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Case report

Paclitaxel-coated balloon dilation for central airway obstruction

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ABSTRACT

Introduction: Central airway obstruction (CAO) often requires repeated interventional procedures which offer variable efficacy, a time-limited effect, and have inherent limitations. Paclitaxel has been used to prevent restenosis in blood vessels. The literature describing the use of paclitaxel to prevent recurrent airway stenosis is limited. We sought to describe our experience using a paclitaxel-coated balloon (PCB) for CAO.

Material and methods: We performed a retrospective review of all patients who underwent PCB airway dilation. We collected: basic demographics, details of the CAO, details of the bronchoscopes used, PCB size, PCB dilation pressure, duration of PCB inflation, concurrent non-PCB interventions, estimated pre- and post-PCB CAO luminal diameter, follow up bronchoscopy date and luminal diameter, and spirometry results.

Results: PCB dilation was performed in 10 cases on 5 patients. Eight PCB dilations were performed for CAO related to distal airway stent stenosis. Concurrent non-PCB interventions were performed with 6 PCB dilations. Nine cases documented improvements and 1 was unchanged immediately post-PCB dilation. Median luminal diameter pre-PCB dilation was 2 mm. Immediately post-PCB dilation, the median change in luminal diameter was 2 mm. Follow up bronchoscopy information was available for 9 cases. For these 9 cases, luminal diameter was unchanged in 5 and worse in 4 when compared to immediate post-PCB dilation.

Conclusion: PCB dilation in benign CAO produced a modest effect in this cohort of challenging airways. Larger prospective studies are needed to assess how a PCB would perform when compared to a non-drug coated balloon.

1. Introduction

Central airway obstruction (CAO) can be from benign or malignant etiologies and is defined as occlusion of > 50% of the trachea, mainstem bronchus, bronchus intermedius, or a lobar bronchus [1]. Depending on the degree, extent, and severity of the narrowing, CAO can be functionally limiting and physically debilitating for patients. Benign strictures constitute the majority of benign forms of CAO and include airway stenosis related to post-intubation tracheal stenosis, post-tracheostomy tracheal stenosis, post-tuberculosis infection, transplant-related and idiopathic stenosis [1]. There are various methods for alleviating symptoms in patients with CAO, which include mechanical debulking, rigid bronchoscopic dilation, stent placement, and balloon dilation.

A balloon can be used to provide mechanical dilation of the stenotic or strictured airway segment, though the stenosis often recurs. Methods aimed at delaying or preventing recurrence include the topical use of mitomycin C and corticosteroid injection [2,3]. Paclitaxel-coated balloons (PCB) (IN.PACT Admiral, Medtronic, Santa Rosa, CA, USA) have been shown effective in preventing restenosis in the vascular setting [4]. PCBs have shown some efficacy in airway stenosis for lung transplant recipients [5], though there is still very limited data regarding PCBs for airway stenoses.

Paclitaxel is a hydrophobic and highly lipophilic antiproliferative drug that has been shown to prevent neointimal hyperplasia after endovascular balloon angioplasty by inhibiting cell division and assembly of microtubules [6,7]. The balloon coating consists of paclitaxel and a hydrophilic excipient urea which facilitates the transfer of paclitaxel from the balloon surface to the luminal surface [8]. Evidence suggests that the balloon delivers paclitaxel concentrations in the vascular wall via paclitaxel reservoirs. These reservoirs provide a source of soluble drug with extended drug availability allowing paclitaxel to exert its anti-proliferative effect for over 180 days [8]. PCBs have been described for the treatment of coronary and peripheral artery disease [6], dysfunctional dialysis access [9], in-stent restenosis in TIPS [10], and biliary anastomotic stricture after liver transplantation [11]. One study reported encouraging results describing the use of PCBs in 12 lung transplant recipients who developed treatment refractory non-anastomotic airway stenosis [5]. The aim of this study is to describe our experience with PCB airway dilation for CAO.

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Abbreviations

CAO	Central airway obstruction
PCB	Paclitaxel-coated balloon
YAP	Yttrium aluminum perovskite
LMB	Left mainstem bronchus
RMB	Right mainstem bronchus
BI	Bronchus intermedius
NK	Natural killer
RA	Rheumatoid arthritis
atm	Atmosphere
FEV1	Forced expiratory volume in 1 second

2. Materials and methods

We performed a retrospective case series review of all patients who underwent a PCB airway dilation of their CAO between March 2016 and July 2016. Five consecutive patients who developed recurrent CAO from a stenosis or stricture and underwent PCB airway dilation were included. There were no exclusion criteria. If documented in the electronic medical record, the following data points were collected: basic demographics, etiology of the CAO, prior CAO interventions attempted, CAO location, specific details of the bronchoscopes used, size of PCB used, duration of PCB inflation, PCB dilation pressure, non-PCB interventions performed concurrently, estimated pre- and post-PCB airway stenosis luminal diameter, follow up bronchoscopy date and estimated stenosis luminal diameter, and spirometry results. Rather than using radiographic software or expensive airway sizing instruments, the known outer diameter of the bronchoscope and/or other instruments used to traverse the stenosis or stricture was used as the estimated luminal diameter pre- and post-PCB dilation. The first bronchoscopy post-PCB was used for the follow up bronchoscopy data points.

In this report a 7 Fr 130 cm long catheter, 6.0 mm or 7.0 mm inflated balloon outer diameter, 40 mm balloon length, IN.PACT™ Admiral™ Drug-Coated Balloon (Medtronic; Minneapolis, MN) was advanced and inflated through the working channel of an adult therapeutic bronchoscope (Olympus T-180 Bronchoscope, Olympus USA). The balloon coated paclitaxel drug dose density was 3.5 μg/mm^2. All PCB dilations were performed at a nominal pressure of 8 atmospheres (811 kPa).

Informed consent was obtained from all patients prior to PCB airway dilation. This study was approved by the Mayo Clinic Institutional Review Board, #17-008149. Our retrospective review was deemed a minimal risk study and was granted consent waiver.

3. Results

There were 5 patients who underwent 10 separate PCB dilations. All 5 patients were female and had benign intrinsic CAO. Three patients had recurrent stent-related granulation tissue CAO and two patients had primary stenoses from benign inflammatory airway disease. All had at least one prior airway intervention and one non-drug coated balloon dilation attempt prior to PCB dilation.

One patient underwent 4 separate PCB dilations and another patient underwent 3 separate PCB dilations. Three patients had a single PCB dilation performed. Eight PCB dilations were performed for CAO related to stenosis that developed at the distal end of their silicone stent. A 7-mm PCB was used in 9 of 10 PCB dilations (Fig. 1). A 6-mm PCB was used in 1 case. Four cases described the duration and number of balloon dilations performed. Each case performed 2-3 PCB dilations for 2–3 minutes. Concurrent non-PCB interventions were performed for 6 PCB dilations. The non-PCB airway interventions included various size non-drug coated balloon dilations, yttrium aluminum perovskite (YAP) laser, and cryoprobe debulking.

Nine of 10 cases documented improvements in the airway stenosis immediately post-PCB dilation. One case was unchanged compared to pre-PCB dilation (Table 1). Median stenotic airway diameter pre-PCB dilation was 2 mm (mean, 2.5 mm; range, 1–5 mm). Immediately post-PCB dilation, the median improvement in the stenotic luminal diameter was 2 mm (mean, 2.5 mm; range, 0–6 mm). Nine cases had follow up bronchoscopy information available for review. For these 9 cases, stenotic airway luminal diameter was unchanged in 5 and worse in 4 when compared to immediate post-PCB dilation. There were no cases showing improvement from the time of post-PCB dilation and the follow-up bronchoscopy. Median follow up bronchoscopy was 20 days (mean, 24 days; range, 1–61 days). There were no significant peri- or post-procedural complications.

Four cases had pre- and post-PCB spirometry data available for comparison. Three patients showed improvement in their forced expiratory volume in 1 second (FEV1) with a median change of 0.13 liters (mean 0.16; range 0.03–0.33). The median number of days from PCB dilation to spirometry testing was 40.5 (mean, 40.5; range, 20-43). There was one patient who recorded worsening FEV1 of −0.24 liters at 61 days post PCB airway dilation.

4. Discussion

CAO can be very problematic for both the patient and the bronchoscopist. Optimal management of recurrent or refractory airway stenosis remains unclear; long-term endobronchial luminal patency rates are modest and repeated interventional procedures are often required. Currently, there are various treatment modalities that demonstrate efficacy, yet offer a time limited effect, and have inherent limitations. Non-drug coated balloon dilations represent the mainstay of treatment with silicone or self-expanding metal stents used as a last resort [5]. A well-documented drawback of placing a silicone stent in the airway is the development of excessive granulation tissue [12] which can occur in up to 50% of patients who have an airway stent [7].

We looked at 10 cases where a PCB was utilized to treat benign CAO. Nine cases documented a significant improvement in the stenotic

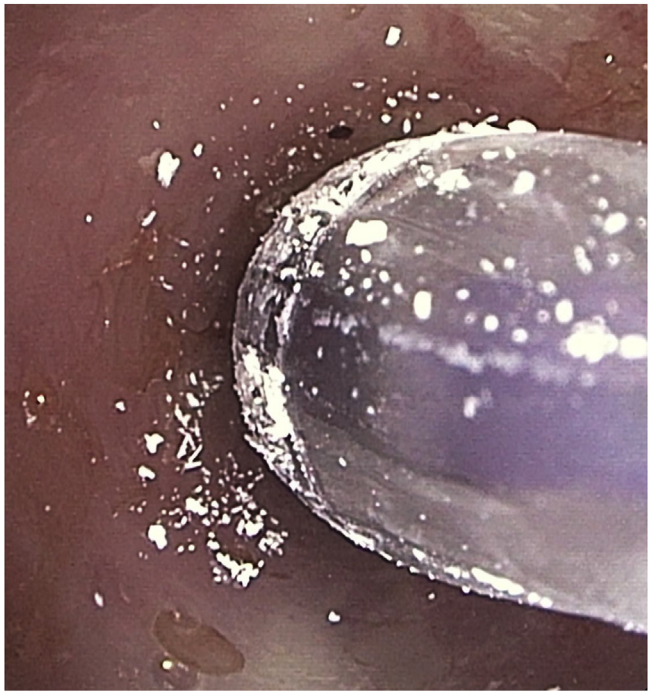

Fig. 1. Fully inflated size 7 mm paclitaxel-coated balloon airway dilation.

Table 1
Ten cases describing our experience with PCB airway dilation for CAO.

	Age	Gender	Location	Diagnosis	PCB size (mm)	PCB dilation pressure	Non-PCB interventions	Pre-PCB luminal diameter	Post-PCB luminal diameter	Days to follow up	Luminal diameter at follow up	Days to next PCB dilation
1	30	F	LMB	NK/T-cell lymphoma	7	8 atm	None	2.0 mm	6.0 mm	3	6.0 mm	64
	30	F	LMB	NK/T-cell lymphoma	7	8 atm	YAP laser, cryoprobe debulking	4.4 mm	6.0 mm	1	6.0 mm	33
	30	F	LMB	NK/T-cell lymphoma	7	8 atm	None	2.0 mm	2.0 mm	19	2.0 mm	N/A
	30	F	RMB	NK/T-cell lymphoma	7	8 atm	YAP laser, cryoprobe debulking	5.0 mm	6.0 mm	33	6.0 mm	N/A
2	54	F	LMB	Bilateral lung transplant	6	8 atm	None	2.0 mm	3.8 mm	20	3.8 mm	0
	54	F	LMB	Bilateral lung transplant	7	8 atm	8 mm balloon	3.8 mm	6.0 mm	43	2.0 mm	0
	54	F	LMB	Bilateral lung transplant	7	8 atm	None	2.0 mm	5.3 mm	61	2.0 mm	N/A
3	30	F	BI	Fibrosing mediastinitis	7	8 atm	6 mm balloon	1.0 mm	7.0 mm	N/A	None	N/A
4	70	F	RMB/BI	RA inflammatory tracheitis	7	8 atm	6 mm balloon, 8 mm balloon	1.0 mm	5.1 mm	1	3.8 mm	N/A
5	58	F	LMB	Bilateral lung transplant	7	8 atm	YAP laser, cryoprobe debulking	2.0 mm	3.0 mm	39	2.0 mm	N/A

LMB – left mainstem bronchus; RMB – right mainstem bronchus; BI – bronchus intermedius; NK – natural killer; RA – rheumatoid arthritis; YAP – yttrium aluminum perovskite; PCB – paclitaxel-coated balloon; atm - atmosphere.

airway diameter immediately post-PCB dilation and 1 case was unchanged. Five of 9 maintained the same luminal patency at follow up bronchoscopy, while 4 cases had documented a recurrent decrease in the stenotic luminal diameter. While the short term follow up showed stability of the airway stenosis, 3 patients showed no demonstrable effect of PCB when comparing their pre-PCB dilation luminal diameter to their last reported luminal diameter at follow up. These findings are similar to what was reported by Greer et al. [5], who were the first to describe the use of PCB dilations in treatment refractory non-anastomotic airway stenosis post lung transplantation. They found that following a single application, luminal patency was maintained in 6 of 12 patients at 270 days.

To minimize damage to the paclitaxel coating, Greer and colleagues [5] advanced and positioned the PCB in the airway over a guidewire. The flexible bronchoscope was inserted simultaneously and adjacent to the guidewire to directly visualize the PCB dilation. Our group advanced the balloon directly into the working channel of the bronchoscope. The majority of the drug coating is protected as the balloon is coated in an inflated state, shielding most of the balloon surface area in the folds of the balloon. During inflation, the coating comes into contact with the bronchial mucosa.

Stability of the stenosis post-PCB dilation, rather than subsequent improvement can be explained by the mechanism of action of paclitaxel. Paclitaxel inhibits mitosis by causing cell-cycle arrest in the G1 phase without cellular apoptosis [13]. This results in a static response prohibiting the proliferation of fibroblast [7]. In vivo and in vitro studies have shown that when paclitaxel is applied topically, formation of airway granulation tissue and scar formation are inhibited [7,14]. Any meaningful effect on malacic airways or continued increase in the stenotic luminal diameter would not be expected with the use of PCBs.

Previously, investigators have attempted the application of antiproliferative agents to the tracheobronchial tree, most notably with injectable mitomycin [2,3]. Drug concentration levels are difficult to maintain in the airway, particularly if the drug has a short half-life. This is especially true with paclitaxel which has a half-life of 5.8 hours [7]. In an effort to produce a longer lasting paclitaxel effect, non-PCB interventions were performed concurrently in 6 cases to cause mild mucosal irritation and microvascular exposure to allow for deeper drug penetration. Of those that had additional intervention, follow-up showed that three had worsening stenosis, 2 were unchanged, and 1 did not have a follow up bronchoscopy. Additional intervention prior to PCB dilation did not appear to have any significant impact on the immediate result or the duration of benefit.

Modest improvements were seen in 3 of 4 patients with available spirometry data. The stenotic luminal diameter appeared to correlate with FEV1. The patient that had an FEV1 decline of 0.24 liters was shown to have a reduction in her luminal diameter from 5.3 mm to 2.0 mm. Whether the objective findings of achieving a stable stenotic luminal diameter and improvements in FEV1 translated into symptomatic improvement was unclear from review of the medical records.

The cost of a PCB at our institution is roughly four times higher than a standard non-drug coated balloon. Evidence of a sustained improvement in airway patency would be an argument for the use of a PCB for the patient who requires multiple bronchoscopic interventions for CAO. Our results suggest that the modest stability seen with the use of PCB can be considered as a feasible and safe option if prior attempted therapies have been unsuccessful. At present, commercially available PCBs only come in diameters up to 7 mm, which may not be adequate for the central-most lesions, such as tracheal stenosis.

We acknowledge that our study has multiple limitations which include its retrospective design, small sample size, short follow up period, that the majority of the dilations were in stent related stenosis, and that other concurrent interventions were applied. Due to the lack of a control group, it is unclear whether a non-drug coated balloon would have achieved the same effect or slowed the progression of the airway stenosis. However, it is important to point out that all of our patients had a

minimum of 1 failed non-drug coated balloon dilation plus a non-PCB intervention prior to PCB dilation.

5. Conclusion

PCB airway dilation in benign CAO produces a modest short term effect on improving and maintaining airway patency. Larger prospective randomized controlled studies are needed to assess how a PCB would perform when compared to a non-drug coated balloon.

Conflicts of interest

Dr. Ryan Kern reports personal fees for consulting from Boston Scientific, Auris Surgical Robotics, and Olympus Corporation of Americas during the conduct of this study.

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Off label use

Paclitaxel-coated balloon for airway dilation.

Author contributions

All authors provided equal substantial contributions to the conception, acquisition, analysis, and interpretation of data for the manuscript. Drs. Sakata and Kern are responsible for the final version to be published.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmcr.2018.05.011.

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