Invited lecture/Review

Materials of Absorbable Tracheal Stents and their Potential use for Treatment of Canine Tracheal Collapse

Novak Manca[1]*, Erjavec Vladimira[1]

1. University of Ljubljana, Faculty of Veterinary Medicine, Ljubljana, Slovenia
* Correspondence: Manca Novak; mn8532@student.uni-lj.si

Abstract:
Tracheal collapse in dogs can be treated by inserting tracheal stents. Currently used methods are placement of silicone or metallic intratracheal stent or extraluminal prosthetic rings, which have many post-operative complications and relatively short median survival times. The recent research is oriented in development of absorbable tracheal stents. Absorbable materials are showing great potential in preventing granulation formation, furthermore, the possibility of slow release of drugs incorporated into the stent could add to prevention of restenosis and even affect the tracheal cartilage properties. However, complications such as stent migration and fragmentation during degradation lead to many losses in in-vivo research. The aim of this article is to provide an overview of the current research on absorbable materials for tracheal stents, their complications, and advantages.

Keywords: Canine tracheal collapse; Absorbable materials; Copolymers; Drug release; Granulation prevention

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1. Introduction

1.1. Canine tracheal collapse

Canine tracheal collapse is a progressive disease in middle-aged small and toy breed dogs. It is characterized by focal or generalized dorsoventral flattening of the trachea. 71-93% cases respond to medical treatment, and in half of cases the medication can be gradually withdrawn. In severe cases, structural support of the trachea may be required (Tappin, 2016). Surgical correction is recommended in patients who have no other medical conditions, do not respond to medical treatment, and have a grade II or higher disease with severe clinical signs (Payne et. al., 2006).

1.2. Non-absorbable tracheal stents and complications after placement

The currently used stents are intraluminal stents (ILS) and extraluminal prosthetic rings (ELR). In a study of 74 dogs, major complications occurred in both ELR (42%) and ILS (43%). The median survival time of ELR of 1460 days was significantly higher than of ILS (365 days) (Tinga et al., 2015). Widely used silicone stents can disrupt mucociliary function of the epithelium due to their thickness and tubular geometry. Commonly observed complications include prosthesis migration, granulation formation, and sputum retention (Liu et al., 2011). In a review of 75 cases by Weisse et al. (2022) 7% of cases did not survive to hospital discharge, and 44 % of cases required more than 1 stent placements due to complications, most commonly stent fracture and tissue ingrowth.

1.3. Absorbable tracheal stents and complications in in-vivo studies

A bioabsorbable stent that is self-supporting and dissolves after competition of the remodeling process has advantages over metallic and silicone stents (Liu et al., 2011). An ideal airway stent should (1) be easy to place and remove, (2) provide effective airway expansion, (3) maintain position by being appropriately sized and adhering to the tracheobronchial wall, (4) be flexible enough to mimic airway physiology but have sufficient radial force to resist airway compression, (5) be biodegradable, (6) not cause tissue irritation during material degradation, (7) avoid granulation tissue reactions, (8) not impair mucociliary clearance, and/or (9) provide effective pharmaceuticals for a sustained period of time (Chao et al., 2013; Li et al., 2020)

Complications after placing the tracheal stent include airway obstruction due to degradation fractions leading to patient death (Liu et al., 2011) and stent migration, which is one of the most common reasons for stent failure. Complications occur with high incidence in clinical practice, especially in the initial period after stent placement (Jin et al., 2018).

2. Materials of absorbable tracheal stents

2.1. Polycaprolactone (PCL)

PCL showed good flexibility, fully regaining shape after loading, and had 90% of mechanical strength compared with metallic stents. There was no evidence of fracture or fragmentation. Complications included moderate excretion and intermittent stridor. Marked infiltration of lymphocytes, plasma cells, and eosinophils in the submucosa, although the cilia were preserved (Chao et al., 2013).

2.2. Poly-lactic acid (PLA)

Robey et al. (2000) state that adding PLA to PLGA makes the stent stronger under compressional stress. However, it also increases the degradation time and thus the potential for inflammation or foreign body reaction to the stent.

2.3. Poly-l-lactide acid (PLLA)

PLLA stents showed good mechanical properties (Zhu et al., 2011). However, PLLA has degradation time of 2-4 years. Saito et al. (2007) researched their implication in the

treatment of benign stenosis of the gastrointestinal tract. The radial force was 117 gf, comparable to commercially available metallic stents.

2.4. Polydioxanone (PDO)

12 patients (52%) had significant benefit from treatment, early failure (migration and inadequate radial force) occurred in 2 patients, inadequate or questionable effects were recorded in 7 patients, and 2 patients died of comorbidities before the stent was fully degraded (Stehlík et al., 2016). Novotny et al. (2012) concluded that the highest tracheal damage occurred 5 weeks after implantation, which included immediate necrosis. Stent degradation was complete after 10 weeks, and trachea was completely healed after 15 weeks. Morante-Valverde et al. (2022) found that PDO stenting caused mild inflammatory changes and no increase in collagen matrix in the rabbit trachea. Grolich et al (2015) used PDO for biliary stent research. It degraded in 13 weeks and showed no cholangitis, necrosis, abscess, or excessive fibro-plasia.

2.5. Poly(lactic-co-glycolic acid) (PLGA)

Robey et al. (2000) concluded that stents in buffer solution almost completely degraded at 14 weeks. In vitro data showed that the stents tended to break after only 4 weeks in buffer solution.

2.6. PLLA-PCL copolymer 70/30

In the experiment with tubular stents by Zhu et al. (2011), mucous plugging occurred in 5/5 rabbits, and one died. Tracheal stenosis was more severe compared to silicone stents. To increase water absorption into the copolymer and shorten the degradation time from 6 weeks to 3 months (Zhu et al., 2011). Duvvuri et al. (2019) found that the PLLA-PCL construct demonstrated superior mechanical strength and greater drug elution compared to PLGA stents.

2.7. Poly(lactic-co-glycolic acid) – polyisoprene (PLGA-PI) copolymer

Schopf et al. (2018) compared a complete stent with a stent fragment, although the fragment group had fewer complications, both groups showed stridor, agitation, and had inflammatory damage.

2.8. Biodegradable magnesium alloy stent

After complete degradation of the LZ61-KBMS stent, the tracheal tis-sue was normal compared with the healthy rabbit tracheal tissue as shown by both endoscopic and histological analysis. The tracheal mucosa was also fully restored in the LZ61-KBMS stent after 8 weeks. This is criti-cal because scarring of the mucosa can promote the formation of stenotic tissue (Wu et al., 2020). Magnesium alloys are attracting interest due to their mechanical properties, excellent biocompatibility and unique biodegradability. High performance Mg alloys are mainly Mg-Zn-based alloys, Mg-Ca-based alloys, Mg-Li-based alloys, Mg-Cu-based alloys and Mg-RE-based alloys.
Zn has a strengthening effect in the Mg matrix, and the Mg-Zn alloy has three times the yield strength and Young's modulus of pure Mg. Mg-Ca alloy has the best corrosion resistance. Mg-Ca-Zn-Ag had even better bio-compatibility, osteogenic activity, and corrosion resistance. Mg-Li en-hances the plasticity of the alloy (Chen et al., 2022).

3. Drug-impregnated stent options

The incorporation and controlled release of various drugs gives bio-absorbable stants great potential for various clinical applications (Liu et al., 2011). The combination of a drug-loaded film and a stent can provide high drug loading and meet various drug release requirements to maintain effective drug concentration. Reportedly the drug loading of the film on the stent can reach up to 50% and the drug release can last for more than 3 months (Jin et al., 2018). Tatekawa et al. (2010) reported the use of biodegradable gelatin hydrogel sheet for controlled release of drugs, which degrades

by hydrolysis in about 2–4 weeks. These authors also reported the use of PLGA-collagen hybrid mesh for drug release. The mesh degraded in 2-3 months.

3.1. Dexamethasone

Results from PLLA stents showed near-linear release profiles for dexamethasone (Zhu et al., 2011).

Neutrophils and macrophages ingest pathogens, debris, and damaged tissue, allowing for protection and healing (Alhajj and Goyal, 2022). However, many authors report severe inflammatory reactions in the tracheal submucosa after stent placement. Chao et al. (2013) found marked infiltration of lymphocytes, plasma cells and eosinophils in the submucosa. Jin et al. (2018) reported severe inflammation and exudation of inflammatory cells on day 10 after insertion, and mild inflammation without exudation 30 days after insertion.Anti-inflammatory drugs could alleviate inflammation in the early days after stent insertion.

3.2. Mitomycin C (MMC)

MMC is an antimitotic drug that is widely used to treat various cancers. After 12 weeks, the tracheal stenosis in bioabsorbable tubular PLLA stents with MMC was half of that in silicone stents, taking into account that the stenosis in silicone stents was even smaller than in PLLA stents without MMC (Zhu et al., 2011).

3.3. Cisplatin

Polycaprolactone stents coated with cisplatin released cisplatin in vivo for 5 weeks, with minimal concentration detected in blood. High concentrations could be released for more than 30 days. The ciliated epithelium remained intact, but marked submucosal leukocyte infiltration occurred (Chao et al., 2013).

3.4. Polysaccharides, derivatives of cellulose and poly(acrylic acid)

The mucoadhesive delivery of drugs can prolong the residence time of the drug, leading to an improvement of the bioavailability of the drug and a reduction in the frequency of administration. In addition, it is pos-sible to achieve targeted delivery to specific site or tissues using specific mucoadhesive polymers. The mucoadhesion of carbomer can be used to prevent stent migration and achieve local drug release (Jin et al., 2018).

3.5. Carbopol

The nitinol tracheal stent was combined with a bilayer film containing Carbopol 974P to maintain mucoadhesion, to prevent migration and to achieve effective local drug delivery. The mechanical performance of the stent was not affected by the combination with the mucoadhesive bilayer. However, upon degradation, the fractions caused airway obstruction, leading to patient death (Liu et al., 2011).

3.6. Rapamycin

The addition of rapamycin to nitinol stents significantly decreased airway inflammation and granulation tissue formation compared with bare metallic stents (Chen et al., 2022).

3.7. Paclitaxel

The use of paclitaxel coated tracheal stents in a canine model significantly reduced granulation tissue formation after stent implantation, but granulation tissue still grew through the stent mesh (Wang et al., 2016).

3.8. Arsenic trioxide (ATO)

In cardiovascular stents, exposure of ATO reduced porcine coronary artery smooth muscle cell viability and promoted endothelial cell proliferation and re-endothelialization faster than rapamycin (Zhao et al., 2018). ATO also prevented the

growth of granulation tissue through the stent mesh into the lumen of the trachea (Li et al., 2021).

3.9. Collagenous gel seeded with cells

Nomoto et al. (2006) reported that epithelialization of trachea is accelerated when covered with a collagenous gel seeded with isolated autologous tracheal epithelial cells, adipose-derived stem cells or multipotential bone marrow-derived cells (mesenchymal stem cells).

3.10 bFGF and BMP-2

Controlled and sustained release of growth factors could promote accelerated cartilage growth across the reconstructed segment. The growth of new cartilage across the reconstructed segment would ultimately provide the greatest stability for a newly reconstructed airway (Robey et al., 2000). Tetekawa et al. (2010) concluded that although the use of bFGF in stents did not develop complete cartilage the regeneration of cartilage was evident. bFGF also significantly improved the elastic modulus of the stent, but still did not reach the levels of the native trachea. Stable release of bFGF was achieved by impregnation of a gelatin hydrogel.

Igai et al. (2006) also used bFGF and bone morphogenetic protein (BMP)-2 collagenous sponge as scaffold to promote the regeneration of the tracheal cartilage. The use of BMP-2 is also reported by Yasumichi et al. (2003).

3.11. Antibacterial drugs

Granulation tissue formation results from repetitive motion trauma and infection. Lower respiratory tract infections were associated with lower survival (Ost et al., 2012). Shuai et al. (2018) reported that Mg-Cu- based alloys during degradation enhance the antibacterial ability and de-stroy bacterial cells.

4. Conclusion

Absorbable tracheal stents have great potential to reduce complica-tions in the treatment of canine tracheal collapse. Granulation formation can also be reduced by incorporating drugs into the stents. Further re-search should focus on developing thinner stents without fragmentation or migration and with high biocompatibility

Conflicts of Interest: The authors declare no conflict of interest.

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