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Experimental Pilot Study of a Novel Endobronchial Drug Delivery Catheter

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Abstract

Background—An endobronchial infusion catheter introduced through a flexible bronchoscope channel has not been previously described. The aim of this study was to evaluate the technical feasibility of a new device.

Methods—Four porcine models underwent bronchoscopy with the infusion catheter. In the first experiment, Methylene blue was injected into airway in volumes of 0.1 ml, 0.3 ml or 1.0 ml into two animals. One animal was sacrificed at 1 hour and one at 24 hours after the procedure and gross dye diffusion was visually assessed. In the second experiment, a mixture of 80% sterile normal saline and 20% contrast media was injected into the airway in volumes of 0.3 ml, 1.0 ml and 3.0 ml into two animals. One animal was sacrificed at 7 days and one at 20 days. Histological evaluations were performed according to a bronchial damage scoring system.

Results—There was no perioperative morbidity. In the first experiment, infusion volumes of 0.1ml, 0.3ml and 1.0ml resulted in dye surrounding $67\pm 29\%$, $55\pm 17\%$ and $80\pm 20\%$ of the infusion site circumference, and longitudinal distribution of $4.0\pm 1.7\text{mm}$, $8.1\pm 4.1\text{mm}$ and $18.0\pm 3.0\text{mm}$, each respectively. In the second experiment, infusion of 0.3 to 3.0 ml resulted in mild injury, inflammation and hemorrhage/fibrin/thrombus at 7 and 20 days after surgery.

Conclusion—Endobronchial infusion of dye and contrast media by the Endobronchial Drug Delivery Catheter [EDDC] showed dose dependent fashion spread media macroscopically and

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histologically. Further investigation will be required to assess the catheter as a new tool for localized drug delivery into the airway.

Introduction

The most popular local drug delivery route to treat airway disease is inhalation. Steroid inhalation therapy has long been an established treatment method for asthma and chronic obstructive pulmonary disease patients.¹ Direct airway wall infusion of drugs may provide elevated drug concentration at the target while minimizing systemic side effects. Local delivery of chemotherapeutic agents for lung cancer patients with airway obstruction may reduce airway narrowing after tumor debridement², local delivery of sclerotic agents may build up the strength of the bronchial wall in patients with tracheomalacia³, or local delivery of bronchodilator may reduce the hyperconstrictiveness of bronchial smooth muscle in severe asthmatics. Despite the potential benefit for local drug infusion therapy for airway diseases, there has previously been no device available to deliver medication safely and reliably into the airway wall. The limitation of current commercially available endobronchial aspiration needles is that its needle insertion angle can only be controlled by the flexible bronchoscope angulation due to the fact that the needle comes out tangentially to the long axis of the catheter. We examined an endobronchial balloon catheter (Blowfish, Mercator Medsystems, San Leandro CA USA) that extrudes a single microneedle into the bronchial wall when the balloon is inflated, thus allowing direct therapeutic access to the submucosal bronchial wall and adventitia. The original system has been used to treat blood vessels, and it had been discovered that vascular adventitial delivery leads to cylindrical deposition of drugs around the vessel, creating a natural drug-eluting reservoir.⁴ This intravascular catheter has been modified so that it can be used through the flexible bronchoscope channel. Little is known about the delivery of fluid directly into the airway wall. The aim of this study was to evaluate primary technical feasibility of this catheter by 1) determining how the volume affects distribution, and 2) histopathological change of the bronchial tissue.

Material and Method

The study was approved by the Beth Israel Deaconess Medical Center's Institutional Animal Care and Use Committee. All animals were cared for by a veterinarian in accordance with US Department of Agriculture regulations and the Guidelines for the Care and Use Committee of Laboratory Animals of Beth Israel Deaconess Medical Center and the National Research Council's Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animals and published by the National Institutes of Health (Publication No. 5377-3, 1996).

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Catheter

Endobronchial Drug Delivery Catheter [EDDC] is shown in Figure 1 which has 510K approval for the endobronchial application. The system has a 145 cm working length and fits through working channels of 2.6 mm in diameter or greater. At the distal end of the catheter, a 0.9 cm long, 34 Ga needle is sheathed by a deflated balloon, which protects both the needle and the bronchoscopy channel against damage during the introduction of the catheter into the airway. Once positioned at a target site, the balloon is inflated in the airway lumen and the microneedle is extruded radially outward, perpendicular to the long axis of the catheter. The maximum balloon pressure is two atmospheres, which is well tolerated by airway mucosa without overstretch injury of the bronchial wall. After the balloon is inflated and the needle is seated in the bronchial wall, therapeutic or diagnostic fluids can be slowly infused to the bronchial tissue through the needle. The balloon inflation and drug infusion are maintained through separate lumina of the catheter, so that the infusion of drug is completely independent of the inflation of the balloon. Deflation of the balloon withdraws the needle from the bronchial wall and re-sheaths it for removal through the bronchoscope.

Anesthesia

Four porcine subjects weighing 35 to 40 kg were anesthetized with 40 mg ketamine (Fort Dodge Animal Health, Fort Dodge, IA) intramuscularly and 25 mg/kg thiopental (HOSPIRA, Inc, Lake Forest, IL) intravenously and were then intubated. Ventilation was maintained (model 2000 ventilator; Hallowell EMC, Pittsfield, MA) at a tidal volume of 10 mL/kg and 10 to 15 breaths/min. General anesthesia was maintained with inhaled 60% oxygen and 1% to 3% isoflurane (Webster Veterinary, Sterling, MA). The animals also received a crystalloid solution (10 mL/kg/h) during the procedure. Oxygen concentration (pulse oximetry), heart rate, and body temperature were monitored throughout the procedure.

Bronchoscopic procedure

With the animal supine, a flexible bronchoscope (Olympus 1T160, Tokyo Japan) was inserted into the airways through the endotracheal tube. Brief surveys of the central airways were conducted and secretions were removed. Then the catheter balloon was primed with 20% contrast medium (Isovue 370, Bracco Diagnostic Inc.) in saline for injection, and inserted through the working channel of the flexible bronchoscope. The lumen of the catheter was primed with the infusion agent, which was either a mix of contrast/saline or a similar mixture containing methylene blue dye. The balloon was placed at target airway sites having an airway diameter between 3 mm and 11 mm according to the balloon maximum inflation size. Target infusion area was limited in needle insertion point was directly visualized by bronchoscope and avoiding area adjacent to major intrathoracic vessels. Once the target area was determined, the balloon was inflated up to 2 atmospheres of pressure to fill the bronchial lumen under visual and fluoroscopic guidance. Full apposition of the microneedle in the airway wall was confirmed when the catheter was anchored into the airway during breathing. The acute phase of dye distribution was evaluated bronchoscopically with methylene blue infusions or fluoroscopically for contrast/saline infusions. After each infusion, the catheter was deflated and withdrawn into the

bronchoscope while navigating the bronchoscope to the next treatment region. Each infusion site was spaced longitudinally at least 5cm apart from each other to avoid overlapping of the desired effects. The entire bronchoscopy procedure was recorded and C-arm fluoroscopy images were obtained before, during and after each infusion. The animal was extubated immediately after awaking from anesthesia and returned to standard animal care.

Agents

A mixture of 4% Methylene blue, 76% sterile saline and 20% contrast medium (Isovue 370, Bracco Diagnostic Inc.) was used for the dye infusion group. Infusion volumes were 0.1 ml (n=3), 0.3 ml (n=7), and 1.0 ml (n=3) respectively.

A mixture of 80% sterile normal saline and 20% contrast medium (Isovue 370, Bracco Diagnostic Inc.) was used for the histopathology group. Infusion volumes were 0.3 ml (n=17), 1.0 ml (n=16), and 3.0 ml (n=12) respectively.

Follow-up and Evaluation

All animals were examined daily after the surgery. Animals were euthanized in accordance with Beth Israel Deaconess research protocol at 1 hour (n=1) or 24 hours (n=1) after the procedure in dye infusion group and the rest of group was sacrificed 7 days (n=1), or 21 days (n=1) after the surgery. Macroscopic dye distribution was evaluated by autopsy specimen in Methylene Blue injected group which was sectioned in 3 mm steps.

Histology

Autopsied lung was inflated with 10% Neutral Buffered Formalin and held in for 24 hours. The entire lung was sectioned in 3 mm step increments around each infusion site, and sections containing injected bronchi were placed into embedding trays to make paraffin blocks. Slides were made from paraffin embedded tissues and were stained with Hematoxylin and Eosin stains. Bronchial sections were analyzed by a pathologist according to the semi-quantitative scoring system defined in the Table 1 which evaluated degree of injury, inflammation, epithelial loss and a combined score for the presence of hemorrhage, fibrin or thrombus (HFT) ^{5, 6}).

Results

The first experimental group

Bronchoscopic views of the dye injection sites are shown in figure 2. Injection speed was 0.1ml/5sec. There was no bleeding at the needle puncture site when the bronchoscope was withdrawn from the target site. A cross-section of the airway 1 hour after the dye infusion is shown in figure 3. Circumferential distribution was measured at each cross-section at every 3mm distance along each injected airway and circumferential distribution results plotted with reference to the injection site to show proximal and distal diffusion length. Average circumferential and longitudinal distribution of the dye is shown in figure 4. On an average, 0.1ml infusion was distributed only within two cross-sections (3-6 mm total diffusion length), while 0.3 ml infusions traveled to five sections (12-15 mm) and 1.0 ml traveled to seven sections (18-21 mm). The animal sacrificed at 24 hours had no residual methylene

blue dye visibly detected in the airway tissue, possibly due to oxidation or lymphatic drainage.

The second experimental group

There was no perioperative mortality and morbidity. There were no bronchoscopic airway abnormality findings at injected sites just before animals were sacrificed. A total of 126 tissue cross-sections at 7 days and 188 cross-sections at 20 days were examined according to the criteria in Table 1. The histogram plots show a trends toward improvement in damage from day 7 to day 20, though the only statistically significant improvement ($P < 0.05$) was in the category of epithelial loss (Figure 5). Broncho-adventitial infusion of 0.3 to 3.0 ml resulted on average in mild injury, inflammation and HFT seven to 20 days after infusion of 20% contrast in saline. Mild to moderate damage is expected to heal with additional time. One porcine model had long-term and diffuse bronchial inflammation at 20 days, potentially as a result of reaction to the iodinated contrast medium injected into the bronchial wall.

Discussion

Many types of transbronchial aspiration needles for airway application are commercially available today for sampling lymph nodes and tumors.^{7, 8} However, there has been no FDA-cleared or approved device labeled to infuse into airway tissue through a needle. (this is not true, soften the sentence). We introduce an intravascular micro-infusion device that delivers drugs with a precision, 130 μ m diameter needle into adventitial tissue around blood vessels. A Phase I clinical study of coronary adventitial delivery of stem cells has been published using this new technology.⁴ The structural characteristics of both the vascular and transbronchoscopic devices include an elongate catheter with a needle that can be actuated perpendicularly to the long axis. Previously described aspiration needles are actuated tangentially to the long axis of the catheter and needle insertion angles can only be controlled by the flexible bronchoscope angulation. In the catheter described here, the needle is protected by the walls of the balloon while the catheter is inserted into the airway; then when inflated, the balloon works to secure the needle position and prevent dislodgement. With standard aspiration needles, it is difficult to prevent the dislodgement of the needle after it is penetrated into tissue. The catheters used here are able to be inflated to a final diameter between 3 and 16 mm diameter for bronchial use while remaining compatible with the 2.8 mm working channel of bronchoscopes. This catheter is still at a developmental stage and further modification is required such as needle rotate steering system enable control of the needle direction 360 degree easily through the long bronchoscopy channel. This new technologies may open up a variety of endoscopic interventional options for airway diseases. The technical feasibility of delivering drugs directly into airway wall by this new catheter needs to be assessed.

In the first experiment, circumferential and longitudinal distribution of Methylene blue was positively correlated with amount of injection. The maximum circumferential distribution was 100% cylindrical at the needle insertion site. Decreasing percentage of distribution was proportional to distance from the injection site and was a bell shaped symmetrical distribution according to the distance from the injection site. Longitudinal distribution was

up to 9 mm from the injection site symmetric proximally and distally. Length from the injection site was approximately proportional to the amount of agent delivered. Distributions may vary based on the diameter of the airway, agent viscosity, injection speed and pressure. Injection speed and pressure was limited by the needle size and agent viscosity. Some amount of dye might travel into lymphatic vessels⁹ however there was dye uptake seen in neither hilar nor mediastinal lymph nodes at the time of autopsy one hour after the injection.

The second experiment was focused on evaluating histopathological change after saline injection to determine the capacity of airway tissue to accommodate volumetric injection. Quantitative histological scoring system was modified from previous publications.^{5,6} Tissue injury was characterized by submucosal layer laceration and dissection secondary to injection volume and pressure. Minimal injury was observed with 1 ml injection after 7 days. The balloon pressure is limited to 2 atm based on a safety valve integrated into the catheter design, which may prevent tissue laceration. Inflammation was observed at all injection volumes and on both 7 and 20 days after the infusion. Inflammation had been due to a reaction of the tissue to the iodinated contrast media that was mixed with each infusate. Prolonged inflammation of up to 20 days may have been due to local residual contrast media, although inflammation was minimal in nature. Needle insertion and balloon pressure may have direct influence to the epithelial loss. Small area of epithelial loss had re-epithelized in the short period secondary to vigorous airway reepithelialization.¹⁰ Hemorrhage, fibrin and thrombus formation may be directly related with needle insertion and mechanical disruption of the airway wall. Mild to moderate HFT was observed at 7 days and it showed trend towards improvement on day 20.

Conclusions

Endobronchial infusion of dye and contrast media by the Endobronchial Drug Delivery Catheter [EDDC] showed a dose dependent fashion spread macroscopically and histologically. Endobronchial infusion by this catheter is technically feasible and holds promise as a new tool for localizing drug delivery into the airway wall. The pharmacokinetic and toxicity profiles of common drugs that could be used for interventional pulmonology procedures must be characterized before further studies can be performed, leading to human clinical studies.

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Figure 1.

Endobronchial Drug Delivery Catheter [EDDC] : The Catheter is introduced into the bronchus while deflated and the needle is sheathed within a balloon (a & b). When the balloon is inflated, the needle is extruded outward, perpendicular to the axis of the catheter (c & d) .

Figure 2.

Bronchoscopic images of methylene blue injection: Inflation of the balloon and catheter was secured at the target area by the protruded needle into the bronchial wall (a). Balloon deflated followed by infusion of 0.3 ml of methylene blue (b).

Figure 3. Example cross-sections of bronchi after methylene blue injection. A 60% of the circumferential distribution was measured as noted in the images.

Figure 4.

Average circumferential and longitudinal distribution after dye injection to the bronchial adventitia: Data were averaged among consistent injection volumes to determine distribution along and around bronchi. On average, 0.1 ml injections were distributed only within two cross-sections of bronchus, while 0.3 ml injections traveled to five sections and 1.0 ml injections traveled to seven sections. Cross-sections were taken approximately every 3 mm.

Figure 5.
All bronchial cross-sections were scored according to the criteria in Table 1. Maximum scores were taken for each bronchus injected with contrast and saline.

Table 1**Bronchial Damage Scoring System**

Score	Bronchial Injury	Inflammation	Epithelial Loss	Hemorrhage, fibrin, and luminal thrombus (HFT)
0 (None)	No injury	no inflammatory cells	complete epithelialization	absence
1 (Mild)	Epithelium denuded and basement membrane lacerated	mild inflammatory response but not circumferential	between 25 and 75% of the circumference	focal findings involving any portion of the bronchus but <25% of the circumference of the bronchus
2 (Moderate)	Smooth muscle lacerated	moderate to dense cellular aggregate but non-circumferential	present but <25% of the lumen circumference	moderate accumulations involving <25% of the circumference of the bronchus
3 (Severe)	Adventitia lacerated	circumferential dense cell infiltration	absent epithelium	severe, involving >25% of the circumference of the bronchus