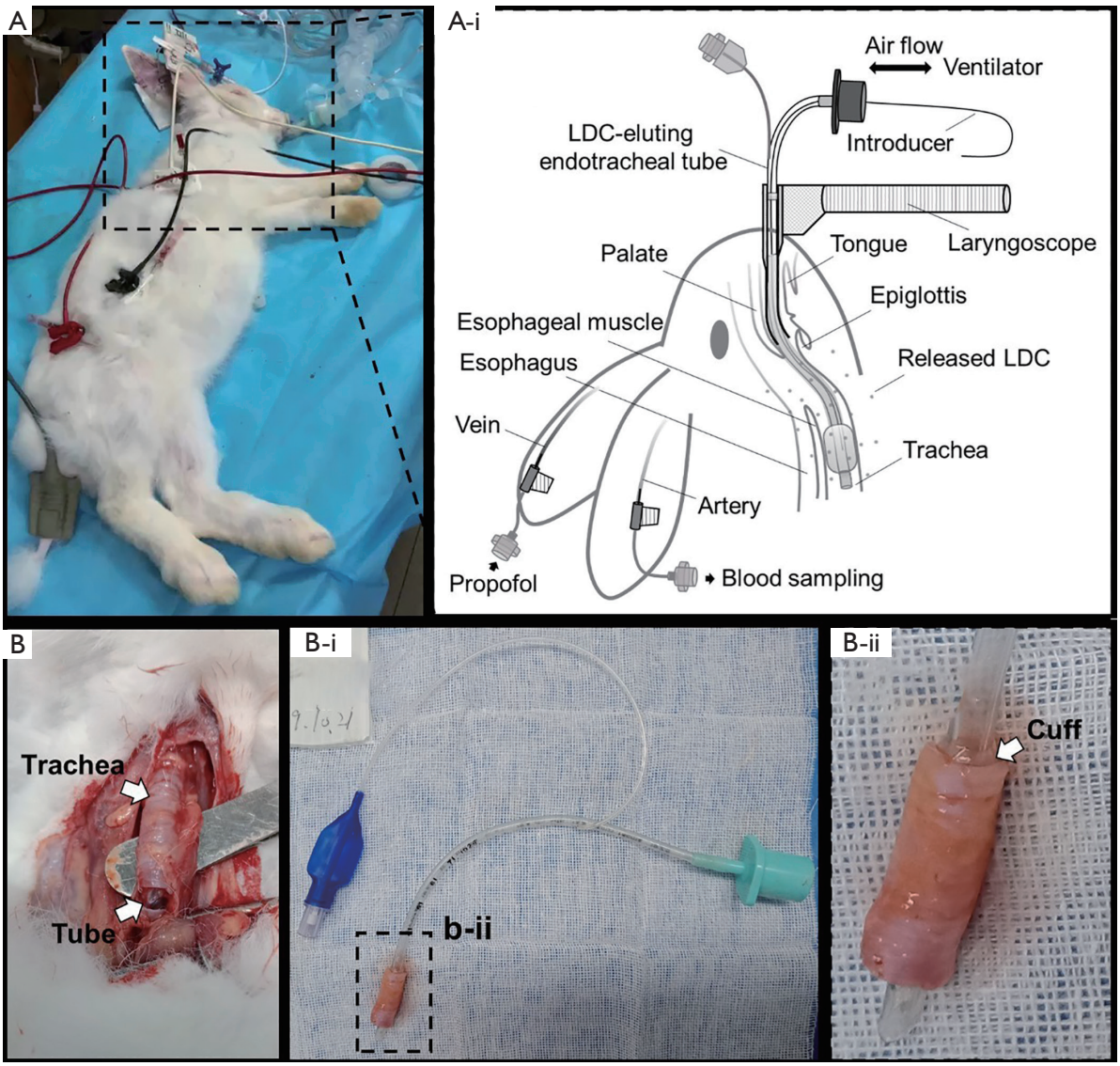

Figure 2 Schematic of the rabbit model used for the intubation test. Photo of intubated rabbit (A) and method (A-i). Trachea tissue attached to the tube cuff was harvested after experiment (B).

overdose of propofol (40 mg) (n≥3) for each group, and the tracheal tissue close to the cuff carefully excised (*Figure 2B*, *B-i*, *B-ii*). The harvested tissues were fixed in 4% paraformaldehyde for 3 days, then embedded in paraffin and cut into 5 μm sections. Hematoxylin and eosin (HE) staining of paraffin sections was performed for histological analysis and the sections were analyzed using Pannoramic MIDI FL digital slide scanner (3DHISTECH Ltd., Hungary) with CaseViewer software (3DHISTECH Ltd., Hungary). The mucosal thickness and cross-section area of tracheal mucosal edema were measured in four areas of each section, and the average mucosal thickness and edema area were calculated (n≥6).

Statistical analysis

GraphPad Prism (Version 8.0.2, GraphPad Software Inc.) was used for data analysis. All data were presented as mean ± standard error of the mean (SEM). Data were not included if the animals were dead due to the intubation

into esophagus. Group comparisons were performed using one-way ANOVA followed by Sidak post-hoc testing and a P value of less than 0.05 was considered statistically significant.

Results

Characterization and morphology of LDC-eluting ETT

As shown in *Figure 3A*, transparent LDC-eluting coatings were deposited onto the PVC discs by airbrush spraying with different times. The coating weight could be controlled by the spraying time, and ~5 mg/cm^2 coatings (~2.5 mg/cm^2 LDC) could be obtained by 10s (PLGA3000 + LDC and PLGA10000 + LDC) or 15s (PLGA6000 + LDC) spraying, which made the theoretical amount of LDC on each tube ~25.9 mg (coating area was estimated as 0.33 cm × 3.14 × 10 cm =10.36 cm^2). These spraying times were selected for the tube preparation (dashed line boxes in *Figure 3A* and *B*). The PLGA6000 + LDC sample showed the smoothest and most evenly distributed coating, compared with PLGA3000 + LDC and PLGA10000 + LDC (*Figure 3C*). The measured dose of LDC per area and loading dose on all tubes was 2.45–2.58 mg/cm^2 and 25.32–26.52 mg, respectively, which had no significance compared with coatings on PVC discs (Table S1). Although the coating weights were similar (*Figure 3D*), the coating thickness in PLGA3000 + LDC was significantly greater than PLGA6000 + LDC and PLGA10000 + LDC (P<0.01 and P<0.001 respectively, *Figure 3E*).

Chemical analyses of the drug-eluting coatings, pure polymers, and LDC were performed by RA-FTIR spectroscopy over a range of 4,000 to 500 cm^{-1} (*Figure 3F*). The drug-eluting coatings showed similar spectroscopic profiles compared to pure PLGA polymers (such as the characteristic O-C=O pick of PLGA at ~1,780 cm^{-1}), although with some minor differences. The emerged peaks at ~3,300 and ~1,500 cm^{-1} in all coatings may be attributed to the N-H stretching and N-H bending (Amide II) of LDC, respectively. The increasing absorption of each coating at ~2,850 and ~1,650 cm^{-1} corresponded to (N)C-H stretching and C=O bonds (Amide I) of LDC, respectively (24) and the characteristic peaks shared by coatings and LDC indicated the presence of LDC in the eluting coatings.

The water contact angle of PVC and each coating are shown in Figure S1. The significant decrease (P<0.01) in the water contact angles of the LDC-eluting samples indicated the successful deposition of PLGA and LDC, which are more hydrophilic than the PVC surface.

The SEM morphology of uncoated PVC and LDC-eluting coating ETTs are shown in *Figure 4A,B,C,D*. While PLGA3000 + LDC and PLGA6000 + LDC coatings demonstrated even distribution and smooth surfaces (*Figure 4B,C*), PLGA10000 + LDC showed uneven and gullied formation, which may be attributed to the higher MW of PLGA10000 polymer that provided a higher cohesive force of polymer chains (*Figure 4D*). The effect of DCM spraying on PVC tube was evaluated, and as shown in Figure S2, DCM has little influence on the PVC, although minor swelling could be observed under SEM.

In vitro release of LDC from coatings

The drug release profile from LDC-eluting coatings are shown in *Figure 5*. Initial burst release occurred within the first 4 h, which may be due to the diffusion of LDC on the coating surface. Higher MW PLGA was associated with a lower release rate: 56.0% and 46.6% LDC were released within the first 4 h from the PLGA3000 + LDC group and PLGA6000 + LDC group, respectively. In contrast, only 20.3% LDC was released from the coating of the PLGA10000 + LDC group, which was significantly lower than the PLGA3000 + LDC and PLGA6000 + LDC groups at 4 h (P<0.001 and P<0.05, respectively *Figure 5A*). As illustrated in *Figure 5B*, all LDC-coated groups achieved a sustained release for at least 5 days, while the higher MW of PLGA resulted in a significantly lower release rate (PLGA10000 + LDC < PLGA6000 + LDC < PLGA3000 + LDC). Approximately 48%, 56%, and 68% of the loaded LDC was released over 5 days of incubation from PLGA10000 + LDC, PLGA6000 + LDC, and PLGA3000 + LDC, respectively. Thus, the release rate and desired dose of LDC during intubation could be adjusted by controlling PLGA MW, which determines both the diffusion rate of loaded drug and degradation rate of the polymer.

In vivo drug release

LDC plasma concentration levels were measured at different time points post intubation (*Figure 6*). The peak plasma concentration of LDC in all drug-eluting groups was less than 1,400 ng/mL, which is much lower than the peak LDC plasma concentration by conventional intravenous administration [IV; e.g., 2,200±100 ng/mL (15)]. The LDC plasma concentration in the LDC spray group dropped

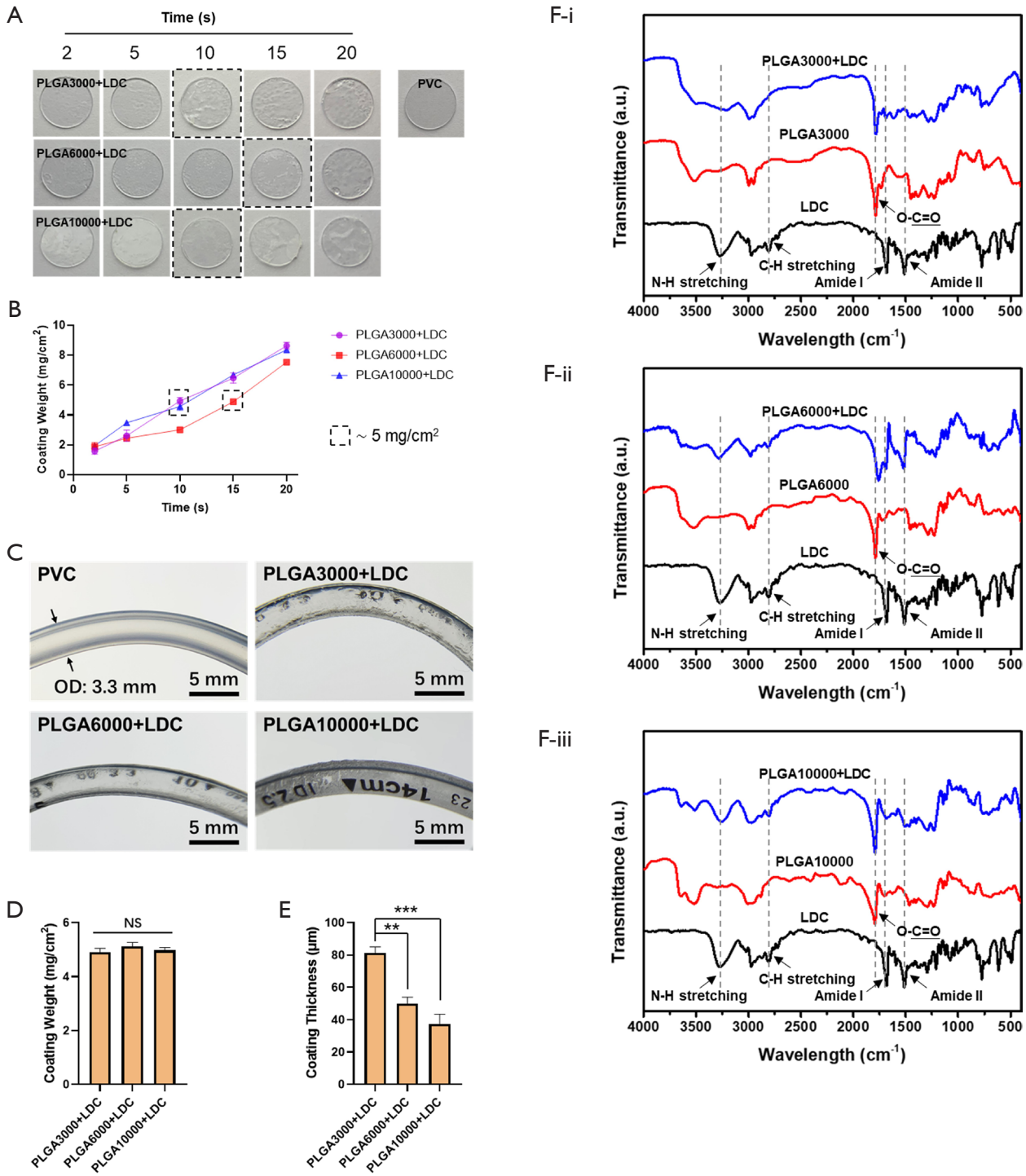

Figure 3 Characterization of LDC-eluting coatings. The images of LDC-eluting coatings prepared by airbrush spray with different times (A). The coating weight was spraying time-dependent, where 10 s spraying of PLGA3000 + LDC or PLGA10000 + LDC, and 15 s spraying of PLGA6000 + LDC obtained similar weight of coatings (~5 mg/cm^2, P>0.05, non-significance) (B). The images of LDC-eluting ETTs (C). The measured coating weight (D) and coating thickness (E) on ETTs. RA-FTIR spectra of LDC-eluting coatings (F-i: PLGA3000 + LDC; F-ii: PLGA6000 + LDC; F-iii: PLGA10000 + LDC). **, P<0.01; ***, P<0.001 (n≥5). LDC, lidocaine; PLGA, poly lactic-co-glycolic acid.

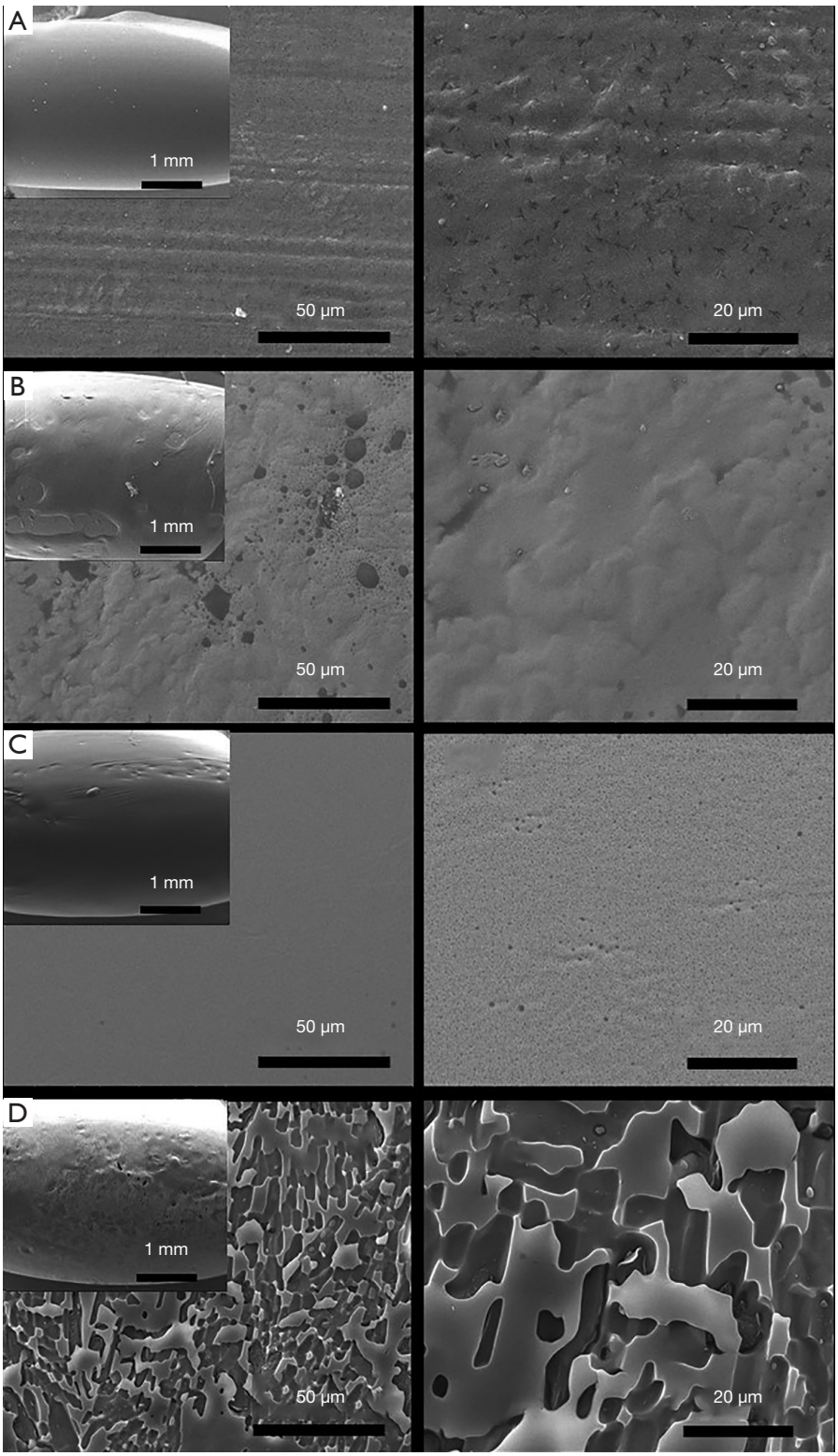

Figure 4 SEM morphology of endotracheal tubes. Uncoated PVC tube (A) and LDC-eluting coatings: PLGA3000 + LDC (B), PLGA6000 + LDC (C) and PLGA10000 + LDC (D). SEM, scanning electron microscopy; PVC, polyvinyl chloride; PLGA, poly lactic-co-glycolic acid; LDC, lidocaine.

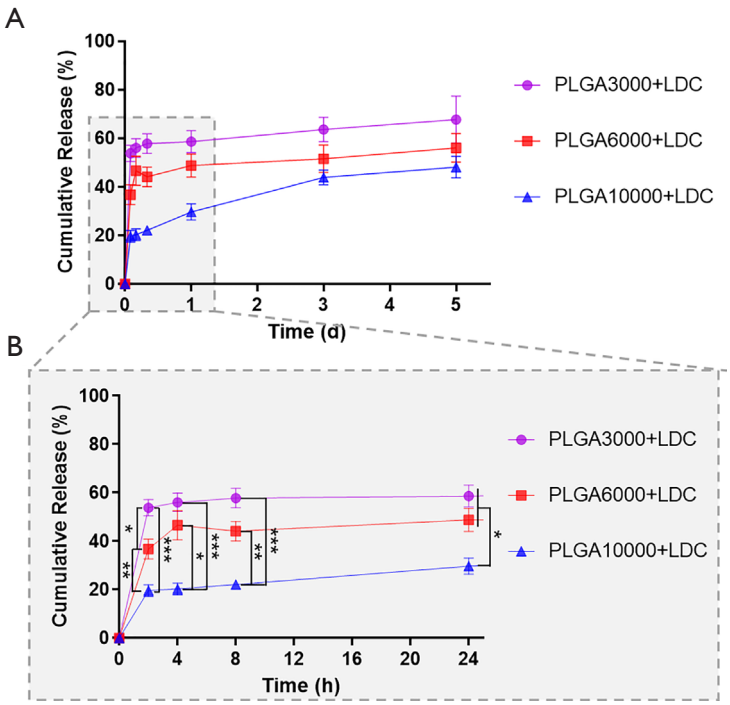

Figure 5 *In vitro* LDC release from coating. The cumulative release of LDC from PLGA3000 + LDC, PLGA6000 + LDC, and PLGA10000 + LDC in the first 5 days and 24 h. *, P<0.05; **, P<0.01; ***, P<0.001 (n≥5). PLGA, poly lactic-co-glycolic acid; LDC, lidocaine.

rapidly and was eventually not detected at 4 and 5 h, which was comparable to the control group. However, all LDC-eluting coated groups demonstrated sustained LDC release. In accordance with *in vitro* LDC release, PLGA3000 + LDC and PLGA6000 + LDC released more LDC than PLGA 10000 + LDC, and after 5 h intubation, the plasma LDC concentration in the PLGA6000 + LDC group was significantly higher than the PLGA 10000 + LDC (P<0.05) and LDC spray groups (P<0.01). However, there was no significant difference between PLGA3000 + LDC and the other groups.

Physiological variables

Physiological variables including SBP, DBP, and heart rate during 5 h of intubation are shown in *Figure* 7. Among all groups, the control group presented a trend of higher SBP, DBP, and heart rate throughout the intubation period, and compared with the control and LDC-spray group, all LDC-eluting groups had a trend of lower heart rate values. Despite having similar heart rate values as those in the LDC eluting groups in the first hour of intubation, the LDC spray group showed higher heart rate values from the second to the fifth hour and greater SBP from the third to the fifth hour than that in all LDC-eluting groups.

During the 5 h period of anesthesia, approximately 95% SaO_2 and 35–45 mmHg $EtCO_2$ were maintained and no significant differences in SaO_2 and $EtCO_2$ were seen among all groups (Figure S3), which revealed proper intubation depth and satisfactory respiratory function were maintained. No adverse events (e.g., dyskinesia, ataxia, restlessness, or death) were seen in any animals during the 7-day follow-up.

Efficacy and safety evaluation of LDC-eluting ETTs

Figure 8A demonstrates the total consumption of supplemental propofol of each group during intubation. Compared to the control group (113.3±6.7 mg) and LDC-spray group (76.2±4.2 mg), significantly less propofol was supplemented in the three LDC-eluting groups (44.7±6.1 mg in the PLGA3000 + LDC group, 34.7±6.5 mg in the PLGA6000 + LDC group, and 55.7±6.1 mg in the PLGA10000 + LDC group). Among the LDC-eluting groups, the PLGA 6000 + LDC group consumed the

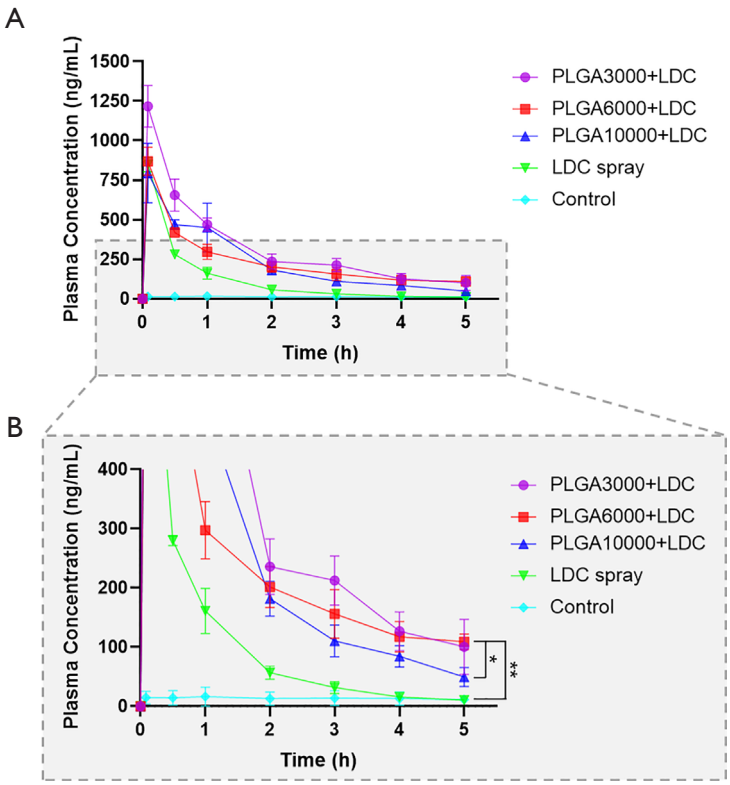

Figure 6 LDC plasma concentration-time profiles in intubated rabbits: full graph (A) and zoom in (B). *, P<0.05; **, P<0.01 (n≥5). LDC, lidocaine.

least propofol, which was significantly lower than the PLGA10000 + LDC group (P<0.05). The post anesthesia tube tolerance duration in each group is shown in *Figure 8B*. There was no significant difference between control and LDC-spray, which may be because oropharyngeal spray LDC has a limited drug action duration. A longer post anesthesia tube tolerance duration in LDC-eluting ETTs (44.9±7.7 min in the PLGA3000 + LDC group, 62.0±7.8 min in the PLGA6000 + LDC group, and 38.6±5.7 min in the PLGA10000 + LDC group) was in accordance with higher plasma LDC concentration compared to the control and LDC spray groups (6.9±1.9 and 7.5±1.4 min, respectively).

Intubation-associated tracheal tissue damage was evaluated by measuring the mucosal edema area and mucosal thickness. Rabbits without intubation presented the minimal mucosal edema area (6.2%±2.2%, *Figure 9A* and *B*) and a significantly increasing edema area was shown in the control and LDC-spray groups (37.7%±8.5% and 28.5%±5.6%, respectively, P<0.05. *Figure 9A*, *C* and *D*).

As demonstrated in *Figure 9A*, *E*, and *F*, the use of PLGA3000 + LDC and PLGA6000 + LDC-eluting ETTs were associated with a significant reduction in the edema area compared to the control and LDC-spray groups (11.4%±1.8% in PLGA 3000 + LDC and 7.8%±1.5% in PLGA 6000 + LDC *vs.* 37.7%±8.5% in control and 28.6%±5.6% in LDC-spray; P<0.05 and P<0.01, respectively). Among all LDC-eluting groups, the PLGA6000 + LDC group demonstrated the least edema area and the PLGA10000 + LDC group showed the greatest edema area (7.8%±1.5% *vs.* 30.4%±9.8%, P<0.05, *Figure 9A*,*F*,*G*). Despite the different degrees of tracheal mucosal edema, no significant differences were found in the mucosal thickness among all groups (*Figure 9H*).

Discussion

In this study, we presented a novel method based on the PLGA polymer to deliver LDC locally with the aim of increasing the drug concentration and prolonging the

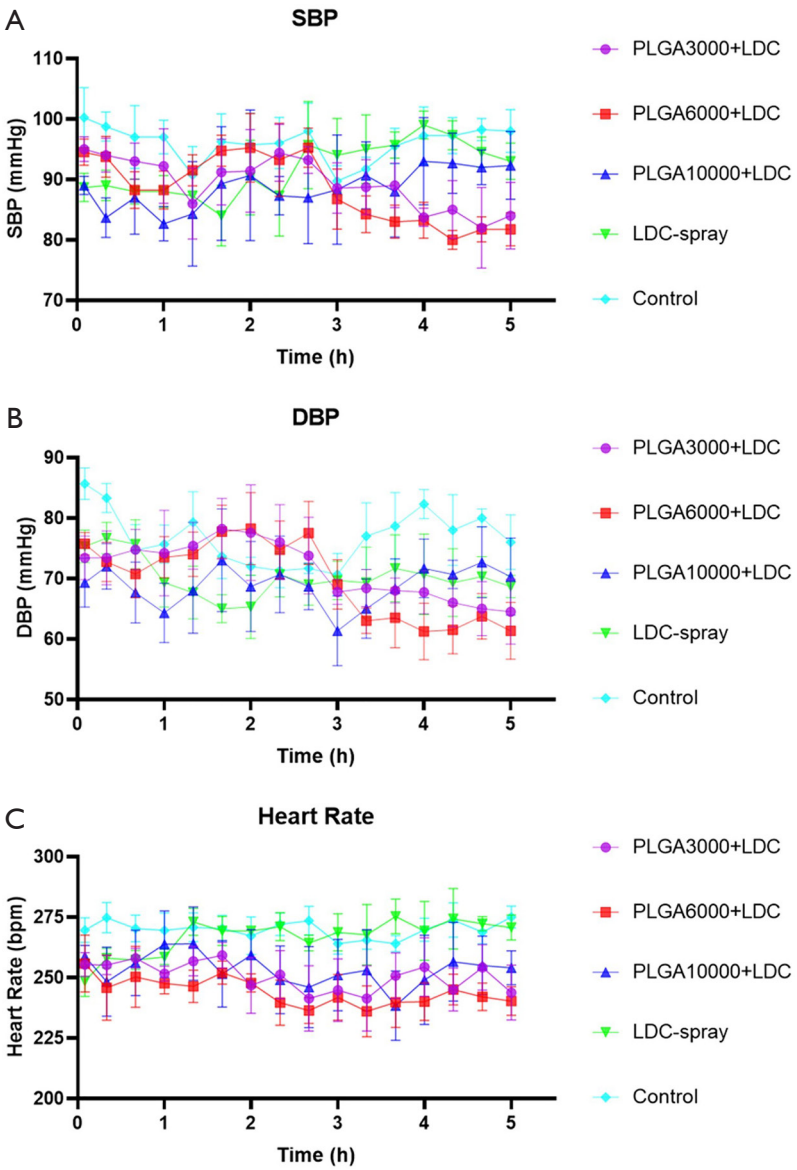

Figure 7 Physiological variables in intubated rabbits. (A) SBP, (B) DBP, and (C) heart rate in PLGA3000 + LDC, PLGA6000 + LDC, PLGA10000 + LDC, LDC-spray, and control groups at different points during 5 h of intubation (n≥5). SBP, systolic blood pressure; DBP, diastolic blood pressure; PLGA, poly lactic-co-glycolic acid; LDC, lidocaine.

anesthetic duration. Compared with uncoated tubes, the LDC-eluting tubes significantly attenuated the intubation-related airway response, improved tube tolerance, and reduced tracheal mucosal thickness. To our knowledge, this is the first study to apply drug release techniques to deliver local anesthetic agent on the surface of ETTs.

Endotracheal intubation is widely known as a critical procedure in the management of unstable patients with COVID-19. However, coughing of patients with COVID-19 during intubation can generate aerosols which increase the risk of cross-infection (1). Herein, our LDC-eluting ETT may benefit the protection of medical workers from hospital-acquired COVID-19 infection by reducing severe coughing.

The degradation rate and drug release profile of PLGA is influenced by several factors, including, but not limited

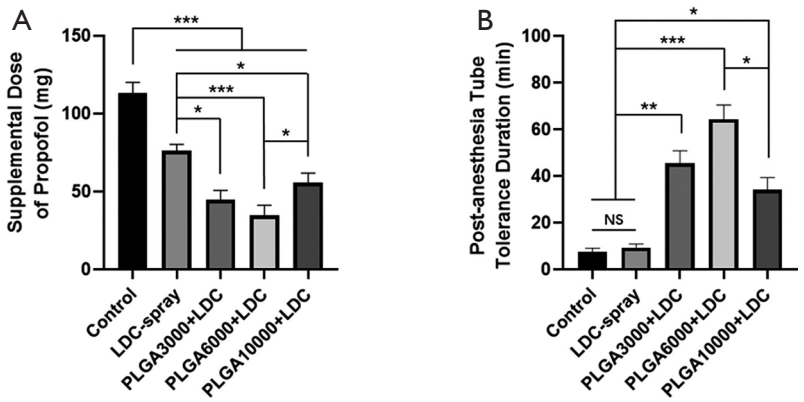

Figure 8 The enhanced anesthesia effect of LDC-eluting ETTs. (A) The supplemental dose of propofol in each group during intubation; (B) post-anesthesia tube tolerance duration. *, P<0.05; **, P<0.01; ***, P<0.001 (n≥5). LDC, lidocaine; ETTs, endotracheal tubes.

to, the initial MW, monomer composition ratio, drug properties, and processing method (25). The reason for selecting low MW PLGA polymers (MW: 3000–10,000; LA/GA ratio was fixed to be 50:50) in this study is based on the clinical needs for ETTs and endotracheal anesthesia. Generally, the retaining time of ETTs is from several hours to days, which requires PLGA polymers to provide rapid drug release to inhibit an intubation-related airway response and the sustainable release of a considerable amount of LDC to maintain an anesthetic effect. For a typical LDC administration for endotracheal intubation, the total dose of LDC can be as high as 200–500 mg for intracuff (26), or 40–50 mg for LDC-gel lubrication (27,28). However, the duration of action was less than 1.5 h or 30 min, respectively. Although a larger MW PLGAs could prolong drug release for weeks, it will delay the onset time of local anesthetic and not meet the clinical needs of rapid anesthesia. Moreover, the MW of PLGA significantly influences the physical properties of PLGA copolymers as the glass transition temperature (Tg) of PLGA decreases with decreasing MW. Thus, low MW PLGA are softer than common PLGA, which was well-known to be "stiff" (29,30).

Several studies have reported biodegradable nanofiber membrane for the sustainable release of LDC significantly relieves the pain from surgical wounds or bone fractures in animal models (31-33). In our study, we set up the ratio of PLGA-to-LDC as a 1:1 mixture to facilitate higher amounts of LDC and more rapid drug release (33). The total dose of loaded LDC on the surface of size 2.5 tubes was 26.52± 0.80 mg, which was significantly higher than sprayed LDC (~10 mg) for a ~2.5 kg rabbit. Theoretically, ~70 mg LDC can be loaded on patient used tubes (e.g., size 7.0, PLGA6000 + LDC, Table S1), and although some studies reported that more lidocaine can be instilled into the cuff of an ETT [e.g., 200 mg for patient (26)], the concentration of diffused LDC was extremely low (17 μg/mL for 200 mg intracuff LDC in 20 mL distilled water after 60 min) and the anesthetic effects were limited (34). The *in vitro* drug release in this study was 5.4~14.9 mg LDC in the first 4 h, which was much greater than the diffused amount of intracuff LDC and would be adequate to provide a topical anesthetic effect (*Figure 5B*). Clinically, lidocaine can be safely administered by bolus injection of 50–100 mg for ventricular arrhythmia treatment. As the dose of lidocaine on the surface of ETTs is much less than the clinically used dose, it will not cause overdose and, if needed, higher amounts of LDC can be deposited on tubes easily.

The *in vitro* study showed that the LDC release from each coating extended over 5 days, which meets the need of most patients receiving common surgeries under general anesthesia and endotracheal intubation. For long-term intubation, such as required in patients undergoing major surgeries or suffering from respiratory failure, additional replacement of LDC-eluting ETT can easily be performed to achieve an additional 5 days of topical anesthetic effect, which is also recommended for prolonged mechanical ventilation (>10–14 days) (35-37). The *in vitro* study was translated to sustained release onto the surface of the trachea and into the plasma of our rabbit model. As LDC-spray is the most used local anesthetic approach, we set up one LDC-spray group in this study to simulate LDC use in clinical practice, and *in vivo* plasma drug concentration testing revealed that LDC-spray lasted less than 3 h. In contrast, LDC-eluting coatings allowed a longer duration

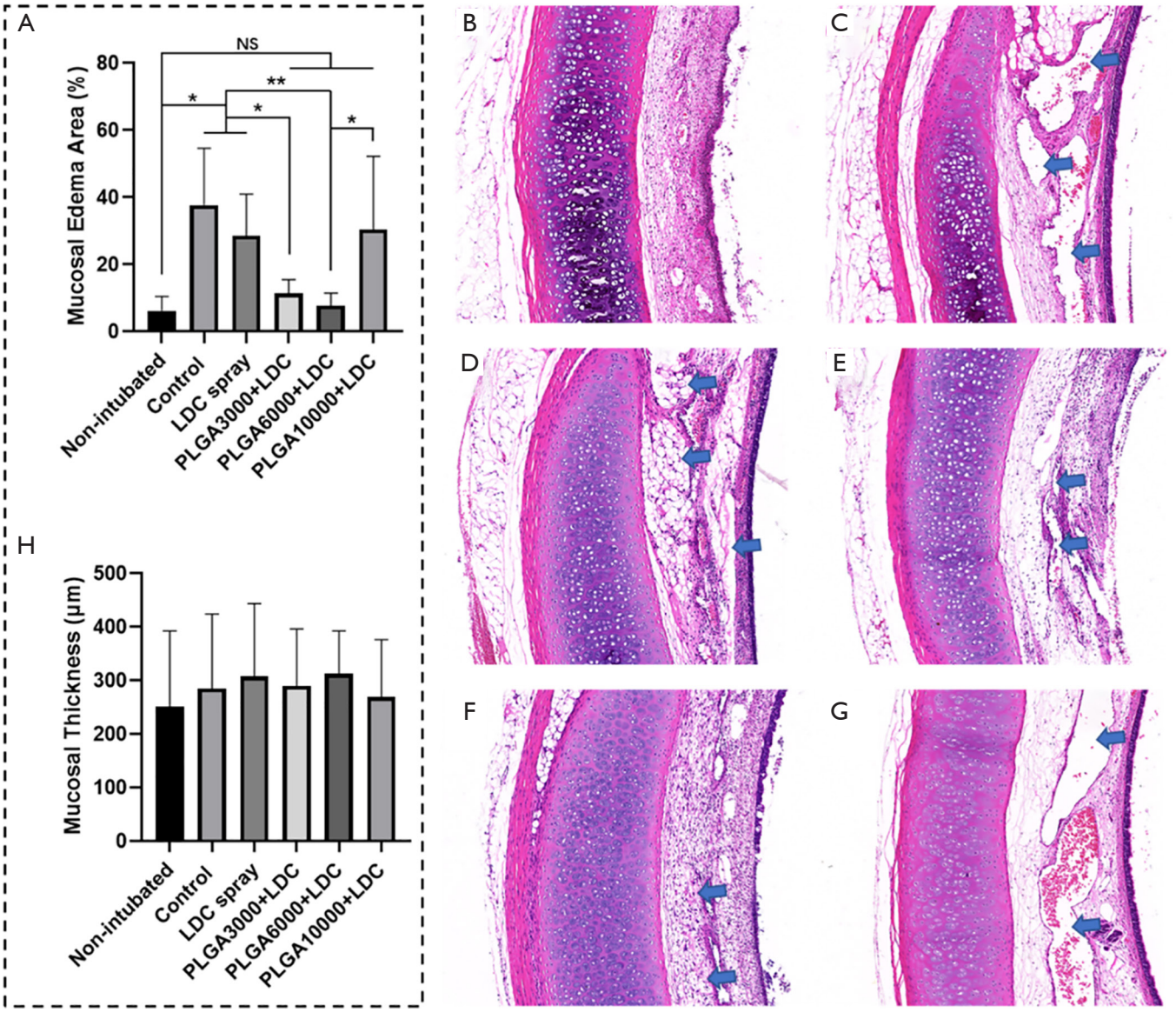

Figure 9 Representative HE stained sections of trachea tissue (×100). (A) Cross-section area of tracheal mucosal edema, (B) non-intubated, (C) control (uncoated tube), (D) LDC spray, (E) PLGA3000 + LDC, (F) PLGA6000 + LDC, (G) PLGA10000 + LDC. Blue arrows indicate the mucosal edema. (H) Tracheal mucosal thickness. *, P<0.05; **, P<0.01 (n≥5). PLGA, poly lactic-co-glycolic acid; LDC, lidocaine.

of LDC release (at least 5 h), and this trend was more significant in the PLGA6000 + LDC group which exhibited higher plasma drug concentration than in the PLGA10000 + LDC group. Additionally, all the LDC-eluting coatings manifested the characteristics of "eruptive" drug release, which conformed to the requirement of rapid anesthesia for avoiding an airway response in the intubation procedure (*Figure 6*).

Corresponding to higher drug concentration and longer effective duration, the animals that received LDC-eluting tube intubation had dramatically less propofol consumption and significantly longer post-anesthesia tube tolerance duration (*Figure 8*). In addition, records of physiological variables revealed that the three LDC-eluting groups experienced more stable hemodynamic parameters (HR, SAP, and DAP) compared to the control and LDC spray groups (*Figure 7*). These results may be attributed to the superior LDC coating-related anesthetic effects.

Clinically, tracheal damage and tissue edema are important factors resulting in intubation-related complications. Histological assessment in this study demonstrated there were no significant differences in mucosal thickness in all groups (*Figure 9H*). Interestingly, less mucosal edema area was found in the PLGA3000 + LDC and PLGA6000 + LDC groups compared to the control, LDC-spray, and PLGA10000 + LDC groups (*Figure 9A*). The mechanism underlying the reduced edema area in the PLGA3000 + LDC and PLGA6000 + LDC groups may be related to less motion from the animals due to the superior anesthesia effects. Despite a similar anesthesia effect to the other LDC-eluting groups, the PLGA10000 + LDC group had a greater edema area, which might be due to the material features of PLGA10000. The morphological assessment from SEM revealed that PLGA10000 + LDC presented a more irregular surface (*Figure 4D*), which might result in an adverse airway response and cause mucosal edema. Of all the LDC-coated ETT groups, the PLGA6000 + LDC group showed the most uniform coating, which may be associated with the physical property of PLGA6000, which is less 'sticky' than PLGA3000 and not as 'crisp' as PLGA10000 (*Figure 4*). Therefore, the development of soft polymer coatings with self-lubricating and drug-releasing functions could be a direction for future research. Moreover, the co-delivery of local anesthetics and anti-inflammatories from ETTs is also worthy of further study.

Conclusions

An LDC-eluting coating based on PLGA on the surface of ETT provides rapid and sustained drug release, reduces tracheal tissue damage, and improves intubation tolerance, and due to its appropriate material features, PLGA6000 + LDC is suitable to serve as an LDC delivery coating. This study provides an innovative attempt and presents a potential treatment approach for the care of patients undergoing intubation.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-1930

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-1930). Dr. Jing Lu and Dr. Lei Lu report that patent application is pending with the number CN111035815. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee and animals were treated in accordance with the Guide for the Care and Use of Laboratory Animal of the US National Institutes of Health (NIH).

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Supplementary

Table S1 The loaded dose of LDC-eluting coatings on PVC discs and size 2.5 endotracheal tubes

Coating	PVC discs		Endotracheal tubes	
	Dose per area* (mg/cm^2)	Loading dose** (mg)	Dose per area* (mg/cm^2)	Loading dose** (mg)
PLGA3000 + LDC	2.47±0.11	25.63±1.18	2.49±0.09	25.32±0.70
PLGA6000 + LDC	2.44±0.06	25.31±0.63	2.58±0.09	26.52±0.80
PLGA10000 + LDC	2.35±0.09	24.36±0.97	2.45±0.04	25.78±0.56

*: Dose per area = (Loading dose/coating area); **: Loading dose = coating weight/2; coating area was estimated as: 0.33 cm × 3.14 × 10 cm =10.36 cm^2. Data are represented as mean ± SEM, n≥5.

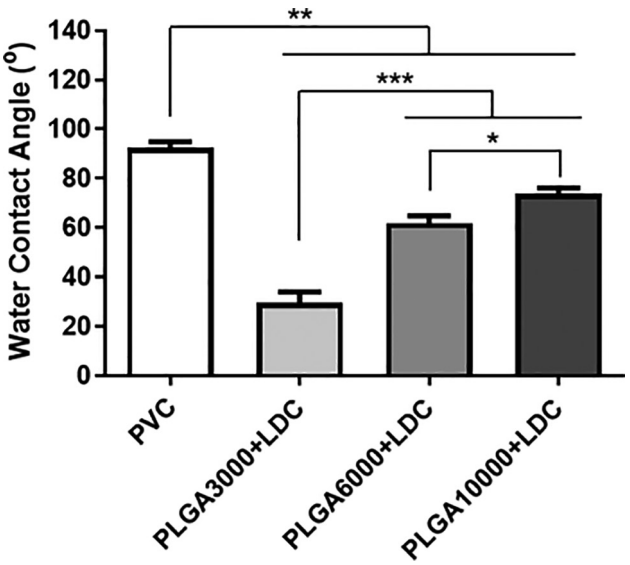

Figure S1 Water contact angles of the PVC, PLGA3000 + LDC, PLGA6000 + LDC, and PLGA10000 + LDC surfaces. Data are represented as mean ± SEM, n≥5. The significance was evaluated for *P<0.05, **P<0.01, ***P<0.001.

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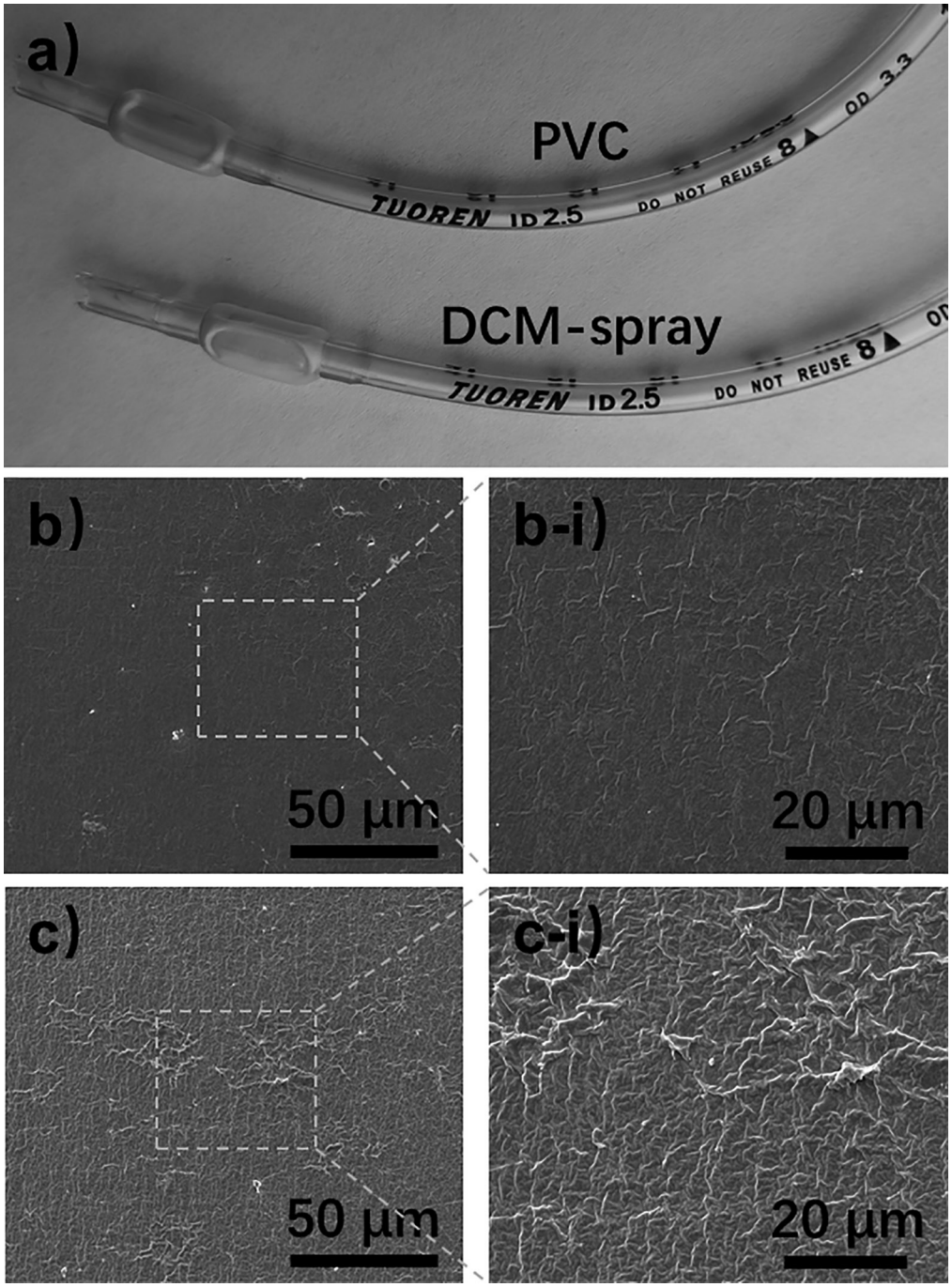

Figure S2 Images and SEM morphology of uncoated PVC tube and tube with DCM spraying for 15 s. Both tubes remain transparent (A). Compared with uncoated PVC tube (B), only minor swelling due to the DCM can be observed under SEM (C). The representative area of the highest degree of swelling due to the DCM was observed (C-i).

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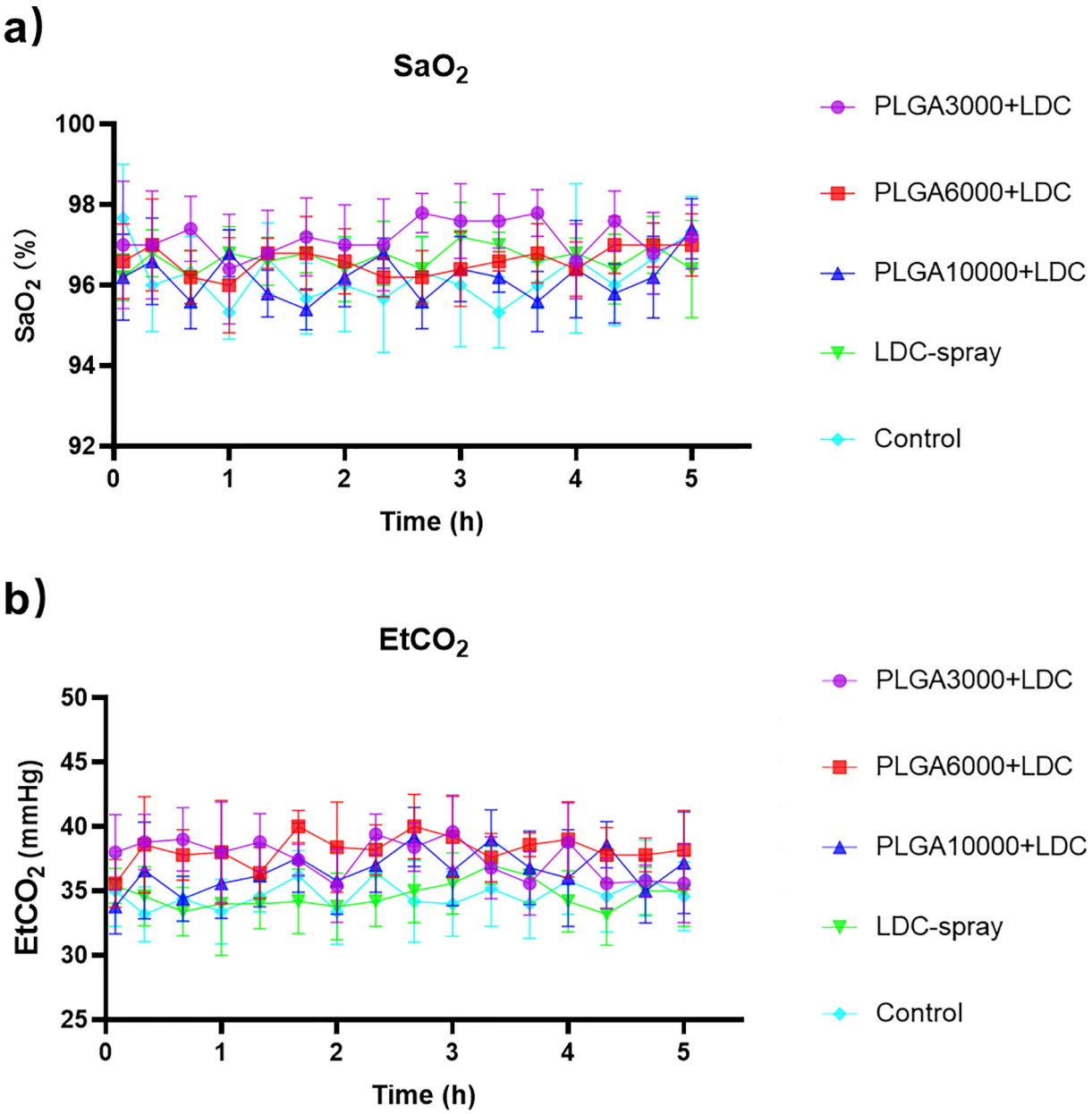

Figure S3 SaO2 and EtCO2 variables in different groups during 5 h of intubation. (A) SaO2; (B) EtCO2. Data are represented as mean ± SEM, n≥5.

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