



Effect of topical Mitomycin C application in the treatment of post-intubation tracheal stenosis.

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Abstract

Objectives: To assess the efficacy of topical Mitomycin C (MMC) in the treatment of post-intubation tracheal stenosis patients and to report on any complications from its use.

Patients and methods: This is a retrospective study in which patients with post-intubation tracheal stenosis who received topical MMC in their management regardless of age and sex were included in the study. All patients had undergone multiple endoscopic dilatation and topical MMC (0.3 mg/mL) application for 2 min. Patients who did not show any improvement were scheduled for tracheal resection and anastomosis with application of temporary stent "Montgomery T-tube". Patients developed granulation tissue, managed with the same concentration and duration of MMC.

Results: 18 patients had multiple endoscopic dilatation plus MMC application, 11 patients (61.1%) showed an improvement in the degree of airway stenosis. The rest seven patients (38.9%) did not show any improvement. Six of them underwent tracheal resection and anastomosis, while the seventh patient underwent permanent tracheotomy. All the patients developed granulation tissue after resection and anastomosis and Montgomery T-tube application were treated with endoscopic application of MMC and all of them show complete improvement. We did not report any complications or side effects from the use of MMC intraoperatively or during the follow-up period.

Conclusion: Topical MMC (0.3mg/mL) application could be used safely and effectively in patients who showed initial failed response to MMC after endoscopic dilatation and developed granulation tissue after tracheal resection and anastomosis.

Keywords: Mitomycin C, Post-intubation, Tracheal stenosis, Endoscopic dilatation.

INTRODUCTION:

Tracheal stenosis is a major problem which accounts for high rates of morbidity and mortality in our locality. Various surgical methods applied to treat this condition include open and endoscopic techniques to restore free and patent airway of the patients ¹.

However, no single maneuver is conclusive as the main cause of failure is the intense inflammatory reaction produced by the initial injury to the mucosal airway. This injury can result in formation of granulation tissue and subsequent fibrosis ². Therefore, different materials have been used to arrest and prevent scar formation. Mitomycin C (MMC) is an

antiproliferative agent. Its mechanism of action appears to be related to the inhibition of fibroblast proliferation and decreasing the rate of scar formation in the laryngotracheal complex³.

Despite animal and human studies were conducted to evaluate the efficacy of MMC, the benefit of MMC in the treatment of airway stenosis remains questionable⁴⁻⁵.

The aim of this study is to assess the efficacy of topical MMC in treatment of post-intubation tracheal stenosis patients and to report on any complications from its use.

Material and Methods

This is a retrospective study in which recorded medical, clinical, and surgical details of patients with tracheal stenosis treated with topical MMC were analyzed. All the patients were presented to the Ear, Nose, and Throat Department of Assiut University Hospital, Egypt, from May 2013 to May 2017. Patients with post-intubation tracheal stenosis who received topical MMC in their management regardless of age and sex were included in the study. We excluded the following patients: patients with supraglottic, glottic, subglottic stenosis, and other causes of stenosis e.g. Congenital, inflammatory diseases, and neoplastic etc. (Table 1) shows the reason of intubation in each patient.

All patients underwent a preoperative high-resolution CT scan of their airway. The perioperative medication included intra operative intravenous (IV) steroids, surgical intervention in the form of endoscopic dilatation with topical application of MMC, postoperative oral steroid, and oral antacid medication.

Table (1): the etiology and reason of intubation in each patient with tracheal stenosis.

Etiology	No.	%
Post corrosive	1	5.55 %
Mythenia gravis, Respiratory distress	1	5.55 %
Post-partum sepsis	2	11.11 %
Fall from height, brain contusion	2	11.11 %
Motor car accident	12	66.67 %
Total	18	99.99 %

The surgical technique:

All patients were operated under general anesthesia provided via a tracheotomy tube, or IV anesthesia and Venturi jet ventilation. Regarding the management with endoscopic technique, the site, size, and length of the airway stenosis were measured with a rigid ventilating bronchoscope. We used a ventilating rigid bronchoscope (size 6.5 and 7.5, Karl Storz, Tuttlingen, Germany), and dilatation with balloon dilators or the rigid bronchoscope itself was done. A pledge soaked in MMC (0.3 mg/mL) was applied for 2 min. No rinsing of the operative site was performed after MMC application.

The postoperative follow-up consisted of the routine follow-up. All patients underwent interval laryngoscopy and bronchoscopy after two and four weeks. Any patients with stridor or any kind of relapse were subjected to subsequent interventions.

At each interval evaluation, the amount of granulation tissue and the airway diameter were recorded. Patients who did not show any improvement in their symptoms or failure of tracheostomy decannulation after multiple procedures were scheduled for another line of management in the form

of tracheal resection and anastomosis with application of temporary stent "Montgomery T-tube". During the follow-up period, patients developed dyspnea, hoarseness, aspiration or stridor were subjected to a direct laryngoscopy and bronchoscopy to check the mobility of the vocal folds, the position of Montgomery T-tube as well as the patency of the tracheal lumen. The Montgomery T-tube is removed after 6 months and evaluation of tracheal lumen is done with evaluation of the amount and site of granulation tissue, and management in the form of insertion of topical application of MMC.

In all the steps, written informed consent was obtained from each patient and all modalities of treatment were approved by the Ethics Committee of our faculty.

Results

During the study period, 18 patients had endoscopic dilatation plus MMC application. There were fourteen (77.78%) males and four (22.22%) females, and the mean age was 28.67 ± 14.68 years (range 16-67 years). All patients had a history of stridor after discharge from the intensive care unit. Twelve patients (66.67%) were presented to us with tracheostomy while the rest of six patients (33.33%) were not. The site of stenosis was in the cervical trachea (about 2-3 cm below vocal cords, with involvement of 1-3 tracheal rings) in all the cases. Airway diameter and length of stenosis were not consistently documented, but the degree of stenosis was grade III for all the cases according to the Myer-Cotton grading system. In all the applications, the concentration of MMC was (0.3 mg/mL) for two minutes. The mean number of MMC sessions/patient was 2.67 ± 1.08

(min 2; max 5). The number of endoscopic airway procedures performed is shown in (Table 2).

Table (2): Number of endoscopic dilatation and MMC application procedure.

No. of initial endoscopic procedures	No. of patients
2	12 (66.66%)
3	2 (11.11%)
4	2 (11.11%)
5	2 (11.11%)
No. of endoscopic procedures needed after tracheal resection and anastomosis	No. of patients
2	5 (83.33%)
3 or more	1 (16.66%)

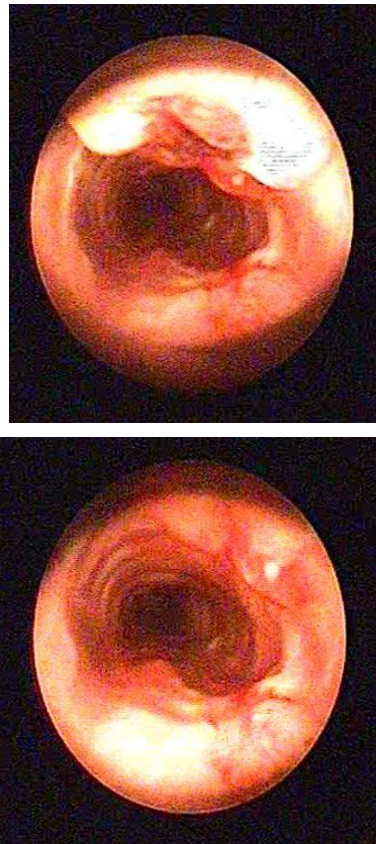
Out of the 18 patients, 11 patients (61.1%) showed an improvement in the degree of airway stenosis and resolution of their preoperative symptoms after repeated endoscopic dilatation and MMC application. The rest seven patients (38.9%) did not show any improvement and they had stenosis more than 75% of their tracheal lumen. Six of them were in need for further surgery in the form of tracheal resection and anastomosis, while the seventh patient with a history of Guillain-Barre syndrome, underwent permanent tracheotomy because of worsening of his pulmonary status.

Regarding patients treated with tracheal resection and anastomosis, the complete tracheal stenosis was excised with end-to-end anastomosis and Montgomery T-tube application for six months in all the six cases. All the patients developed granulation tissue at either one single site or more than one site; the upper end of Montgomery T-tube in one case (16.66%), at site of anastomosis in 3 cases (50%), and in both sites in 2 patients (33.33%). The

degree of stenosis was grade II according to the Myer-Cotton grading system. All the patients treated with endoscopic application of MMC and all of them show complete improvement (Figure 1).

The follow-up period for all the cases in our study ranged from 6 to 36 months, with an average of 21 months. We did not report any complications or side effects from the use of MMC intraoperatively or during the follow-up period.

Figure.1 (a,b): Improvement of airway caliber.



Discussion

Post-intubation tracheal stenosis is caused by ischemic pressure necrosis of the airway, it occurs most commonly

following endotracheal intubation and tracheostomy. Stenosis can occur anywhere from the level of the endotracheal tube tip up to the glottic and subglottic area, but the most common sites of stenosis are where the ETT cuff has been in contact with the tracheal wall and at the tracheal stoma site following a tracheostomy⁶. Accurate assessment of the degree of tracheal stenosis is important for each patient to decide the best method of management. However, there is no single line of management that gives 100% result in PITS and all procedures can cause additional injury with possible restenosis by granulation tissue formation and fibrosis⁷.

MMC is an antineoplastic antibiotic agent that inhibits in vitro fibroblast proliferation and can prevent the formation of scars and fibrosis in humans. Its topical application as adjuvant treatment in endoscopic management of stenosis has been investigated as it can play a role in improving the success rate and reducing the need for frequent procedures in PITS⁸. There were previous studies which have been conducted to evaluate the efficacy and safety of topical use of MMC in the treatment of airway stenosis and showed promising results⁸⁻¹¹.

In 2005, Hueman and Simpson reported complications related to low toxicity of MMC. Two concentrations of mitomycin C were used: 0.4 mg/mL, referred to as “low” concentration, and 1% formulation of 10 mg/mL, referred to as “high” concentration. The toxicity occurred in 4 cases out of 85 patients for both concentrations, the complications were in the form of accumulation of fibrinous debris at the operative site, resulting in partial airway obstruction and the need for emergent airway

intervention¹². In our study, there were no complications or side effects reported from the use of MMC (0.3 mg/mL).

A prospective animal study has shown that the use of a high dose of MMC (0.5 mg/mL) may produce more stenosis compared with the low-dose of MMC (0.2 mg/mL). The authors suggested that caution should be used when using MMC in high doses¹³. That's why we decided to use the (0.3 mg/mL) concentrate. We found also in the literature that, the duration of topical application of MMC varied from 2 to 5 minutes. We decided to use a 2 minutes application time as it is more conservative but effective at the same time and recommended by many authors^{10-11,14}. In this study, the percentage of failure of endoscopic dilatation and MMC application was (38.9%). The cause of this percentage is most probably due to late presentation of the cases with formation of mature fibrous stenosis. In the other hand, patients presented early with the stage of fresh granulation tissue showed a good response to dilatation and MMC application.

Also, patients with failed endoscopic dilatation and MMC application showed a good response to MMC application for granulation tissue developed after tracheal resection and anastomosis. The cause of granulation tissue formation in cases with tracheal resection and anastomosis could be the use of non-absorbable sutures in some cases. However, patients operated with absorbable suture showed also development of granulation tissue at the site of anastomosis.

Behrend and Klempnauer in 2001, used three different types of suture material, two absorbable and one nonabsorbable suture in tracheal resection and anastomosis in sheep.

They found that there was no significant difference between the three types of suture. Also, they concluded that the technique is more important than the choice of suture material¹⁵. Another cause of granulation tissue formation in our cases with tracheal resection and anastomosis was fashioning of the proximal intraluminal limb of Montgomery T-tube which led to loss of the tapered smooth end with subsequent mucosal abrasion and granulation tissue formation as a result of frequent rubbing against the respiratory mucosa.

Montgomery T-tube was applied as a routine in our tracheal resection and anastomosis cases to add more secure to the anastomosis, but recently, as we are gaining more experience, we changed our policy for the application of Montgomery T-tube as a routine and limit its use to certain cases to avoid its complications.

Finally, we found in the literature different tools used in endoscopic management of tracheal stenosis. These include the use of a Co2 laser, microdebrider, tapered tracheal dilators, and the balloon dilators. We used in our work balloon dilators as we do not have the laser device. The results of balloon dilatation ranged from fair to good in the literature. However, the long-term efficacy of balloon dilation in a large number of patients has rarely been reported¹⁶⁻¹⁸. The limitations of our study are the relatively small size of patients and the need for longer follow-up period.

Conclusion

Like other retrospective studies, definitive conclusions cannot be drawn as the results are limited by the study design and the absence of patient randomization or a control group.

However, we found that topical MMC (0.3mg/mL) could be used safely and effectively in the same patients who showed initial failed response to MMC after endoscopic dilatation and developed granulation tissue after tracheal resection and anastomosis.

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