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Histological and structural effects of biodegradable polydioxanone stents in the rabbit trachea

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Key question

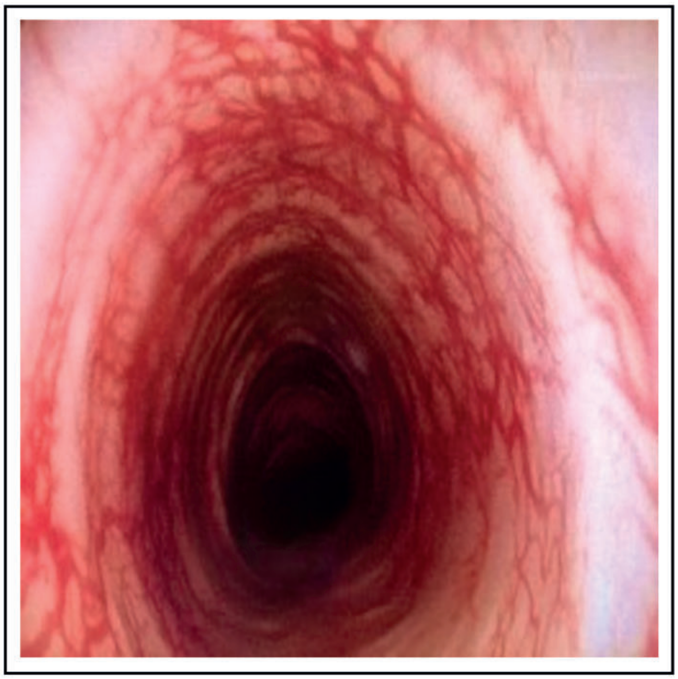
What changes occur in the rabbit tracheal wall when placing three consecutive polydioxanone (PDO) endoluminal stents?

Key finding(s)

Serial PDO stenting caused mild inflammatory changes and no increase in the collagen matrix of the rabbit trachea.

Take-home message

Biodegradable PDO stenting of the rabbit trachea seems to be safe and show good biocompatibility in the long-term.



Abstract

OBJECTIVES: The aim of this study was to evaluate the potential biologic effects caused by the successive placement of biodegradable polydioxanone (PDO) stents in the rabbit trachea. PDO stents could eventually induce a fibroproliferative reaction in the submucosa that could be beneficial in the treatment of malacia due to an increase in its consistency without impairing the tracheal lumen.

METHODS: Sixteen adult NZ rabbits were distributed into 3 groups with different survival times according to the number of stents placed: 1 stent (14 weeks), 2 stents (28 weeks) and 3 stents (42 weeks). Stent insertion was performed endoscopically in the cervical trachea of the animal. Histopathological studies included Masson's trichrome staining for submucosal fibrosis and Safranin O to assess the structural integrity of cartilage. Potential inflammatory changes were analysed by means of immunohistochemistry determining the number of CD45-positive cells.

RESULTS: Stent placement was successful in every case. Histological studies did not show a statistically significant increase in tracheal wall collagen area and cartilage structure was not modified in those rabbits with 1 or more PDO stents inserted compared to non-stented tracheal sections. Furthermore, no statistically significant changes in the number of CD45^{+} cells were observed in stented tracheal segments compared to normal tracheal tissues.

CONCLUSIONS: According to our data, successive PDO stenting caused mild inflammatory changes in the tracheal wall and no increase in the collagen matrix, and the cartilaginous support was not modified during a long follow-up period (up to 42 weeks). These findings suggest that they may be safe and show good biocompatibility in the long term.

Keywords: Animal model • Airway stents • Polydioxanone stents • Tracheomalacia

ABBREVIATIONS

BD	Biodegradable
PDO	Polydioxanone
TM	Tracheomalacia

INTRODUCTION

Tracheobronchial obstruction in children is infrequent and usually due to non-malignant conditions. Both congenital and acquired lesions may cause central airway obstruction being malacia and stenosis most common [1]. Management is challenging due to the small size of the infant's airway and the specific features of these rare diseases. In tracheomalacia (TM), the tracheal wall is abnormally soft and postero-anterior collapse occurs during expiration. Malacia may comprise a limited portion of the trachea, as it happens with oesophageal atresia and vascular rings, or involve the whole trachea together with the main bronchi known as tracheobronchomalacia (TBM) [2]. Treatment of TM varies from a conservative approach, in mild cases, to complex surgical procedures in those patients exhibiting severe symptoms [2, 3]. Recently, endoluminal airway stenting has emerged as an alternative to more invasive techniques when dealing with severe TM or TBM in children [4–6]. Silicone and covered metallic stents are the most frequently used in adult practice, but these are difficult to place in the small paediatric airway and may cause severe complications such as migration, mucous plugging and granulation tissue formation [7, 8]. To avoid or decrease these events, recent research has focused on absorbable stents [9–11]. The idea of using a biodegradable (BD) stent that does not need to be removed and shows fewer complications than the classic ones is an attractive concept, but it raises specific concerns. Our group has a relevant clinical experience with endoluminal airway stenting in children with tracheobronchial obstruction and we have endoscopically placed >40 polydioxanone (PDO) BD stents in 20 patients (median age, 4 months) in the last 10 years. Most of these patients showed severe or persistent TM or TBM and some of them required consecutive BD stenting to overcome their anomaly [5, 12].

The main objective of this work was to study the biologic effects in the tracheal wall of healthy experimental animals caused by the placement of BD PDO stents. Moreover, we aimed to examine the clinical response after the insertion and resorption of consecutive stents (up to 3) and the potential inflammatory or fibroproliferative response in the tracheal wall. Our working hypothesis relied on the concept that PDO stents could induce a fibroproliferative reaction in the tracheal submucosa that could be eventually beneficial in the treatment of malacia due to an increase in its consistency without impairing the tracheal lumen.

MATERIALS AND METHODS

Ethical statement

This research study was approved by our institutional (Hospital U. 12 de Octubre, Imas12) Ethics Committee for the Care and Use of Laboratory Animals (ID number PROEX 088/19), in compliance with the ARRIVE guidelines, and carried out in accordance with the European Union Directive 2010/63/EU for animal experiments.

Study subjects

The study initially included 21 adult male white New Zealand rabbits with a median weight of 3.3 kg (range, 3.0–3.5 kg). The animals were housed in our institutional research centre and placed in individual cages, in a separate room, with 12-hour light cycles and were fed unrestrictedly with full access to water. Due to different reasons, 5 animals were excluded from the study, so 16 rabbits were available for final analysis. They were randomly divided into 3 groups with different survival times: group 1 (6 rabbits), with 1 tracheal stent and an expected sacrifice 14 weeks after stent placement; group 2 (5 rabbits), 2 consecutive stents with a 14-week interval and planned sacrifice in week 28 since first stent insertion; and group 3 (5 rabbits), with 3 consecutive stents (14-week interval between each stent) and expected sacrifice 42 weeks after tracheal placement of the first stent. The 14-week time pattern was chosen because it is the estimated time for the PDO stent to degrade completely.

Stent

The type of stent was selected according to our previous clinical experience and commercial availability. PDO stents are manufactured by ELLA-CS sro (Hradec Kralove, Czech Republic) and are braided with a single PDO monofilament. These stents are self-expandable and custom made and are provided separately from the delivery system. PDO is a semicrystalline polymer that degrades completely by random hydrolysis 14–15 weeks after placement. This material is frequently used as a surgical suture and experience with this type of stent in the airway, oesophagus and biliary tract has been previously published [13, 14]. To identify the stent in a chest X-ray and to assist with bronchoscopic insertion, the stent usually has radiopaque gold markers at each end. Although these are very useful on clinical grounds, we considered that they were not necessary in this setting because of

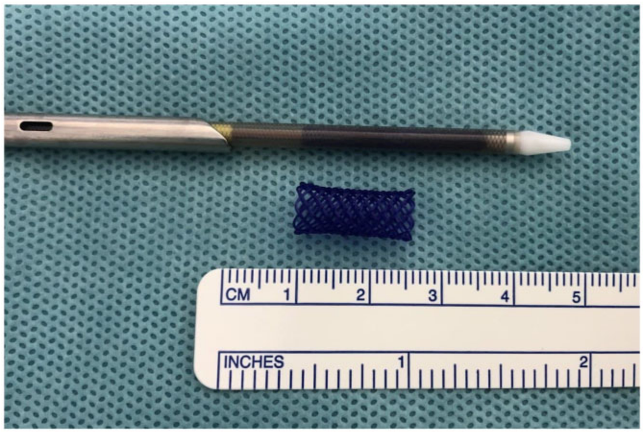


Figure 1: Polydioxanone stent: expanded shape and loaded into the delivery device (the distance between the distal end of the rigid bronchoscope and the proximal rim of the stent can be observed).

our distinct insertion technique (described below), so our stents were manufactured without them. According to previously published data [9] and considering the size of a rabbit trachea, with a body weight of 3.0–3.5 kg, our custom-made PDO stents had a diameter of 6 mm and a length of 20 mm. This diameter represents a 15–20% oversize of the normal tracheal section; hence, good stent stability is achieved and the risk of migration is decreased.

Stent placement technique

The whole procedure was performed under general anaesthesia with spontaneous ventilation. Intramuscular xylazine 20% (0.1 mg/kg), ketamine 5% (25 mg/kg) and atropine (0.08 mg/kg) were initially administered. Further doses of ketamine were provided intravenously through the aural lateral vein If deemed necessary. Local anaesthesia with lidocaine 2% (0.4 ml) was administered topically in the rabbit's larynx before exploring the airway. Monitoring was kept during the whole procedure. Subcutaneous meloxicam (0.3 mg/kg) was used for postoperative pain control.

Stent placement in the rabbit trachea was performed by means of rigid bronchoscopy together with telescopic rod lens image amplification connected to a TV camera. We used a purely endoscopic technique, without fluoroscopic or X-ray guidance, during the procedure. Prior to stent placement, the rabbit's airway was examined with a 2.9-mm diameter, 36-cm long, telescopic 0° lens (Karl Storz GmbH & Co. KG, Tuttlingen, Germany) from the glottis to the carina. Our insertion technique comprised the following steps: (i) the PDO stent was loaded manually into the dedicated delivery system (10.5 F, length 45 cm). When loaded, the stent elongates and is then covered by a plastic sheath; (ii) before tracheal placement, the delivery system was pushed inside the working channel of a paediatric rigid bronchoscope no 3 with an internal diameter of 4.3 mm and a length of 26 cm (Karl Storz GmbH & Co. KG) until its distal end, with the loaded PDO blue stent, showed completely. Then, the whole device was pushed forward 1 more centimetre and a tape mark was placed in the proximal part of the plastic coat in the exact site where it entered the bronchoscope's main port; (iii) the rigid bronchoscope was inserted orally placing its distal end immediately above the vocal cords; (iv) the delivery device was put inside the working channel of the bronchoscope and pushed until the tape mark in the plastic sheath matched with the main port; and (v) finally, the stent was delivered in the cervical trachea and the device removed from the bronchoscope (Fig. 1). The position of the stent was checked with a 2.9-mm telescopic rod lens and readjustments were done with an ultrathin (1-mm diameter, 35-cm long) semi-rigid alligator forceps (Karl Storz GmbH & Co. KG) if deemed necessary. The same technique was used in animals with 1 or consecutive stents (2 or 3) placed. An uneventful procedure was considered technically successful.

After the endoscopic procedure, the animals were returned to their individual cages and clinically assessed daily. Any signs of respiratory distress and/or changes in the feeding pattern, including water intake, were recorded. Follow-up was continued until the preset survival period (14, 28 and 42 weeks depending on the study group). No bronchoscopic control was performed during surveillance unless the rabbit showed significant respiratory symptoms. Prior to animal sacrifice, with pentobarbital sodium, the airway was endoscopically explored and any significant changes in the tracheal mucosa were recorded. The entire trachea was collected, fixed in 4% formaldehyde and embedded in paraffin for morphologic and histopathologic studies. To determine the degree of stenosis, the luminal areas at the implantation site of the stent and at the distal non-involved tracheal rings were photographed and the stenotic/normal luminal area ratio was calculated using ImageJ software (http://rsb.info.nih.gov/ij).

Histopathologic and immunohistochemistry analysis

Submucosal fibrosis was evaluated on Masson's trichrome-stained tracheal sections as the fractional collagen-stained area was measured using ImageJ software. Tracheas were also stained with Safranin O to assess the biochemical and structural integrity of cartilage. Immunohistochemistry was performed on deparaffinized and rehydrated tissues after microwave heating in citrate ph6 buffer for antigen retrieval. Immunoperoxidase labelling was performed with rabbit polyclonal anti-CD45 antibody (Bioss Antibodies, Massachusetts, USA) and developed by diaminobenzidine chromogen (Vector Laboratories, Burlingame, CA). Immunostained sections were visualized under a Zeiss Scope.A1 microscope (Zeiss, Jena, Germany), photographed and digitalized using an AxioCam ERc 5S camera and ZEN lite 2012 software. The number of CD45-positive cells per area was determined.

Statistical analysis

Statistical data were analysed using Prism software v6.0 (GraphPad Software, San Diego, CA, USA). Quantitative variables were described as median with interquartile range and were analysed as paired samples (normal versus stented trachea from the same animal) by *t*-test. Tracheal lumen value in each animal represents the proportion between stented and normal tracheal rings and it was expressed as percentage. Unpaired Kruskal–Wallis test was therefore used to compare tracheal lumen between the different groups. A *P*-value of <0.05 was considered significant.

RESULTS

Our endoscopic stent placement technique proved to be effective and technically successful in almost every case. Only in 1

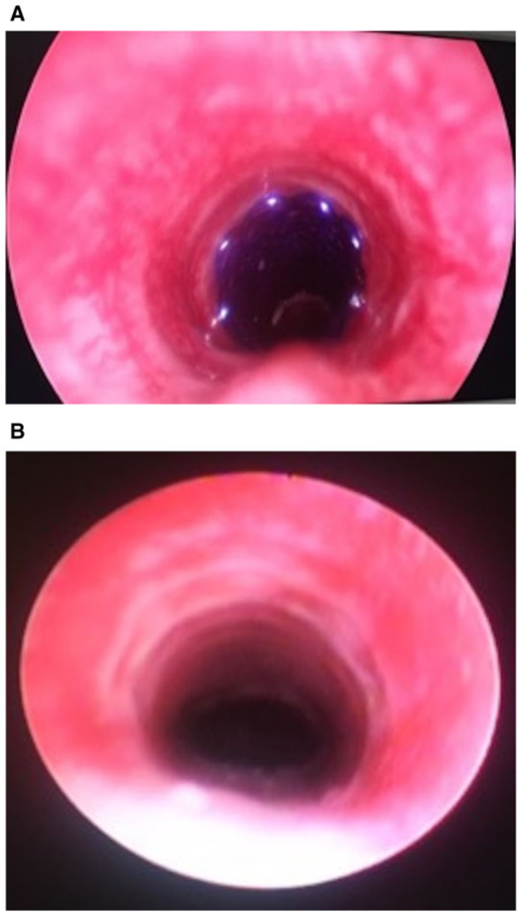


Figure 2: (**A**) Endoscopic view of a polydioxanone stent in the cervical trachea after deployment. (**B**) Endoscopic aspect of the trachea after resorption of the first stent (14 weeks after placement) showing mild changes in the mucosa and no stenosis.

rabbit, the stent was initially inserted into the oesophagus, but it was immediately retrieved and placed accurately in the trachea. From a clinical standpoint, no significant respiratory symptoms were observed in the 16 animals in the study group. In 4 cases (19%), progressive stridor and decreased appetite were detected ensuring an endoscopic exploration, which showed severe inflammatory stenosis with obstructive granulation tissue in both proximal and distal ends of the stent without migration or malposition. No attempts to treat medically or endoscopically the stenotic lesion were performed and the animals were immediately sacrificed and removed from the experimental group. This unexpected outcome, defined as early mortality, occurred before week 7 post-implantation and only in animals with the first stent placed. We considered that this stent-related complication was due to an immediate inflammatory reaction caused by the device in the trachea. Although we do not know the biological rationale, we assume that there must be some type of individual intolerance to PDO stents in certain subjects because there were no distinctive features in these animals. This clinical behaviour was completely different from the observed in the other 16 animals, who achieved the anticipated survival time in the study design. One more rabbit died because of intestinal obstruction due to trichobezoar on week 3 after the first stent insertion. No stenosis or obstructive granulation tissue was found in the histologic study of his trachea.

In the 16 rabbits constituting the study group, complete degradation of the PDO stent was bronchoscopically observed on week 14 after implantation. At that time, macroscopic mucosal inflammation was mild, without airway obstruction, and no migration or small fragments of the degraded stent were detected. These findings were very similar in animals with either 1 or more stents placed (Fig. 2A and B).

Histopathological analysis

Sixteen rabbits with PDO tracheal stents were analysed. Regarding the degree of endoluminal stenosis, we established the stenotic/normal luminal area ratio for every animal. The stenotic area corresponded to the tracheal segment where the stent was endoscopically placed (divided into 3 levels) and the normal area belonged to the adjacent non-stented distal trachea. We did not observe significant changes in this ratio in rabbits with 1 stent compared to those with 2 or 3 consecutive stents ($P = 0.96$). Interestingly, in many cases, we observed an increase in this ratio, above 100%, possibly due to the expansion effect of the stent (Fig. 3).

We histomorphometrically analysed tracheal tissue to identify stent-related potential changes. We first quantified the degree of fibrosis by measuring the collagen area in tracheal tissues stained by Masson's trichrome. As shown in Fig. 4, neither morphological nor quantitative changes were detected in the collagen area of the submucosa in the groups with implanted stents (1 or more) compared to the cross-section of control tracheas (non-stented distal segment) ($P = 0.74$ Ctrl vs 1 stent; $P = 0.80$ Ctrl vs 2 stents; $P = 0.18$ Ctrl vs 3 stents). We also determined whether the cartilage structure was modified by Safranin O staining, which did not show changes in the structure or acidic proteoglycan staining in any of the groups (Fig. 5) ($P = 0.84$ Ctrl vs 1 stent; $P = 0.65$ Ctrl vs 2 stents; $P = 0.70$ Ctrl vs 3 stents). To evaluate potential inflammatory changes caused by stent implantation (single or multiple), we analysed the presence of leucocyte infiltration by immunostaining with the pan-leucocyte marker CD45. We did not detect significant changes in the number of $CD45^+$ cells between stented tracheal segments compared to normal tracheal tissues (Fig. 6) ($P = 0.18$ Ctrl vs 1 stent; $P = 0.88$ Ctrl vs 2 stents; $P = 0.27$ Ctrl vs 3 stents).

DISCUSSION

The estimated incidence of congenital TM is ∼1:2100 children being the most common congenital tracheal anomaly [15]. Most patients show minor degrees of TM/TBM with mild-to-moderate respiratory symptoms. There is general agreement that most of these patients will improve gradually and their symptoms may resolve with time [2, 3]. The malacic trachea tends to become more rigid with growth and clinical improvement may be expected to occur by 1–3 years of age [2, 16]. However, severe life-threatening symptoms, such as apnoeic spells or inability to extubate the airway, may occur in a small group of patients usually under 1 year of age. In this setting, surgical treatment is indicated. Surgical options include tracheostomy, aortopexy, tracheal resection and tracheopexy [3].

Endoluminal airway stenting has recently emerged as an alternative to surgical treatment in selected cases [3–5]. When surgery has failed or is contraindicated for other reasons, stenting the

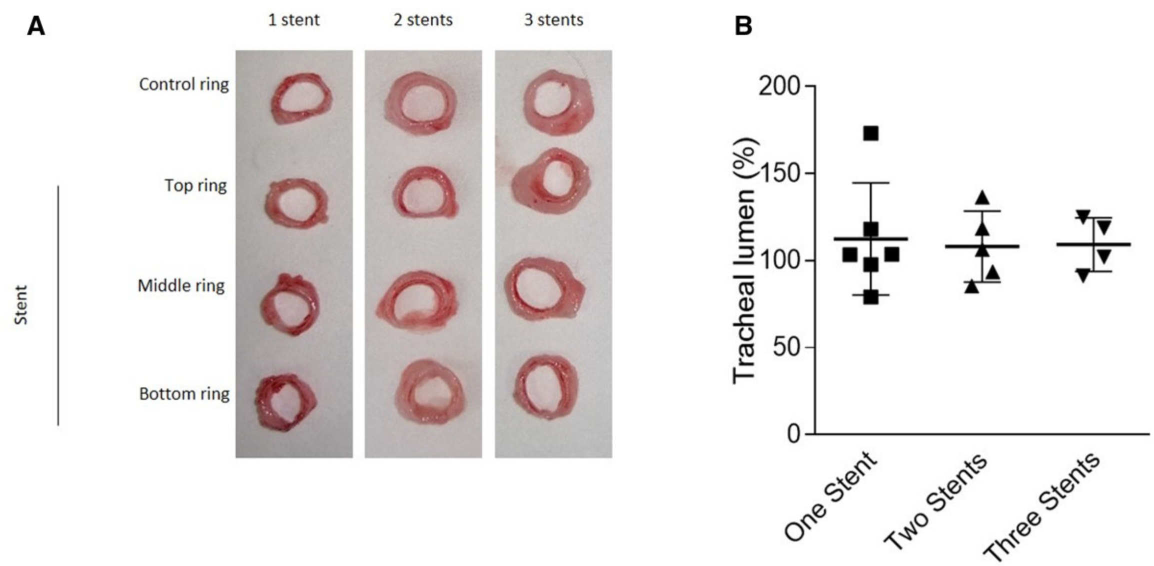


Figure 3: Tracheal lumen in rabbits with implanted polydioxanone stents. (**A**) Representative images of tracheas with stents. Cross-section of control ring (first) and different parts of the tracheal segment with a polydioxanone stent (proximal, middle, and distal). (**B**) Quantitative analysis of tracheal luminal area in the different groups of rabbits compared to control ring (value: 100%). Data are expressed as median with interquartile range.

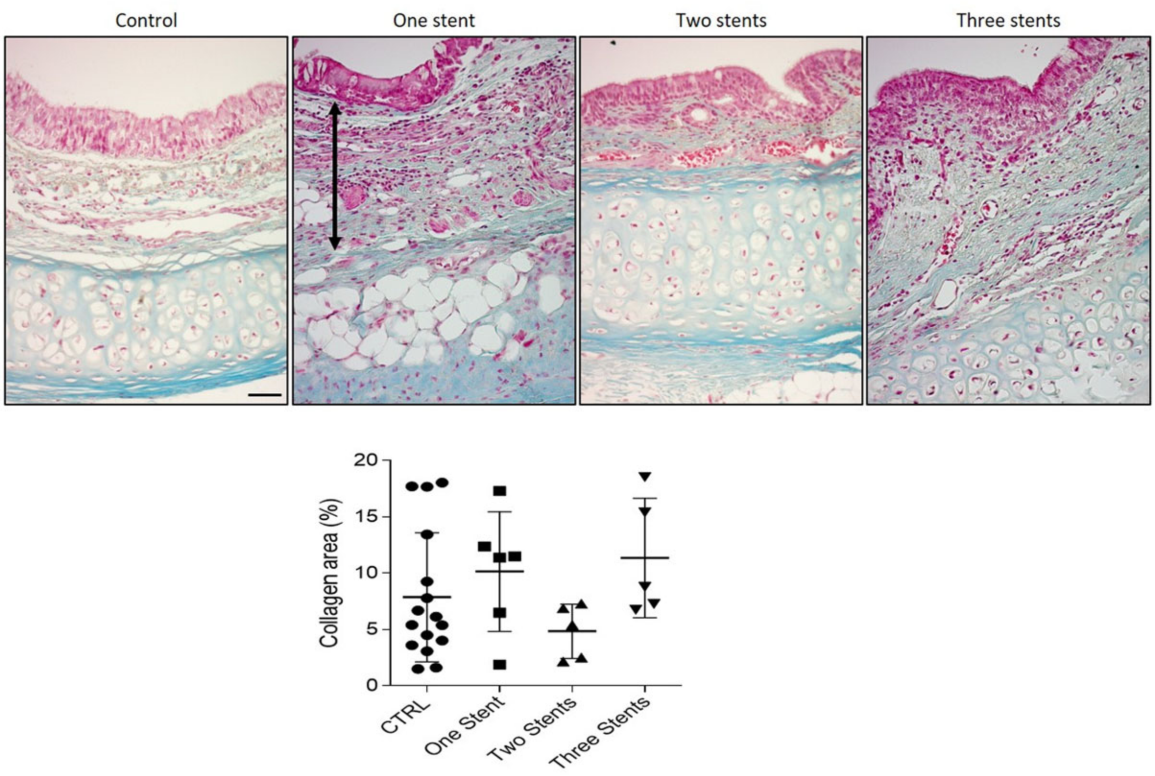


Figure 4: Histopathological evaluation of rabbit trachea with implanted polydioxanone stents. Representative images and quantification of collagen Masson-stained area in tracheal tissues after consecutive polydioxanone stent placement (arrow shows stained collagen area). Data are expressed as median with interquartile range.

trachea and/or main bronchi is an option to be considered, but this decision needs an individualized and multidisciplinary team approach [17]. Certainly, stenting is an attractive concept because it is non-invasive and relatively easy to carry out by an experienced team, but on the other hand, it is not devoid of concerns [3, 17, 18]. Airway stenting in children follows the trail of the adult practice, but in our setting, it is mainly used for treating tracheobronchial obstruction due to benign conditions such as malacia or stenosis [16]. Diverse stent types, with distinct material properties, are currently available. As a general rule, stents are classified into the following 4 groups: (i) metallic, (ii) plastic or silicone stents, (iii) hybrid or covered self-expanding metallic devices and (iv) BD/bioabsorbable stents [8, 17]. Recent research on this topic has focused on the development of BD stents to

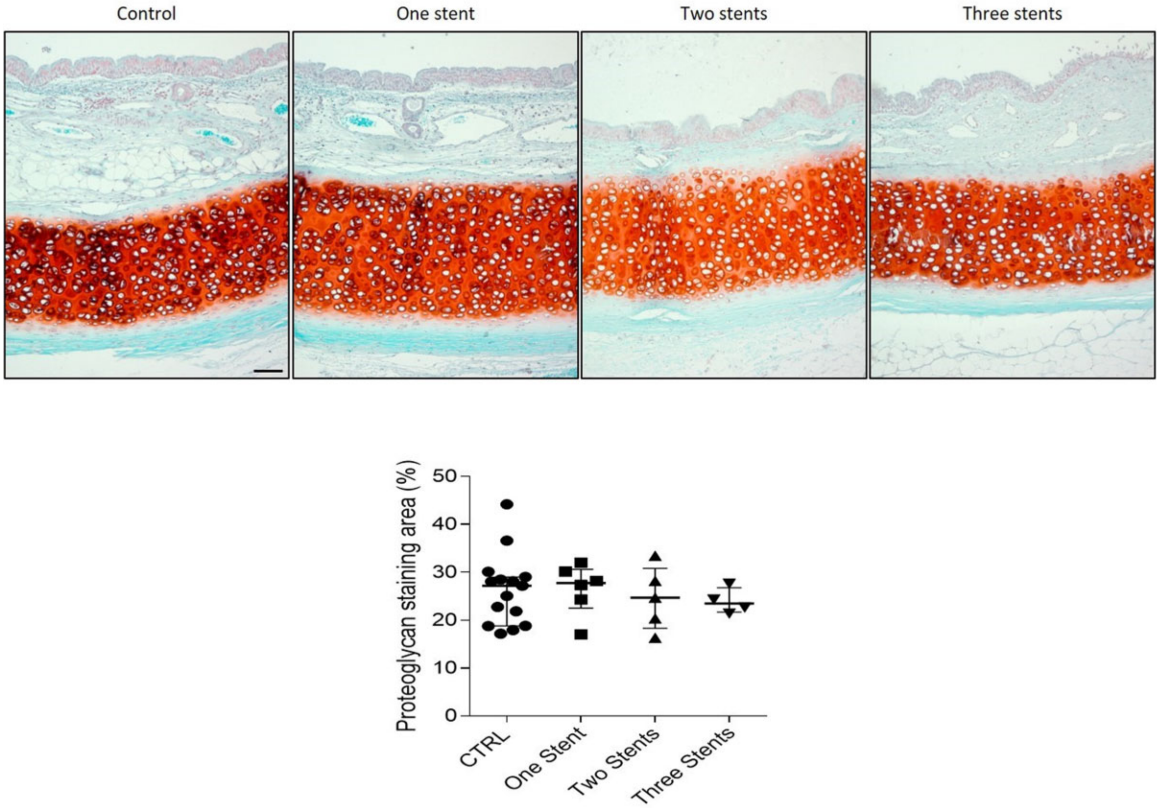


Figure 5: Evaluation of cartilage structure and proteoglycan staining in rabbit tracheal tissues. Representative images of cartilage structure determined by Safranin O-stained area: control and tracheas with implanted polydioxanone stents. Data are expressed as median with interquartile range.

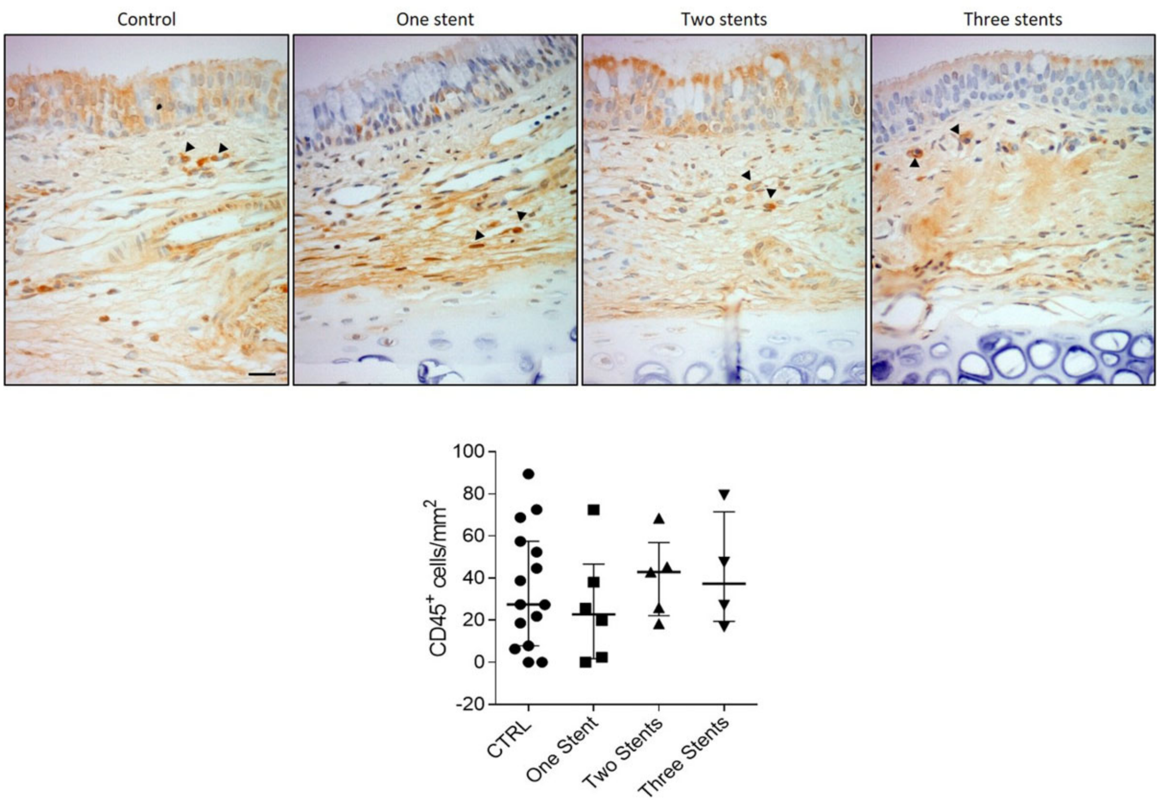


Figure 6: Immunohistochemical analysis of CD45 expression. Number of positive cells per area in the different groups and representative images (small arrow heads show positive cells in the submucosa). Data are expressed as median with interquartile range.

avoid or decrease the complications observed with other types of stents [9, 19–21]. The idea of a stent that achieves an effective airway patency, with few side effects, and does not need removal is really attractive. Nevertheless, stent biocompatibility, eventual toxicity of metabolites and time to resorption are relevant clinical concerns [12, 21].

This research study tries to answer some of these issues, particularly the potential histological changes in the tracheal wall caused by consecutive placement of PDO stents. Our clinical experience has shown that many patients with severe TM/TBM need >1 BD stent to maintain the initial clinical improvement observed after stent insertion [12]. The rationale for successive BD stent placement in children suffering from malacia relies on the stabilization of the airway to allow eventual spontaneous resolution [3, 12]. In other words, it can be a 'bridge treatment' to buy time until the trachea and/or main bronchi grow and their rigidity increases [3, 22]. In addition, restoration of airway patency in these very sick patients may substantially improve their clinical situation and eventually permit surgical correction or even permanent stenting [3, 17, 18].

Recent research has focused on the safety and potential effects of BD stents in the normal rabbit trachea and in a model of TM [19, 23, 24]. However, our study seems to be the first to analyse the eventual tracheal wall changes caused by consecutive insertion of PDO stents during an extended period of time (up to 42 weeks). As we have previously stated, our initial working hypothesis was based on the potential fibroproliferative reaction in the tracheal submucosa caused by serial stenting and the feasible advantageous effect that this could represent in terms of increased rigidity or consistency, without impairing the airway lumen, in cases of TM. This hypothesis was not endorsed by the histopathological findings that did not show an increase in the collagen area of the tracheal submucosa neither with 1 nor more PDO stents. Nevertheless, our study offers some new and relevant data regarding this issue since cartilage structure was not modified and inflammatory infiltrates in the tracheal wall were not observed even after serial stenting. These findings add to previous reports that suggest that PDO stents in the airway may be safe and effective [9, 23, 24]. Moreover, tracheal patency was maintained with consecutive stenting and tissue tolerance was good in most of the animals. Only 4 rabbits showed stent-related severe granulation tissue soon after the first PDO stent insertion. In our series, the animals that tolerated well the first stent did the same with the following and no significant granulation tissue was detected bronchoscopically in those rabbits with 3 consecutive stents and a follow-up of 42 weeks. Some authors claim that granulation tissue formation may be due to a previous lesion of the epithelium [20, 23], although this was not the case in our study. This particular issue, apart from a distinct individual response, remains to be elucidated.

Our study shows some distinct features compared to others with a similar design using PDO stents [9, 23, 24]. First, the implantation of consecutive stents (up to 3) with the ensuing extended time of follow-up (42 weeks), which is much longer than the usually reported (ranging from 1 to 15 weeks). Second, our purely endoscopic insertion technique has proved to be straightforward and successful. We have neither performed a tracheotomy nor used fluoroscopy or balloon dilation of the stent. As far as we know, our endoscopic stent insertion technique and the sequential placement of BD stents in the rabbit trachea have not been described before. Finally, this study adds to our relevant previous clinical experience with airway PDO stenting in children [12]. Although it does not give a full answer to all the possible concerns related to BD stenting, we have obtained very useful data regarding safety and tissue tolerance that supports our clinical practice. Our study agrees with current research stating that PDO stents in the airway are reasonably safe and may cause mild tissue reaction that is reversible in a few weeks after placement. Moreover, no fragments of the degraded PDO stents were observed and eventual airway obstruction caused by these residual pieces did not occur [9, 23, 24]. This issue was an important concern because potential airway obstruction due to large residual fragments has been reported [25], although this finding has not been endorsed by other authors with relevant clinical experience in children [12, 26–28].

Limitations

There are some limitations in our study. First, the sample size may limit the statistical analysis power, but we considered that our findings were consistent enough not to include more animals in the experimental groups. Second, the size of the stents was chosen based on previous reports and was not guided by preoperative image tests. Finally, it was performed in an experimental animal model with a normal trachea. Although a rabbit TM model has been recently developed [24], we consider that it does not fully recreate the specific features of TM seen in children.

CONCLUSION

Our study showed that successive PDO stenting caused mild inflammatory changes in the tracheal wall and no increase in the collagen matrix, and the cartilaginous structure was not modified during a long follow-up period. These findings suggest that they may be safe and show good biocompatibility in the long term. In our opinion, these facts support our clinical experience with PDO stents in the paediatric airway.

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Conflict of interest: none declared.

Data Availability Statement

The authors will provide all relevant data related to the manuscript under reasonable request.

Author contributions

Rocío Morante-Valverde: Formal analysis; Investigation; Project administration; Software; Validation. **Alicia Usategui:** Data curation; Formal analysis; Methodology; Software; Validation; Writing—original draft. **María López:** Data curation; Investigation; Project administration. **Montserrat Grau:** Investigation; Project administration; Supervision; Validation. **Mª Carmen Luna-Paredes:** Funding acquisition; Project administration; Supervision. **Salomé Albi:** Funding acquisition; Project administration; Visualization. **Marina Alonso-Riaño:** Formal analysis; Supervision; Validation. **José L. Pablos:** Conceptualization; Methodology; Supervision; Validation; Writing—original draft. Juan L. Antón-Pacheco**:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing—original draft.

Reviewer information

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