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Original Research Article

Treatment of Tracheal stenosis by rigid bronchoscopic dilatation and topical Mitomycin – C application

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Abstract: Tracheal stenosis is a known complication of prolonged intubation. It is difficult to treat and traditional surgical approach is associated with significant risk and complications. Recurrent stenosis due to granulation tissue necessitates repeated procedures. We have described cases of short web-like tracheal stenosis (concentric membranous stenosis less than 1 cm in length without associated cartilage damage) managed by a minimally invasive thoracic endoscopic approach. Topical application of Mitomycin C, a potent fibroblast inhibitor reduces granulation tissue formation and prevents recurrence.
Keywords: Tracheal stenosis, endoscopy, mitomycin c

INTRODUCTION

The management of benign stenosis of the central airways continues to be challenging. Acquired benign airway stenosis can result from a variety of injuries to the airway wall: ischemia related to endotracheal intubation, surgical procedures such as tracheotomy or airway resection, chemical or thermal injury, direct mechanical trauma after bacterial or mycobacterial infections, from inflammatory diseases affecting the airways such as Wegener granulomatosis or sarcoidosis, after radiotherapy, stent-stimulated granulation tissue, and idiopathic when the cause cannot be identified [1].

After any of the afore-mentioned damages to the mucosa, the following inflammatory process activates fibroblasts to participate in wound healing. Fibroblasts synthesize several factors, such as transforming growth factor B1 and basic fibroblast growth factor that stimulate the production of extracellular matrix components, leading to scar formation and contraction at the stenosis site. The same mechanism takes place in restenosis [2, 3].

Current treatment includes surgical resections as the first option. However, when surgery is unsuitable because of the patient's clinical or respiratory conditions or airway issues, endoscopic approaches need to be considered. Airway patency can be reestablished by means of Mechanical dilation with the bevel of the rigid bronchoscope, balloon inflation, laser ablation, electrocautery or argon plasma coagulator, stent insertion, or usually, a combination of any of the above [1]. However, a high rate of restenosis ranging from 40% to 70% has been reported after the endoscopic treatment of tracheal stenosis, urging a need for therapies aimed to obtain better results. Treatments studied to reduce relapses include steroids, 5-fluorouracil, halofuginone, tamoxifen, and mitomycin-C (MMC) [4].

What is mitomycin-C?

Mitomycin-c is an antibiotic produced by Streptomyces caespitosus. It is referred to as mitomycin –c to differentiate from mitomycin A and B. It has both antineoplastic and antiproliferative properties. Its antineoplastic activity is similar to that of alkylating agents causing cross-linking of DNA and inhibiting RNA and protein synthesis. Mitomycin –c also act as an

antiproliferative agent that can inhibit fibroblast activity and suppress fibrosis and scar formation.

The exact mechanism by which mitomycin-C exerts an antifibroblast activity is unknown. There is evidence to suggest that the reduction of fibroblast . activity may be mediated by apoptosis, which is a gene directed process causing cell death. Apoptotic cells display a characteristic morphology that includes condensation of the nucleus and cytoplasm, nuclear fragmentation, and cytoplasmic blebbing with an intact cell membrane [8, 9]. Mitomycin has antifibroblast ic properties in vivo. A single application of mitomycin could inhibit fibroblast proliferation. Mitomycin has been successfully used for prevention stenosis in glaucoma surgery, dacryo cysto rhinostomy, optic nerve sheath fenestration, and pterygium recurrence [10-14]. The fibroblast population and collagen formation are substantially increased during the wound healing response that follows a mucosal insult such as a surgical procedure. The rationale of use of mitomycin-C is to inhibit fibroblast proliferation during the postoperative phase without damaging the mucosal and epithelial growth.

Below is the data of patients presented at our institution with their pre and post op data and details of the surgical procedure carried out.

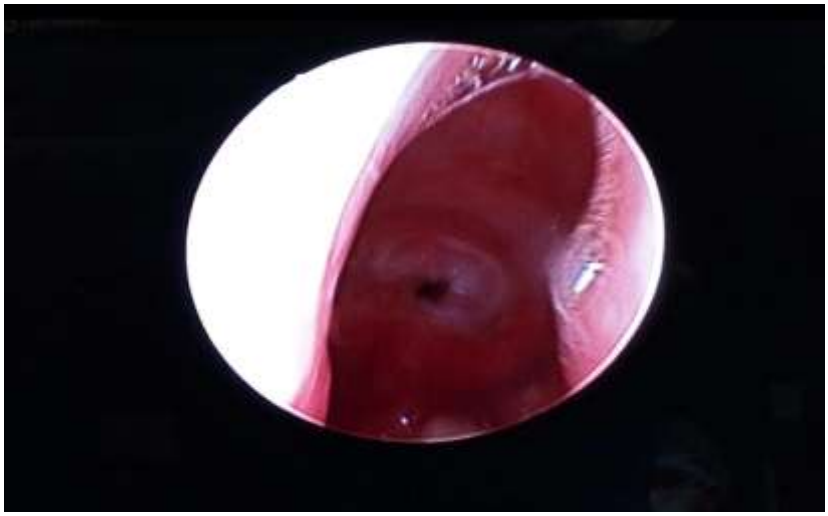

Fig-1:Post op dilatation for subglottic stenosis

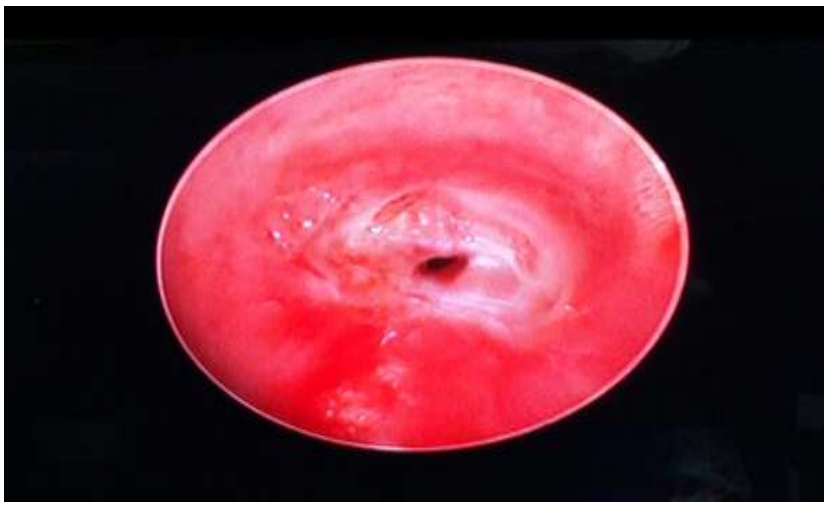

Fig-2:Post op dilatation for subglottic stenosis (closer view)

Fig-3:Preop CT scan for subglottic stenosis (coronal view)

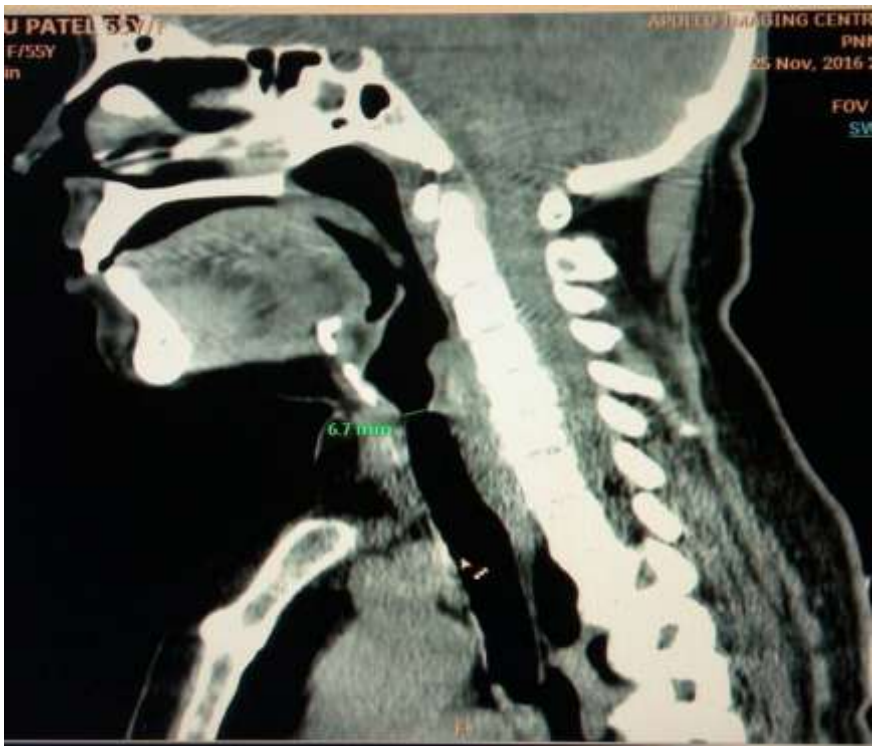

Fig-4:Preop CT scan for subglottic stenosis (sagittal view)

Technique:

We prefer to do the procedure under general anesthesia by rigid bronchoscopy to avoid excessive contact of MMC with the upper airway and normal mucosa, and because most of the times the central airways become occluded for several minutes, limiting tolerability in the patient who is awake [5].

Bougies were then used to dilate the stenotic area in incremental size. MMC is usually available as lyophilized crystals that give the product a pale blue color after preparation with sterile water. In most of the studies in humans, the applied concentration is 0.4mg/mL. However, concentrations of 10 mg/mL did not show to cause statistically more complications than lower doses [6, 7]. The only comparison between these 2 concentrations in terms of effectiveness is inconclusive due to selection bias. In our protocol, we use the 1mg/mL concentration without complications. After preparation of the solution, the forceps is advanced through a rigid bronchoscope until it exits its distal tip. A customized cotton swab is grabbed with the forceps and it is retracted very close to the tip of the scope, just allowing visualization of the most distal part of the forceps.

The size of the cotton swab is made to fit the size of the stenosis that is to be treated. The cotton is then soaked with MMC, and the flexible bronchoscope is advanced through the rigid bronchoscope toward the dilated stenosis, and the cotton is placed in contact with the wall of the lesion. Unlike inside the trachea, when applied to a main bronchus or distally, the cotton can be left in place without holding it with the forceps. In accordance with the application time reported in most of the studies, the cotton is left in place for 5 minutes and is then removed. Mucus, blood, and debris should be aspirated before and after application. We do not recommend flushing the treated mucosa after MMC application, to keep the effect and to avoid possible side effects if the drug-containing fluid reaches the periphery of the lung. We repeat this procedure on a planned schedule until the situation is stabilized. Postoperatively injectable steroids were given for 1 day which was followed by oral steroids.

Table-1:Patient Data

Age/sex	Etiology of stenosis	Chief complain present at	No. Of times dilatation done	Maximum dilatation done	Duration from primary assault	Follow up period	Level of stenosis	Steroids given	Present status #
30yrs/F	H/O intubation	Dry cough	2	14	1 month	3 months	Subglottic	Yes	Good
53yrs/F	RTA	Stridor	1	36	1 month	2 months	Glottic	Yes	Good
34yrs/M	Suicidal hanging	Difficulty in breathing	2	36	1 month	3 months	subglottic	Yes	In the process of decannulation
32yrs/M	OP poisoning	Difficulty in breathing	3	30	2 months	3 months	Subglottic	Yes	Good
30yrs/M	Blunt trauma	Difficulty in breathing	8	32	2 days	3 months	Subglottic	Yes	Good
38yrs/M	H/O intubation	Difficulty in breathing	3	28	20 days	3 months	Subglottic	Yes	Good
42yrs/F	Suicidal hanging	Stridor	2	26	7 days	3 months	Subglottic	Yes	Good

Results as good are defined on the basis of clinical improvement of the degree of stenosis and resolution of preoperative symptoms.

DISCUSSION:

Myer-Cotton scale for tracheal stenosis:

- Grade I: obstruction of 0 to 50%.
- Grade II: obstruction of 51 to 70%.
- Grade III: obstruction of 71 to 99%.
- Grade IV: punctiform obstruction without detectable light.

Patients with acquired or congenital SGS present different clinical features (age, location, severity and length of the stenosis, and associated comorbidities that are closely related to the prognosis and final outcome. Dilation of stenosis and in growing tissue removal should be first achieved by the preferred technique, namely LPR, argon plasma coagulator, electo cauterization, and dilation with balloon or with the rigid bronchoscope being the most commonly used techniques. However, it should be emphasized that most of the published studies in humans used LPR before applying MMC [6].

The first decision is whether an open surgical technique is necessary or whether an endoscopic approach is adequate. Factors such as 1) age, 2) general medical condition, 3) cause, location, degree, length and consistency of stenosis, 4) previous treatment should be considered. These conditions are variable in each patient, so comparative studies between traditional open surgery and endoscopic techniques are difficult to perform. Therefore, descriptive case series are important to know the management and surgical indications in this pathology. The optimal treatment of tracheal stenosis remains undefined. Traditionally, tracheal stenosis has been managed by thoracic and otorhinolaryngology surgeons. Endoscopic procedures are usually performed as a bridge to definitive surgical intervention. Endoscopic treatment had been shown to be useful, especially in patients who are deemed high risk and too unwell for reconstructive surgery. One of the main drawbacks of endoscopic treatment and surgery is the risk of recurrence of trachea stenosis due to granulation and fibrotic tissue. Studies have shown that most of the recurrence of tracheal stenosis occurs within one to three months after the procedure, and use of Mitomycin C has been reported in case studies to reduce the rate of recurrence.

Mitomycin C which is isolated from Streptomyces caespitosus acts as a bifunctional alkylating agent cross-linking DNA thereby inhibiting DNA synthesis. Both in vitro and in vivo, Mitomycin C have been proven to be a potent inhibitor of human fibroblasts at concentrations of 0.04 mg/L. It has been used with some success in inhibiting the vigorous granulation response noted after airway injury in animal models and pediatric patients. It has also been used in ophthalmology to treat glaucoma and pterygium. Nd: YAG laser would be an interesting alternative to APC for coagulation but it was not available to us at the time. Identification of structures which are distorted by granulation tissues should be done. This prevents the formation of false tract and accidental perforation of the trachea. In skilled hands, the use of a suspension laryngoscope would be an alternative to rigid bronchoscope in this case. Suspension laryngoscope is ideal if the lesion is either at the vocal cords or just below the vocal cords (subglottic).

However, suspension laryngoscope needs to be used with a caveat that there may be a higher risk of irritation and injury to the vocal cords during insertion of surgical instruments to reach the target area which was 3 cm below the vocal cords. The use of rigid bronchoscope allows us to introduce surgical instruments multiple times to the target area with minimal risk of irritating or injuring the vocal cords. The application of topical Mitomycin C is made possible with the rigid forceps which allows application of sufficient force to the airway mucosa to allow proper application of Mitomycin C. It is important to apply Mitomycin C with sufficient force and contact time to allow Mitomycin C to work.

With a contact time of 8 minutes, there is evidence of only minimal granulation tissue or scar tissue after 4 months.

Topical Mitomycin C also appears to be safe and there is no detectable myelosuppression. Our results demonstrate that the topical application of mitomycin-C can be beneficial in the modulation of wound healing and in decreasing scar formation in the treatment of airway stenosis. Our study is the first to describe the use of mitomycin-C as an adjuvant treatment in the endoscopic management of laryngeal and tracheal stenosis in both pediatric and adult populations. Further research and randomized prospective clinical trials are needed to determine the most effective concentration and time of exposure of mitomycin-C, and the difference in efficacy and safety between single and multiple applications.

Regardless of the surgical techniques, there is further injury to the airway mucosa that leads to fibroblast proliferation and collagen formation, which are the key to scar formation. Modulation of the wound healing response to prevent excessive scar formation can play a major role in increasing the success of surgical treatment and reducing the need for further surgery. In the past decade the role of growth factors and fibro genic peptides in the regulation and modulation of wound healing leading to fibrosis and scar formation has been reported. Pharmacological agents such as 5-fluorouracil and B-amino propio nitrile (BAPN) have been shown to inhibit the development of collagen cross linking, thus minimizing scar formation. We have defined success as clinical improvement of the degree of stenosis and resolution of preoperative symptoms.

CONCLUSION:

Tracheostomy is a known complication of prolonged intubation. The management of benign stenosis of the central airway continues to be challenging. Endoscopic application of Mitomycin-C is an easy and safe procedure. So far, Mitomycin-C shows to be a valuable adjuvant treatment for benign airway stenosis. Well-designed studies are required to confirm this and to address other areas of uncertainty, such as

which patients benefit the most? What number of applications and intervals give the best results? Mitomycin-C off ers an attractive area of research in the treatment of benign airway stenosis.

Topical Mitomycin C is a useful adjunct in the management of short concentric membranous stenosis which does not involve the cartilage. It reduces granulation tissue and prevents recurrence. Further randomized controlled studies are necessary to explore the possibility of this treatment method in the algorithm for the management of tracheal stenosis. This may obviate the need for invasive reconstruction surgery and repetitive procedures. Different surgical techniques have been proposed and no single approach has been proved satisfactory.

Based on our experience and limitations of our institutional set up we conclude:

In a set up with no laser facility, endoscopic dilatation with mitomycin-c application is a good initial alternative procedure for certain case of trachea stenosis.

Results are satisfactory.

Patient gets a window period after endoscopic dilatation for improving general condition and if required may be referred to higher center for further aggressive management and curative treatment.

REFERENCES

1. Ernst A, Feller-Kopman D, Becker HD, et al. Central airway obstruction. Am J Respir Crit Care Med.2004; 169:1278–1297.
2. Karagiannidis C, Velehorschi V, Obertrifter B, Macha HN, Linder A, Freitag L. High-level expression of matrix-associated transforming growth factor-β1 in benign airway stenosis. CHEST Journal. 2006 May 1; 129(5):1298-304.
3. Chen T, Kunnavatana SS, Koch RJ. Effects of Mitomycin-C on Normal Dermal Fibroblasts. The Laryngoscope. 2006 Apr 1; 116(4):514-7.
4. Smith ME, Elstad M. Mitomycin C and the endoscopic treatment of laryngotracheal stenosis: are two applications better than one? The Laryngoscope. 2009 Feb 1; 119(2):272-83.
5. Murgu SD, Colt HG, Mukai D, Brenner M. Multimodal imaging guidance for laser ablation in tracheal stenosis. The Laryngoscope. 2010 Sep 1; 120(9):1840-6.
6. Warner D, Brietzke SE. Mitomycin C and airway surgery: How well does it work? Otolaryngology-Head and Neck Surgery. 2008 Jun 30; 138(6):700-9.
7. Hueman EM, Simpson CB. Airway complications from topical mitomycin C. Otolaryngology--Head and Neck Surgery. 2005 Dec 1; 133(6):831-5.
8. Desmouliere A, Redard M, Darby I, Gabbiani G. Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar. The American journal of pathology. 1995 Jan; 146(1):56.
9. Lee DA, Lee TC, Cortes AE, Kitada S. Effects of mithramycin, mitomycin, daunorubicin, and bleomycin on human subconjunctival fibroblast attachment and proliferation. Investigative ophthalmology & visual science. 1990 Oct 1; 31(10):2136-44.
10. Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. Ophthalmology. 1991 Mar 1; 98(3):317-21.
11. Urban RC, Kaufman LM. Mitomycin in the treatment of hypertrophic conjunctival scars after strabismus surgery. Journal of pediatric ophthalmology and strabismus. 1994 Mar 1; 31(2):96-8.
12. Kao SC, Liao CL, Tseng JH, Chen MS, Hou PK. Dacryocystorhinostomy with intraoperative mitomycin C. Ophthalmology. 1997 Jan 1; 104(1):86-91.
13. Rubinfeld RS, Stein RM. Topical mitomycin-C for pterygia: is single application appropriate?. Ophthalmic Surgery, Lasers and Imaging Retina. 1997 Aug 1; 28(8):662-9.
14. Schipper I, Suppelt CH, Gebbers JO. Mitomycin C reduces scar formation after excimer laser (193 nm) photorefractive keratectomy in rabbits. Eye-london-ophthalmological society of the united kingdom then royal college of ophthalmologists-. 1997 Jan 1; 11:649-55.