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ORIGINAL RESEARCH

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Effect of continuous local dexamethasone on tissue biomechanics and histology after inhalational burn in a preclinical model

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Abstract

Objective: Inhalational burns frequently lead to dysphonia and airway stenosis. We hypothesize local dexamethasone delivery via a novel drug-eluting electrospun polymer-mesh endotracheal tube (ETT) reduces biomechanical and histologic changes in the vocal folds in inhalational burn.

Methods: Dexamethasone-loaded polymer mesh was electrospun onto ETTs trimmed to transglottic endolaryngeal segments and secured in nine Yorkshire Cross-breed swine with directed 150°C inhalation burns. Uncoated ETTs were implanted in nine additional swine with identical burns. ETT segments were maintained for 3 and 7 days. Vocal fold (VF) structural stiffness was measured using automated-indentation mapping and compared across groups and to four uninjured controls, and matched histologic assessment performed. Statistical analysis was conducted using two-way ANOVA with Tukey's post hoc test and Wilcoxon rank-sum test.

Results: VF stiffness after burn decreased with longer intubation, from 19.4 (7.6) mN/mm at 3 days to 11.3 (5.2) mN/mm at 7 days ($p < .0001$). Stiffness similarly decreased with local dexamethasone, from 25.9 (17.2) mN/mm at 3 days to 18.1 (13.0) mN/mm at 7 days ($p < .0001$). VF stiffness in the dexamethasone group was increased compared to tissues without local dexamethasone ($p = .0002$), and all groups with ETT placement had higher tissue stiffness at 3 days ($p < .001$). No significant change in histologic evidence of epithelial ulceration or fibrosis was noted, while an increased degree of inflammation was noted in the dexamethasone group ($p = .04$).

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Conclusion: Local dexamethasone delivery increases VF stiffness and degree of inflammation compared to uncoated ETTs in an acute laryngeal burn model, reflected in early biomechanical and histologic changes in an inhalational burn model.

KEYWORDS
endotracheal intubation, laryngeal burn, laryngeal injury, local drug delivery

1 | INTRODUCTION

Inhalation burn injuries are estimated to affect 10% of all burn patients, and are associated with a high rate of prolonged intubation and tracheostomy in both adult and pediatric populations.[1,2] Passive airflow patterns and glottic barrier function to protect the distal airway are thought to concentrate both thermal injury and irritant gas inhalation to the endolarynx.[3,4] This results in a reported 50%–70% of patients left with pronounced endolaryngeal and tracheal scarring which can lead to long-term complications including dysphonia, dysphagia, and airway stenosis.[1,5] Frequently, such patients often have significant additional injuries requiring prolonged intubation, which is thought to increase risk of sequelae, such as posterior glottic, subglottic, and tracheal stenosis.[6] While both endoscopic and open surgical techniques exist to treat airway stenosis, these treatments frequently require multiple operations and are often unable to reverse dysphonia.[7–9] Increasing emphasis is being placed on preventing airway stenosis, primarily by appropriate endotracheal tube (ETT) sizing, consideration of early tracheostomy, and reducing laryngeal irritation and inflammation via systemic therapies, such as anti-reflux therapy and steroids. However, these medical therapies confer systemic side effects which may require additional medical management or even preclude their use. Currently, no methods for local drug delivery, outside of direct tissue injection, have been explored in the setting of laryngeal burn injury.

Drug-eluting biomaterials have been used in a variety of medical settings to provide controlled release of therapeutics limited to local tissues.[10–12] Importantly, these biomaterials are often combined with other required medical management such as bandages or stents. Topical biomaterials are beginning to be examined for laryngeal or airway injury, particularly with using ETTs for drug delivery.[13–18] However, while multiple animal models exist for laryngeal burn, drug-eluting ETTs have not been examined in this context.[19–21] Prior work by these authors has established standard ETTs may be coated with biocompatible, biodegradable polyester that, when impregnated with various medical therapies, diffuse medication at a steady rate for more than 4 weeks.[22] We hypothesize topical delivery of steroid to injured laryngeal tissue will reduce acute local tissue inflammation and help keep biomechanical tissue properties closer to those of native tissue. The goal of this study was to evaluate the effect of prolonged local dexamethasone delivery to the endolarynx via these drug-eluting ETTs using a previously-established swine laryngeal burn model.[19,21]

2 | MATERIALS AND METHODS

The current study was approved by the U.S. Air Force 59th Medical Wing Institutional Animal Care and Use Committee (protocol FWH20210102AR). Thirty-six Yorkshire crossbreed swine underwent direct laryngoscopy and laryngeal burn injury. After laryngeal burn, animals underwent endoscopic, transglottic implantation of ETT segments, with nine animals receiving standard ETTs and nine receiving dexamethasone-eluting tubes for either three or 7 days. There were five animals in each group observed for 3 days and four in each group observed for 7 days. At the end of these timepoints, animals were euthanized and larynges harvested. All laryngeal specimens underwent biomechanical testing followed by histologic analysis.

2.1 | ETT coating

Dexamethasone-loaded polycaprolactone (PCL) fibers were deposited on the surface of the ETTs via electrospinning.[23] Briefly, PCL (Mw = 80,000) was dissolved in chloroform (15:85 weight/weight [w/w]). Dexamethasone sodium phosphate was added to the homogeneous mixture at a concentration of 10% (w/w) of the total polymer mass along with ethanol used as its solvent. The solution was loaded into a Luer Lock syringe and dispensed from a blunt needle using a pump (Pump11 Elite, Harvard Apparatus, Holliston, MA) at an infusion rate of 1.8 mL/h. A 5 cm section of ETT (7–0, Aircare®) was positioned on a rotating (300 rpm) collector 20 cm below the needle tip where a voltage of 20 kV was applied (Gamma High Voltage Research, Ormond Beach, FL). The final 5 cm segment was then sterilized with ethylene oxide prior to implantation (Figure 1A). Steady dexamethasone elution from these PCL-coated ETTs has been previously validated and described.[22] All chemicals were purchased from Sigma-Aldrich (St. Louis, MO).

2.2 | Surgery and management

Animals were anesthetized via intramuscular Telazol® and ketamine 2.2 mg/kg and maintained using isoflurane during direct laryngoscopy and subsequent laryngotracheal burn injury. Analgesia was provided with buprenorphine 0.01–0.05 mg/kg intramuscularly. Each animal then underwent direct laryngoscopy with preoperative photodocumentation (Figure 1C).

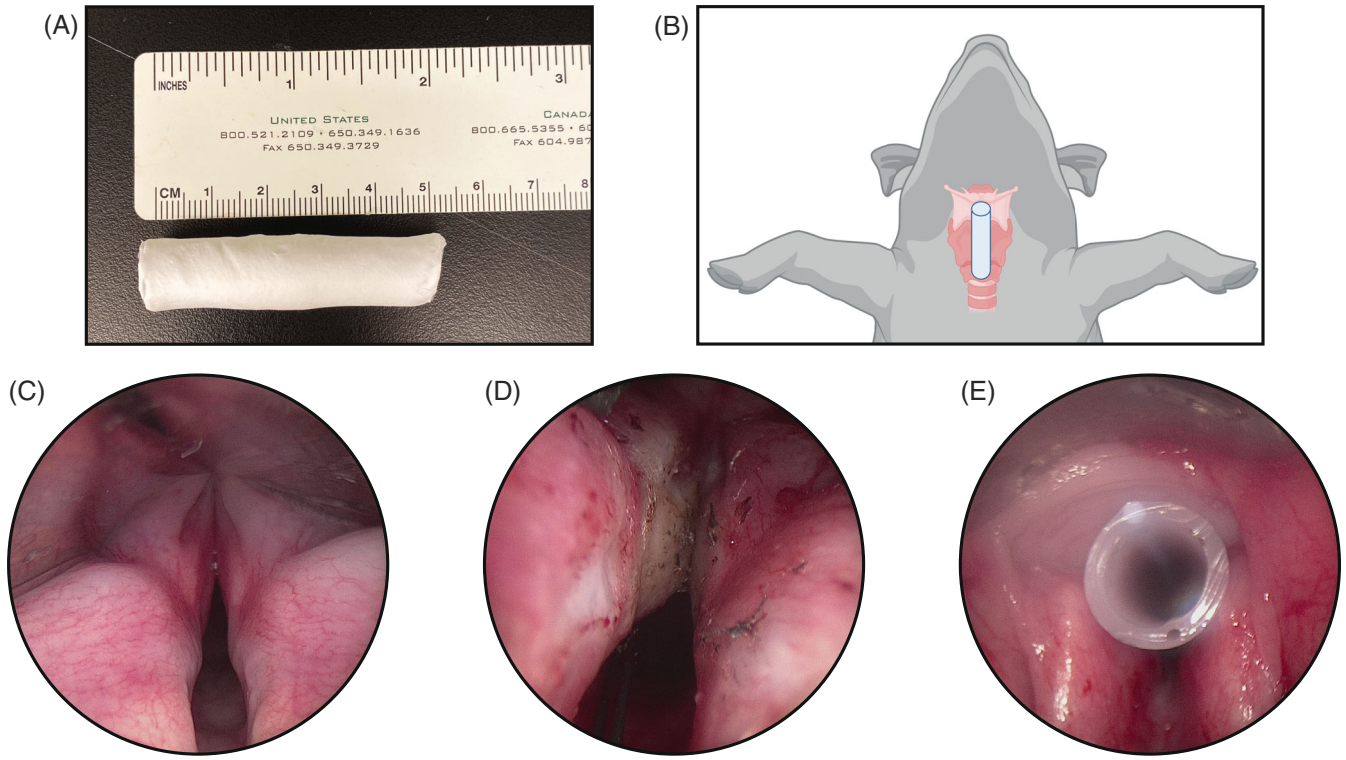

FIGURE 1 (A) A 5 cm segment of dexamethasone-loaded PCL fibers coated on endotracheal tube (ETT) surface; (B) Diagram of ETT placement within larynx in coronal orientation; Intraoperative appearance of endolarynx before burn injury (C), after burn injury (D), and after ETT placement (E).

2.3 | Laryngeal burn

Laryngeal burn injuries were performed in the anesthetized swine immediately after direct laryngoscopy and before the laryngeal ETT segment was placed using our previously validated laryngeal burn injury device.[19] Heated air at 150°C–160°C was administered to the spontaneously breathing swine larynx in 30 s intervals for 5 min at a rate of 5–10 mL/min, with endoscopic visualization and photodocumentation of the burn extent following completion of the burn (Figure 1D).

2.4 | ETT segment placement

Transglottic stents simulating ETT placement were placed in all animals. During direct laryngoscopy, a second surgeon was present at the neck to assist with ETT segment placement. The anterior cervical area was prepped with povidone-iodine solution, and 1% lidocaine with 1:100,000 epinephrine injected at the level of the cricoid cartilage. A 3–4 cm midline incision was created, and blunt dissection was performed down to the cricoid cartilage and the cricothyroid membrane to expose the first three to four tracheal rings. Two 16-gauge angiocatheter needles were passed into the larynx under endoscopic visualization, one through the cricothyroid membrane and the second between the first and second tracheal rings. A urologic snare (Amplatz Gooseneck Microsnare Kit, Medtronic PLC, Minneapolis, MN) was then passed through each angiocatheter and out through the mouth. The surgeon performing direct laryngoscopy passed a 2–0 polypropylene suture through the distal end of the ETT segment and subsequently secured each end of the suture to the snares, which were then retracted back through the angiocatheters and through the neck. The sutures were pulled taut while the ETT segment was advanced into the larynx, resulting in the inferior edge of the ETT segment being secured in the subglottis and the superior segment protruding just past the petiole of the epiglottis in the supraglottic region. Transglottic ETT placement was confirmed under endoscopic visualization (Figure 1E). The ETT sutures were secured to the neck over an external button just superior to the skin incision, and the cervical incision was closed in layers using 4–0 polygalactin suture and Dermabond. Transglottic ETT segment placement is diagrammed in Figure 1B. Post-operatively, each animal was monitored hourly for respiratory status for the first 4 h after surgery, every 4 h for the next 20 h, and then at least twice daily until study completion.

2.5 | Euthanasia and specimen preservation

Animals were euthanized at the designated postoperative euthanasia date or sooner if required due to animal distress or illness. Euthanasia was performed after general anesthesia induction with intravenous pentobarbital (100 mg/kg) and confirmed via vital sign monitoring according to institutional protocol. The larynx was extracted immediately after euthanasia and sectioned in the sagittal plane, with care taken to preserve the anterior commissure.[24–26] Specimens were then frozen at −80°C until biomechanical and subsequent histologic analysis.

2.6 | Biomechanical analysis

In addition to samples collected during this study, control larynges without injury or ETT placement ($n = 4$) were also collected via tissue sharing agreement to allow comparison of biomechanical properties to healthy tissue. Larynges were thawed, fixed within a Plaster of Paris mold, and submerged in phosphate buffered saline (PBS) to maintain moisture.[27] Each specimen was positioned beneath a camera to align a template with predetermined indentation points along the entire glottis and subglottis (Figure 2A). Normal indentation was conducted using a Biomomentum Mach-1 v500css (Laval, Quebec, Canada) with a 1.5 N uniaxial load call as previously established.[26,27] For our evaluation, a 2 mm spherical indenter tip with a velocity of 1.2 mm/s and indentation depth of 0.3 mm was used. The structural stiffness values were calculated from the slope of the linear region of the normal indentation force versus displacement curves. Indentation points along the vocal fold were isolated as shown in the inset displayed in Figure 2A to better evaluate mechanical properties of a consistent region across all samples.

2.7 | Histologic slide preparation and scoring

After biomechanical testing, laryngeal tissues were sectioned into 5 mm sections along the mid-region of the true VF. Samples were fixed in 4% formalin solution, mounted in disposable embedding molds filled with optimal cutting temperature compound (Scigen Tissue Plus O.C.T. Compound, Thermo Fisher Scientific, Waltham, MA), and stored at −80°C prior to sectioning. Frozen tissue segments were cut into 14 µm sections using a cryostat (Epredia™ NX70, Kalamazoo, MI), thaw-mounted on glass slides, and subsequently stained with hematoxylin and eosin (H&E). Stained tissue slides were imaged with MoticEasyScan Pro 6 Slide Scanner (Motic Instruments, Schertz, TX) at 20× magnification.

H&E-stained slides were independently and blindly reviewed by two pathologists (Lisa Marinelli and Christine M. Lee) for the assessment of epithelial ulceration, inflammation, and fibrosis. Values with a discrepant assessment of more than one point were re-reviewed by both pathologists in order to achieve consensus. Epithelial ulceration and fibrosis were graded on a five-point scale based on the percentage of ulcerated surface epithelium and fibrotic submucosa inferior to the vocalis muscle, respectively (0: 0%, 1: 1%–25%, 2: 25%–50%, 3: 50%–75%, 4: 75%–100%). The degree of inflammation was graded on a three-point scale (1: mild, 2: moderate, 3: severe).

2.8 | Statistical analysis

The structural stiffness outcomes are reported as mean (standard deviation). Kruskal–Wallis one-way analysis of variance (ANOVA) testing was performed for ETT Type followed by Dunnett's test for multiple comparisons in SigmaPlot (v 14.5 for Windows, Palo Alto, CA). For histologic assessment, outcomes are reported as median (range) and differences between median scores were evaluated using Wilcoxon rank-sum test using MATLAB R2021b (MathWorks Inc., Natick, MA).

3 | RESULTS

3.1 | Structural stiffness

Control animals not undergoing ETT implantation or endolaryngeal injury had VF stiffness of 13.5 (7.1) N/m. In animals implanted with regular ETTs, VF stiffness after burn decreased with longer intubation time from 19.4 (7.6) N/m at 3 days to 11.3 (5.2) N/m at 7 days ($p < .001$). A similar decrease in VF stiffness after burn was also observed in the groups treated with dexamethasone-delivering ETTs, from 25.9 (17.2) mN/mm at 3 days to 18.1 (13.0) mN/mm at 7 days ($p < .0001$). The laryngeal tissue stiffness was significantly higher in

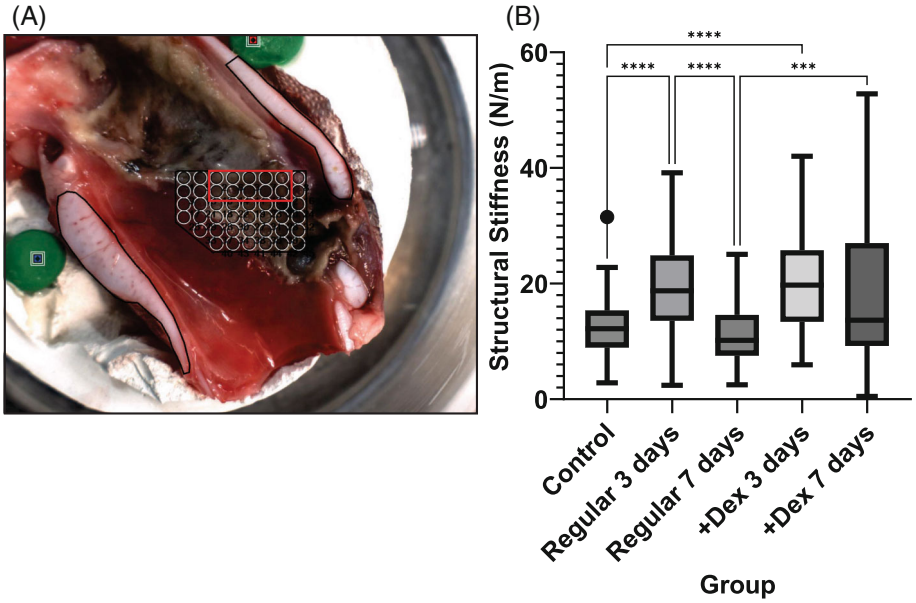

FIGURE 2 (A) Bisected larynx cast in Plaster of Paris with overlaid indentation points and region highlighted for analysis along the true vocal fold. (B) Structural stiffness of control and burned airway tissues with dexamethasone-coated and regular endotracheal tubes after three and 7 days. Statistically significant differences are indicated by * ($p < .05$), ** ($p < .01$), *** ($p < .001$), and **** ($p < .0001$).

burned tissue with both ETT placement groups at 3 days in comparison to the uninjured control ($p < .001$), but differences were no longer statistically significant at 7 days. While there was no difference in VF stiffness between treatment groups after 3 days of intubation, VF stiffness in the continuous dexamethasone delivery group was increased compared to tissues without local dexamethasone at 7 days ($p = .001$). Structural stiffness outcomes are summarized in Figure 2B.

3.2 | Histological analysis

Median epithelial ulceration scores of 0 (range 0–2) at 3 days and 0 (0–1) at 7 days were observed in tissues exposed to regular ETTs. This was not significantly different from tissues treated with dexamethasone coated ETTs, with median epithelial ulceration scores of 0.5 (0–1) at 3 days and 0 (0–2) at 7 days ($p = 1$ at 3 days, $p = .87$ at seven days). Extent of fibrosis was similarly unchanged between timepoints, with median scores of 1 (1–1) at 3 days and 1 (1–2) at 7 days in tissues exposed to both regular and dexamethasone-eluting ($p = 1$). Degree of inflammation was increased in the groups treated with dexamethasone, as groups treated with regular ETT having median inflammation scores of 1 (1 – 3) at 3 days and 1.5 (1 – 2) at 7 days as compared with 2.5 (1 – 3) at 3 days and 3 (2 – 3) at 7 days in the dexamethasone group. These differences did not achieve statistical significance at 3 days ($p = .71$) but did at 7 days ($p = .04$). Representative histologic changes in depth of epithelial ulceration and increased inflammation and fibrosis are demonstrated in Figure 3 and histologic scoring is summarized in Table 1.

4 | DISCUSSION

Patients suffering inhalational burns have a high likelihood of developing airway stenosis, which is further increased with the need for prolonged intubation.[1,2,5,6] While topical therapies to reduce airway scarring—particularly using drug-eluting ETTs—have begun to appear

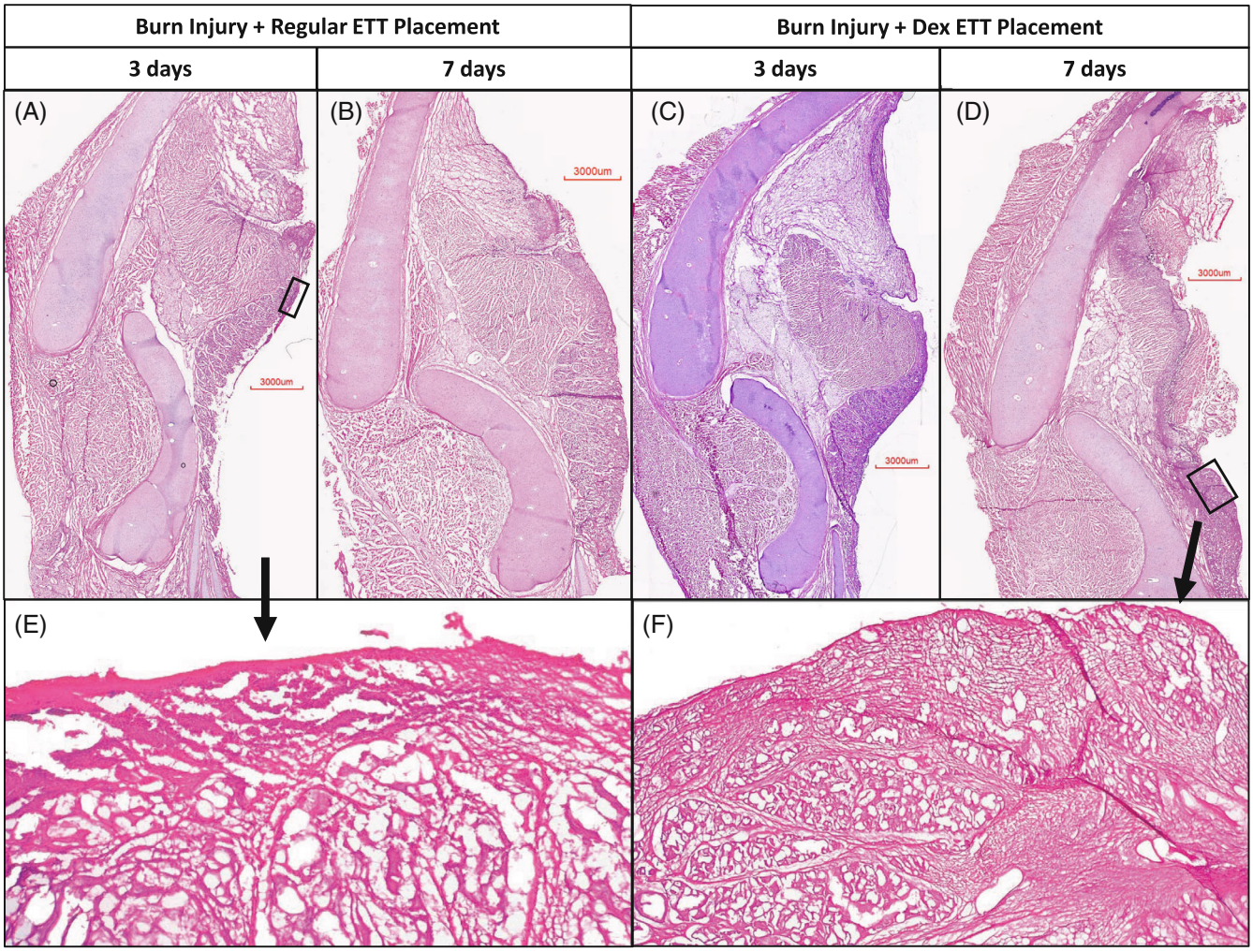

FIGURE 3 Representative hematoxylin–eosin stained sections of the vocal fold from burned tissue with (A) regular endotracheal tube (ETT) placement at 3 days, (B) regular ETT at 7 days, (C) dexamethasone ETT placement at 3 days, and (D) dexamethasone ETT placement at 7 days. Higher power magnification (100×) of the region demarcated by black rectangle demonstrating epithelial ulceration (E) and increased submucosal fibrosis (F), as highlighted with black arrows (40×).

TABLE 1 Summary of histologic scoring schema (left) and median and range of histologic scoring data (right) for both regular and dexamethasone-eluting endotracheal tubes (ETTs).

Scoring	Regular ETT	Dexamethasone ETT	
Epithelial ulceration			
0: 0%			
1: 1%–25%			
2: 25%–50%	3 days	0 (0, 2)	1 (0, 1)
3: 50%–75%	7 days	0 (0, 1)	0 (0, 2)
4: 75%–100%			
Inflammation			
1: Mild	3 days	1 (1, 3)	3 (2, 3)
2: Moderate	7 days	1.5 (1, 2)	3 (2, 3)
3: Severe			
Fibrosis			
0: 0%			
1: 1%–25%			
2: 25%–50%	3 days	1 (1, 1)	1 (1, 1)
3: 50%–75%	7 days	1 (1, 2)	1 (1, 2)
4: 75%–100%			

in pre-clinical models, there is a paucity of data surrounding topical therapeutics for laryngeal thermal injury.[13–21] To the authors' knowledge, this is the first study to examine the effects of local, topical drug delivery in a laryngeal burn injury model.

Across both groups, tissue stiffness decreased as length of intubation progressed. Notably, local dexamethasone delivery via drug-eluting ETT appears to reduce this effect, with significantly higher tissue stiffness noted at both timepoints in this focused assessment of the acute injury period. Notably, this trend appears to bring biomechanical properties of the tissue closer to that of healthy tissue, as uninjured VF tissue had significantly lower stiffness compared to both injury groups at 3 days. However, how this alteration in early tissue stiffness would causally affect long-term scar development remains unknown. While approximating native tissue biomechanics is presumed to imply more favorable outcome, the interplay of vocal fold bulk, tissue edema, and altered cellular composition complicates this relationship early in injury. Furthermore, as an increase in tissue stiffness is associated with improved phonation in vocal fold atrophy, increased stiffness due to drug delivery may result in improvement in post-injury dysphonia among laryngeal burn patients.[24] It should be noted, however, that PCL presence itself is not expected to have had an impact upon tissue response, as PCL-coated tubes without dexamethasone have demonstrated significantly increased tissue stiffness compared to PCL-coated tubes embedded with dexamethasone.[28] Longer-duration studies to evaluate the downstream effect of these changes will be needed to clarify these relationships.

No change in degree of fibrosis or epithelial ulceration was observed across time points or between treatment groups. The parity in extent of epithelial ulceration suggests both groups received similar injury severity at the mucosal level, and unchanged healing between both groups within 1 week is not unexpected. In addition, while the wound healing literature indicates that initial immature collagen synthesis begins within the first week, the majority of mature collagen deposition and remodeling takes place between 8 days and 1 year following injury; the lack of significant detectable fibrosis after 1 week in the present study is congruent with this wound healing timeline and is supported by other vocal fold healing studies.[29,30] Unchanged evidence of fibrosis in these groups within 1 week is predictable in this study on the acute injury period, and future studies examining longer timepoints would help elucidate fibrosis changes histologically between both groups. Interestingly, there was an increase in inflammation in the dexamethasone group at the 7-day timepoint. While initially surprising, this is possibly explained by the complex relationship between glucocorticoids and neutrophilsalthough typically used for their anti-inflammatory effects, glucocorticoids can exert a contradictory, pro-inflammatory effect by increasing neutrophilic activation and decreasing neutrophilic apoptosis.[31] This duality can be demonstrated in airway diseases like asthma and chronic obstructive pulmonary disease, in which patients are variably sensitive and resistant to inhaled steroids. Another possible cause of the increased inflammation is a superimposed infection or biofilm burden due to local neutrophil suppression. The mechanism for increased neutrophilic inflammation in this setting and whether this finding will be translated in the clinical setting is at this time unclear. Additionally, while causation cannot be ascertained in this study, it is possible increased local inflammation is responsible for mediating the increased tissue stiffness seen in biomechanical testing after early laryngeal burn injury.

This study was limited in duration of local dexamethasone delivery during intubation. As many patients requiring long-term airway management may be intubated for up to 14 days before ideally converting to tracheostomy, dexamethasone delivery beyond 7 days may be evaluated in future studies. Such a longer term study would be well suited to identify tissue fibrosis, as this occurs outside the acute injury period. Additionally, because of the requirements of biomechanical testing for multiple freeze–thaw cycles, there was freezing artifact which limited histologic evaluation and precluded assessment of bacterial burden in the mucosa. Finally, due to nature of study requiring sacrifice for histologic analysis, long-term follow up to assess for the development of clinically significant posterior glottic, subglottic, or tracheal stenosis was not feasible. Future studies to focus on delayed healing after laryngeal burn will help elucidate whether early changes demonstrated in these data contribute to the development of airway stenosis.

5 | CONCLUSION

Local dexamethasone delivery via drug eluting ETT placement increases VF stiffness and neutrophil infiltration compared to regular ETTs in a laryngeal burn model, and further increases this stiffness compared to healthy controls. These data suggest continuous local dexamethasone delivery via drug eluting ETTs may alter early biomechanical and cellular pathways in laryngotracheal scarring with laryngotracheal burn, though the long-term implications for laryngotracheal scarring require further study.

CONFLICT OF INTEREST STATEMENT

The authors have no financial conflicts of interest.

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