Further experience with polydioxanone airway stents in children.

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March 12, 2024

Abstract

Introduction The aims of this study were to update our experience with biodegradable polydioxanone (PDO) airway stents in children focusing on effectiveness and safety, and to analyse the factors involved in the different outcomes observed. **Materials and methods** Retrospective study of patients managed with PDO stents from 2012 to 2023. Variables collected: demographics, comorbidities, indication , clinical baseline, stent size, location, complications, clinical outcome, and time of follow-up. Statistical analyses were performed in order to detect the eventual contribution of variables in the different outcomes observed. **Results** 54 PDO stents were placed in 26 patients (median age, 4 m). All showed severe symptoms of central airway obstruction due to: tracheomalacia 9 patients, bronchomalacia 5, tracheobronchomalacia 10, and tracheal stenosis 2. Stent placement was uneventful in every case: 29 stents in the trachea and 25 in main bronchi. 53,8% of patients needed successive stenting and all exhibited comorbidities. Complete clinical resolution was observed in 8 cases (30.7%), partial improvement in 13 (50%), unchanged in 4 (15.3%), and worsen in one. Age had a significant positive impact in outcome (6 months vs 3 m.; p=0.024). Additionally, smaller stents were associated with a better outcome (20 vs 26 mm; p=0.044). Granulation tissue was the most frequent complication (34.6%). Five patients (19.2%) died due to severe comorbidities, follow-up was complete in survivors (median, 58 m). **Conclusions** PDO stents are safe and effective when dealing with severe tracheobronchial obstruction. Stent-related granulation tissue continues to be a relevant matter of concern. This issue together with increased degradation times deserve further research.

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Introduction

Endoluminal airway stenting in children remains a controversial topic. Whilst airway stenting in adults is a well established practice with wide consensus, in pediatric patients it is still far from achieving this goal (1,2). Albeit increasing experience with endoscopic stenting in the pediatric age group, there is lack of agreement regarding indications, risks, and suitability of the different types of stents when addressing tracheobronchial obstruction (3). The small size of an infant´s airway and the limited availability of appropriate stents are determinant issues in this particular setting. In 2016 our group published a preliminary experience with a new biodegradable (BD) airway stent made of polydioxanone (PDO) (4). Persuaded by our initial good results, we continued using BD/PDO stents and even replacing other types, metallic or plastic, that we have used until then (5). Currently, PDO devices are our first choice when endoluminal stenting is considered an option.

The primary aim of this study was to update our experience with this type of BD stent focusing on clinical effectiveness and safety. Secondary goal was to analyse the factors that could be involved in the distinct outcomes observed.

2. Materials and Methods

2.1. Study design and data collection

We conducted a retrospective and descriptive study, based on a prospective database, of pediatric patients treated with PDO stents in our Unit from March 2012 to November 2023 (11 years and 8 months). We retrieved and handled data through the Research Electronic Data Capture (REDCap) system of our institution. The REDCap is a secure online application developed to support data collection for research studies. This study was approved by our Institutional Research Ethics Committee and we obtained informed consent for all patients from their parents in order to perform the endoscopic procedure and obtain photographic content. The following data were collected in each case: demographics, comorbidities, baseline respiratory status, indication for stenting, stent size, anatomic location, insertion technique including the need for balloon dilation, stent-related complications, need for re-stenting, clinical result and time of follow-up. Main outcome measures were related to the respiratory condition achieved after stenting (one or more stents):

- *Resolution* : stenting permits withdrawal of ventilatory support and/or complete resolution of respiratory symptoms.
- *Partial improvement* : some degree of clinical improvement is achieved, either milder respiratory obstructive episodes or a decreased need for ventilatory support.
- *Unchanged* : clinical status similar to pre-stenting.
- *Worsen* : clinical condition aggravates after stenting.

2.2. Management protocol

Every candidate was evaluted with dynamic flexible bronchoscopy (FB) and contrast computed tomography (CT). Data obtained from these explorations were crucial in order to establish the indication and obtain the estimated dimensions of the stent. The decision to perform stenting was made by our multidisciplinary airway team including pediatric surgeons, cardiac and ENT surgeons, anesthesiologists, intensive care and pediatric pulmonologists, and radiology/image specialists. According to our management protocol, stenting

is not a first line treatment and other therapeutic options were considered, or tried, before deciding to place a BD stent in the airway. After thorough evaluation of the clinical situation of the patient, eventual benefits and stent-related risks, BD stenting was offered to the patient´s parents or care givers.

2.3. Stent features and endoscopic technique

We have used BD self-expanding stents (ELLA-CS, Hradec Kralove, Czech Republic) which were custom-made according to the patient´s airway size and needs. This stent consists on a polydioxanone monofilament, which is a semi-crystalline polymer that degrades by random hydrolysis. It has its own dedicated delivery system which comprises a hollow plastic guiding tube with an olive at the end. The stent was placed in the operating room under general anesthesia with complete muscle relaxation. Stent insertion was performed with rigid bronchoscopy (RB) and fluoroscopic control. When a concurrent laryngeal lesion was present and the patient had a tracheostomy, the stent was placed thru the stoma with fluoroscopic visualization or direct vision guidance with an ultrathin FB. This procedure proved to be more intricate than the standard RB technique used in most cases. Bronchography was deemed unnecessary for stent positioning so we did not use it. When deployed, the stent has some degree of shape memory and tends to coil achieving its nominal diameter after a few hours. According to the manufacturer instructions, this stent maintains full mechanical strength for the first 6–7 weeks after placement and degrades completely after 14–15 weeks. More detailed biomechanical and physical properties have been described elsewhere (6).

2.4. Statistical analysis

Quantitative variables were described as median with interquartil range (IQR). Relative frequencies were used for categorical variables. Data were stratified for patients who were positive and negative and their distributions compared with student t test or Mann Whitney test (non-normal distribution). Categorical variables were analysed by Chi-square test. Statistical data were analysed using Prism software v8.0 (GraphPad Software, San Diego, CA, USA). Values of $p< 0.05$ were considered significant for all analyses.

Results

A total of 54 PDO stents were placed in 26 patients during the study period and 14 (53.8%) required more than one stent for management (median, 2 stents). The cohort was constituted by 14 boys and 12 girls with a median age of 4 months [IQR 3-7] when the first stent was placed. The youngest patient in our series was 2 months of age and the lowest weight was 3 kg, while the oldest was 6 years of age and 20 kg.

All patients showed severe symptoms of airway obstruction due to one of the following diseases: tracheomalacia (TM, 9 patients), bronchomalacia (BM,5), tracheobronchomalacia (TBM, 10) and postsurgical tracheal stenosis (TS, 2 cases). As shown, congenital airway malacia was the most frequent disease causing central airway obstruction (92.3%): 13 (54.1%) corresponded to primary malacia and 11 showed airway collapse secondary to extrinsic vascular compression. Respiratory clinical status when airway stenting was as follows: 14 patients had a tracheostomy for ventilatory support, 3 were intubated and ventilated, non-invasive ventilation was required in 5, oxygen therapy in 3 and one patient showed recurrent respiratory infections requiring hospitalization.

Endoscopical placement of PDO stents was uneventful in every patient. In some cases minor readjustements with a semirigid 1mm alligator forceps were performed in order to accurately match the lesion. Balloon dilation of the stent was deemed necessary in 22 stents (40.7%) in order to immediately achieve the nominal diameter and expected radial force. Median stent diameter and length were 7 mm (IQR 5-9) and 22.5 mm (IQR 15 – 35) respectively. Regarding anatomic location, 29 stents (53.7%) were placed in the trachea and 25 in the main bronchi (7 right and 18 left) (figure 1). All patients showed severe comorbidities being cardiovascular anomalies most frequent (65.3%). Ten patients (38.4%) exhibited more than one associated anomaly including genetic syndromes (Table I).

Clinical respiratory status achieved after stent placement was the main outcome measure in our study. According to the previously mentioned cathegorization, 8 (30.7%) patients showed complete resolution of their symptoms and 13 (50%) partial clinical improvement. Airway stenting did not have an impact on

the clinical condition of 4 patients (15.3%) and in one (3.8%) it became even worse due to stent-related complications. Additionally, we evaluated the potential contribution of the collected variables to the four different clinical outcomes observed. Analysing those patients with complete resolution of their respiratory symptoms after stenting and comparing them to the other 3 groups with a different clinical outcome (partial improvement, unchanged, worsen), we observed that age had significantly positive impact (6 months vs 3 m; p=0.024) (Table II). Moreover, putting together patients with complete or partial improvement and comparing them to those with no change or clinical deterioration, we observed that a smaller PDO stent was associated with a better outcome (median length, 20 vs 26 mm; p=0.044) (Table III).

Granulation tissue formation was the most frequent stent related complication observed in our study. Because PDO stents represent a foreign body in the airway, some minor degree of granulation tissue formation is usually expected (fig. 2). Nevertheless, granulation tissue requiring a bronchoscopic procedure in order to remove it with forceps, ballooning or laser, was a relevant issue observed in 34.6% (9/26) of our cases (5 tracheal and 4 bronchial) (fig. 3). Mean size of tracheal stents causing granulation was 23 x 7.6 mm, while bronchial stents were 18.7 x 5.2 mm. These patients were more prone to accumulate secretions needing aspiration and lavage when bronchoscopy was performed. Additionally, stent migration was observed in one case (oldest patient) due to a mismatch between the stent size and the lesion, and severe tracheal stenosis in another requiring surgical resection and Montgomery T-tube insertion. No bleeding, infection or airway erosion were detected in the cohort. No patients showed difficulties in coughing or expelling stent fragments during biodegradation. One stent was too long and we decided to cut it to match the bronchial malacic lesion. This proved to be a wrong decision so it was removed and a new one ordered. In another case of BM the stent was too short to give effective support so it was removed and replaced by a longer one. Stent surveillance relied mainly on clinical assessment. Due to our institutional wide availability for bronchoscopic exploration, FB was immediately performed by our team if deemed necessary.

Five patients (19.2%) died during follow-up due to severe associated anomalies: two with polymalformative syndromes and 3 with complex congenital cardiopathy with pulmonary hipertension or sepsis (2 patients). Currently, no ventilatory support is required in 14 patients (53.8%), 5 (19.2%) carry a tracheostomy without assistance and 2 more patients have a tracheostomy with intermitent ventilatory support. Median follow-up was complete with a median value of 58 months [IQR 12-77].

Discussion

Non-infectious pediatric central airway obstruction is usually due to malacia and stenosis (7,8). The estimated incidence of congenital TM is approximately 1:2100 children being the most common congenital tracheal anomaly (9). Albeit most patients with TM or BM may outgrow their disease, a distinct group may exhibit life-threatening symptoms such as apnoeic spells or inability to extubate the airway. In this settingt, surgical or endoscopical treatment is mandatory (10).

First experience with PDO airway stents in children was reported by Vondrys et al. in 2011 (11). Albeit increasing interest with stenting in the pediatric age group, most of the publications have been case reports or short series of patients (12-15). In 2016 we reported our initial experience with BD-PDO intraluminal airway stents in children (4). These stents were effective when dealing with stenosis or malacia with fewer complications than those exhibited by metallic or plastic stents (5). We have continued using PDO stents, when indicated, and gradually replacing other types of stents. Parallel to our clinical experience, our group has accomplished experimental studies addressing the biologic behavior of PDO stents in the rabbit trachea (16).

In a recent article, Minen et al (17) reported the largest group of pediatric patients with airway PDO stents belonging to a single institution. Interestingly, their experience was very similar to ours: 33 patients and 55 stents in an 8 year period of time. They addressed efficacy and safety of PDO stents and specifically focused on stent-related data (size, time to degrade, and stent related complications). According to their protocol, they intentionally downsized the stents in order to reduce granulation tissue which may be caused by excessive stent pressure on airway mucosa and cartilage (17). This is a very relevant issue because they

did not describe major granulation tissue needing bronchoscopic removal in their series. Although we did not deliberately downsize our PDO stents, stent dimensions in our cohort were very similar to theirs (median values, 7 mm x 20 mm tracheal and 5 x 25mm left bronchial). Conversely, our patients were significantly younger (median age, 4 months vs 13.1 m) so probably this implies that our stents were relativeley larger compared to theirs. Additionally, we observed that patients with complete or partial clinical improvement had statistically significant smaller stents than those with no improvement. Although stent size and radial force may play a role in granulation tissue formation, and ultimately a better outcome, there are probably other factors involved (18). Zhang et al (19) studied the role of tracheal wall injury in the development of benign airway stenosis in rabbits. They demonstrated that cartilage injury was the key factor of airway stenosis and that acute injury of the mucosa alone was unlikely to cause it. We have investigated the biologic effects caused by successive placement of PDO stents (up to 3) in the rabbit trachea (16). According to our data, consecutive stenting did not show a statistically significant increase in tracheal wall collagen and cartilage structure was not modified in those rabbits with one or more PDO stents compared to the non-stented tracheal sections. In this study 4 rabbits out of 21 (19%) showed severe granulation tissue soon after the first PDO stent placement (<7 weeks) and they were excluded from the final analysis. This clinical behavior was completely different from the observed in the other 16 animals who achieved the anticipated survival time in the study design (14, 28 and 42 weeks). Although these experimental data must be interpreted with caution and conversion to clinical grounds must not be considered linear, they give relevant information regarding tissue tolerance of PDO stents. Albeit we do not know the biological rationale, we presume that there must be some kind of individual intolerance to PDO stents in certain subjects. This could apply too for pediatric patients though we have observed good tolerance with mild granulation tissue in the majority of our patients but approximately one third exhibited this stent-related complication. To exemplify this point, one patient received 9 consecutive PDO stents, in a 35 months period, showing excellent tissue tolerance with only mild granulation tissue although stent size was gradually increased (5-9 mm diameter, 15-35 mm length). Conversely, another developed severe granulation tissue, and eventually tracheal stenosis, with the first PDO stent (6x20 mm).

Congenital airway malacia, either primary or secondary, is the most frequent indication for BD stenting (7,17,20). Most of these patients exhibit severe associated anomalies, mainly cardiovascular and syndromic, that have a relevant impact in their clinical status so it is sometimes difficult to establish the precise contribution of airway malacia to the clinical situation. The rationale for using BD stents in this particular scenario relies on what is called the "proof of principle " (10). This means that restoration of patency improves clinical status before attempting surgery or permament stenting. BD stents may also play a role as a "bridge" treatment with stabilisation of the airway to allow spontaneous resolution of malacia or definitive surgical correction (4,17,20).

PDO stent placement with RB and fluoroscopic control has proved to be a safe and straight forward procedure. Some authors advocate stent implantation thru an endotracheal tube with fluoroscopy and broncograms (11,17). We consider that both techniques are sound and selection depends on institutional preferences and local availability. In our center, the procedure is done by general pediatric surgeons with broad experience in bronchoscopy and airway surgery. In our experience, placing a PDO stent in the airway is easier than implantation of other types of stents (5).

Limitations of our study include its retrospective design and the cohort size which precludes more thorough statistical analyses. Additionally, it includes a diverse sample of central airway obstructive diseases associated to other severe congenital anomalies and genetic syndromes that have a relevant impact in the clinical situation.

In conclusión, BD-PDO stents are a safe and effective tool when dealing with severe tracheobronchial obstruction in children. They can be even life-saving in certain critical scenarios where other therapeutic measures have failed or are contraindicated. Albeit stent-related complications seem to be fewer than with other type of devices, granulation tissue formation continues to be a relevant matter of concern. This issue together with increased degradation times deserve further research.

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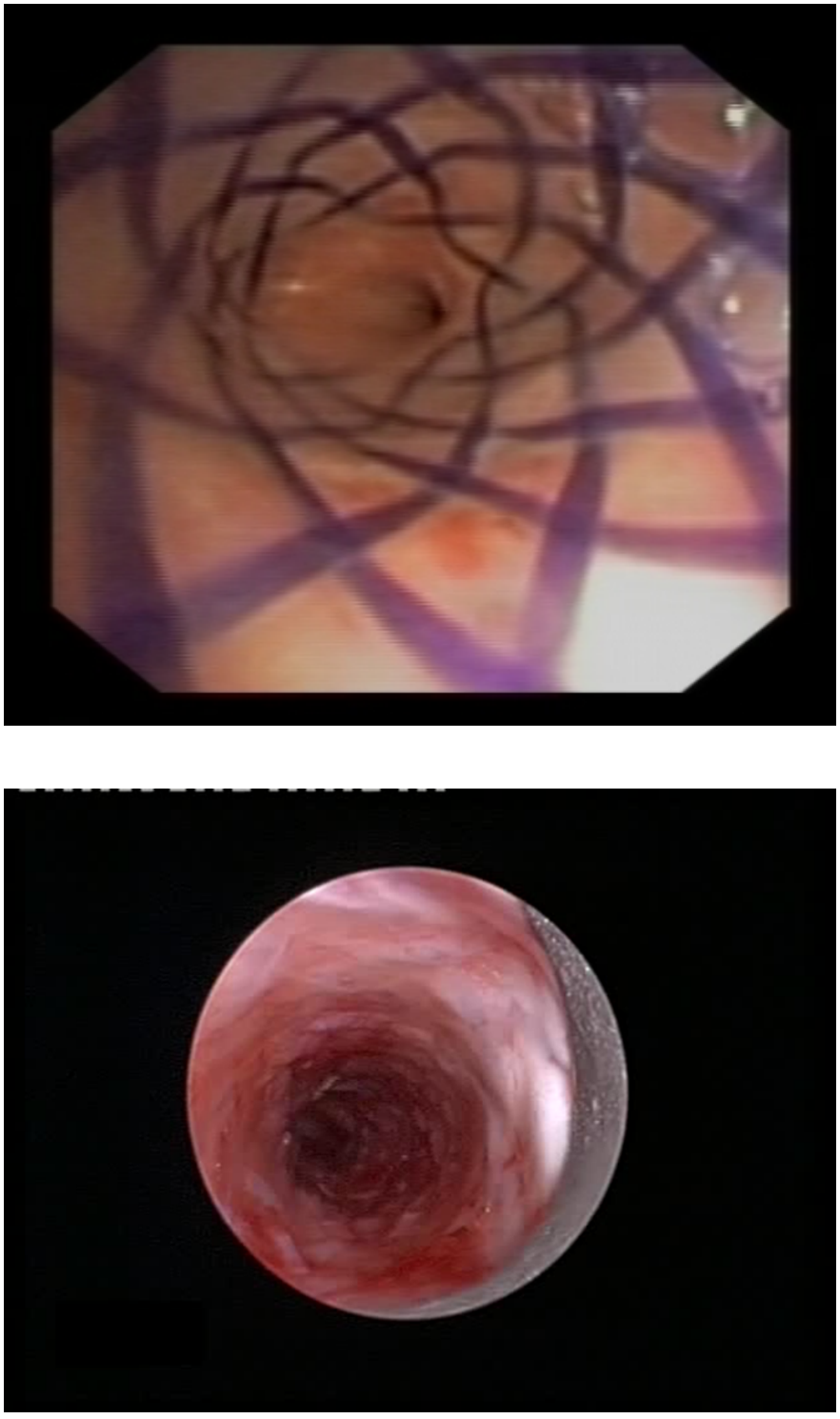
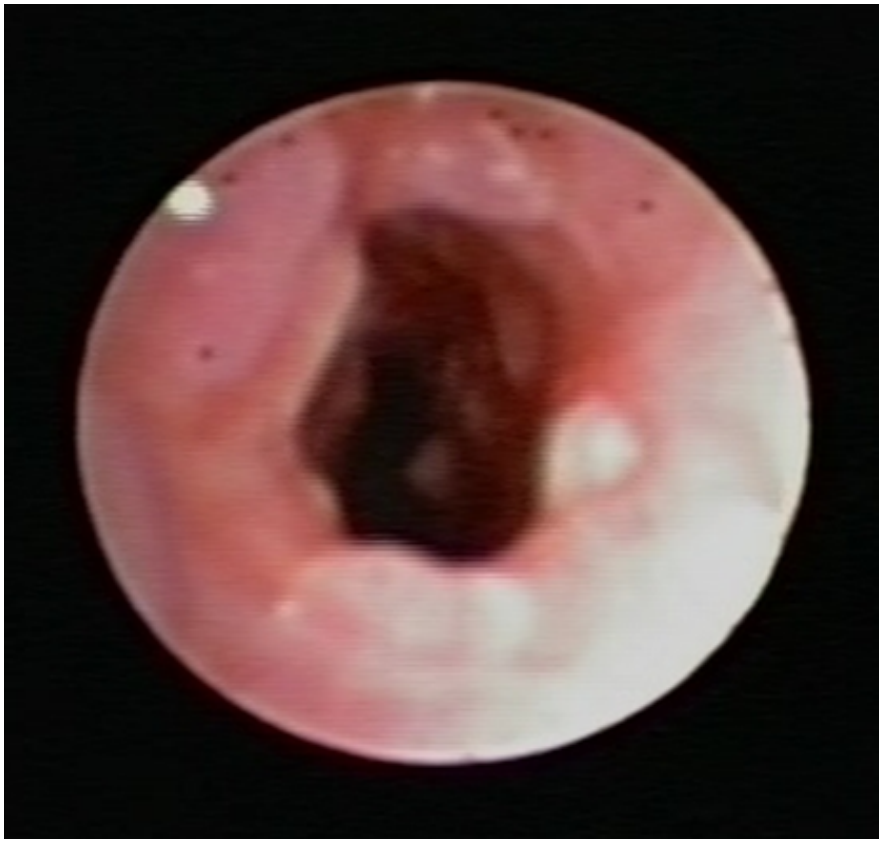
Figure Legends:

Figure 1: Bronchoscopic view of a polydioxanone (PDO) stent in the trachea.

Figure 2: Bronchoscopic aspect of a tracheal PDO stent with mild granulation tissue (fifth consecutive stent).

Figure 3: Bonchoscopic image of a tracheal PDO stent causing severe granulation tissue in its the upper end.





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