Bronchoscopic Application of Mitomycin-C as Adjuvant Treatment for Benign Airway Stenosis

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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 can not 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 β1 and basic fibroblast growth factor, that stimulate the production of extracellular matrix components, leading to scar formation and contraction at the stenosis site.[2,3] The same mechanism takes place in restenosis.

Current treatment includes surgical resection 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.[1] 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,[4–7] 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).[7]

Mitomycin is an antibiotic that was isolated from the bacteria *Streptomyces caespitosus* in 1956. Its C-form is an alkylating agent that inhibits deoxyribonucleic acid synthesis. It was first used as an anticancer drug. It has also been used in ophthalmologic procedures to reduce corneal scarring and recently in the treatment of benign airway stenosis.[8]

THE EVIDENCE FOR MMC

Despite design limitations, there are a number of studies that show its inhibitory effects in modulating the mediators and proteins involved in scar formation, reducing fibroblast density, reducing wound contracture and fibrosis, and improving airway patency. Clinical studies in patients with laryngotracheal stenosis have been published since 1998, most of them being case reports and retrospective reviews. Benefit has been reported in pediatric and adult patients, and some retrospective cohorts suggest better results from the combination of laser photoresection (LPR) and MMC, compared with LPR alone and compared with the combination of LPR and steroids.[9] Although emphasizing careful interpretation, a review indicated that 81% of the patients from 7 selected studies had improved outcomes attributable to MMC.[10] A comprehensive review of this data can be found in the studies by Smith and Elstad[7] and Hirshoren and Eliashar.[11]

These studies also suggested that there is a time window in the wound-healing process, at or

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before the time of injury for optimal effect to occur, and that MMC delays the wound-healing response but does not entirely suppress it. Clinical studies showed no benefit from MMC, when applied several days after reconstruction or dilation, probably because the therapeutic window was already closed and the scar process had already commenced.

A recent prospective, randomized, controlled study in adults with laryngotracheal stenosis found that 2 consecutive MMC applications 1 month apart after dilation, reduced restenosis rate at 3 years compared with a single application. Restenosis rate after 5 years was the same for both arms. However, this restenosis delay reduces the number of endoscopic dilation procedures in about 25% to 50% during a 10-year course, and has proved to be cost effective.[7,12]

TECHNIQUE

We prefer to do the procedure under rigid bronchoscopy and general anesthesia, 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.

To our experience, endobronchial ultrasound can be useful in the assessment of the airway wall and its surroundings at the stenosis site (Fig. 1). Endobronchial ultrasound findings, such as cartilage destruction and persistent hypertrophic tissue after ablation could be associated with a higher chance of recurrence.[13]

Dilation of stenosis and ingrowing tissue removal should be first achieved by the preferred technique, namely LPR, argon plasma coagulator, elecrocauterization, 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.[7,10]

MMC is usually available as lyophilized crystals that give the product a pale blue color after preparation with sterile water (Fig. 2). In most of the studies in humans, the applied concentration is 0.4 mg/mL. However, concentrations of 10 mg/mL did not show to cause statistically more complications than lower doses.[10,14] The only comparison between these 2 concentrations in terms of effectiveness is inconclusive due to selection bias.[15] In our protocol, we use the 1 mg/mL concentration without complications.

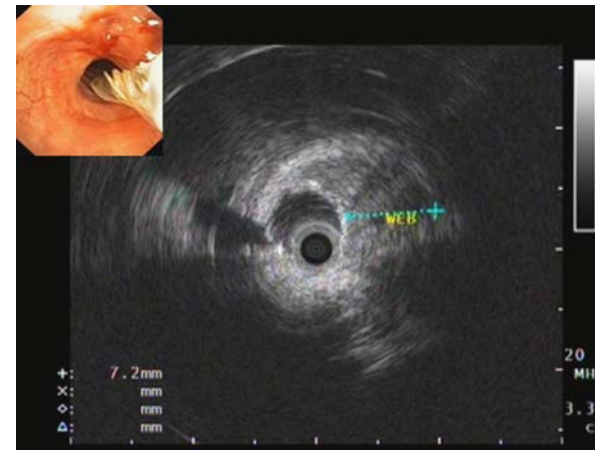

FIGURE 1. Tracheal stenosis: endobronchial ultrasound image measuring the web between the lumen and the cartilage, showing integrity of the latter. Corresponding endoscopic image with a deflated balloon endobronchial ultrasound probe. a+

After preparation of the solution, the forceps is advanced through a flexible 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 (Fig. 3), 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 (Fig. 4). In accordance with the application time reported in most of the studies,[10] 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

FIGURE 2. Appearance of reconstituted Mitomycin-C. a+

FIGURE 3. Soaking the cotton swab with Mitomycin-C. The flexible forceps is preloaded into the working channel. a+

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. For a summarized film of the technique see Video, Supplemental Digital Content 1. http://links.lww.com/LBR/A55.

COMPLICATIONS

So far, no systemic effects of MMC application in the airways have been reported.

When the cotton with MMC occludes the central airways, the team must be aware that the patient might need additional measures to maintain oxygenation during the recommended 5 minutes.

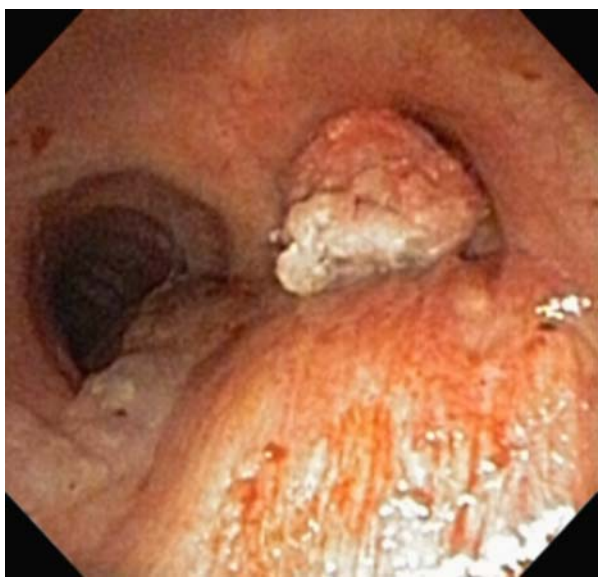

FIGURE 4. Mitomycin-C-soaked cotton inserted into a stenosis of the right main bronchus, occluding its lumen. a+

Sometimes fibrin and debris after MMC treatment can cause airway obstruction, requiring endoscopic aspiration and removal in the following hours or days.[14] This is more likely to occur in pediatric patients due to their smaller airways.

There is a single case report of a patient with a chronic inflammatory process at the larynx that developed laryngeal cancer, in which the researchers suggested that it could be related to a previous single topical application of MMC[16]; but is likely that the lesion was already premalignant when it was first treated.

Importantly, the endoscopist and team members handling MMC should wear eye, skin, and mucosal protection at all times during the procedure.

CONCLUSIONS

Endoscopic application of MMC is an easy and safe procedure.

So far, MMC 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? MMC offers an attractive area of research in the treatment of benign airway stenosis.

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