Farm Hosp. 2011;**35(1)**:32–35

Farmacia
HOSPITALARIA

www.elsevier.es/farmhosp

BRIEF REPORT

Topical endotracheal mitomycin C as a complementary treatment for endoscopic treatment of recurrent laryngotracheal stenosis

S. Cortés de Miguel,[a,*] J. Cabeza Barrera,[a] M. Gallardo Medina,[b] L.F. Cassini Gómez de Cádiz,[b] A. Salmerón-García,[a] F. Rodríguez Lucas[a]

[a]*Servicio de Farmacia, Hospital Universitario San Cecilio, Granada, Spain*
[b]*Servicio de Neumología, Hospital Universitario San Cecilio, Granada, Spain*

Received September 16, 2009; accepted April 22, 2010

KEYWORDS
Laryngotracheal stenosis;
Endoscopic treatment;
Topical Mitomycin C

Abstract
Objective: To describe the preparation of topical endotracheal mitomycin C and the clinical outcomes of four patients with recurrent and severe laryngotracheal stenosis (LTS) treated with adjuvant topical mitomycin C.
Method: Literature review to determine the concentration and method of preparation of topical mitomycin C for endotracheal use. Review of clinical histories.
Results: We established a concentration of 0.4 mg/ml topical mitomycin C for the treatment of laryngotracheal stenosis. In the treated cases, we applied a 0.4 mg/ml solution to the wound site following laser surgery and dilatation with bronchoscope. Three patients remain asymptomatic from a respiratory perspective, and treatment failed in one case.
Conclusions: LTS treatment is complex due to the continuous development of granulation tissue and fibrosis following injury to the airways. Topical mitomycin C seems to be the ideal adjuvant agent thanks to its powerful antifibrotic effects.

PALABRAS CLAVE
Estenosis laringotraqueal;
Tratamiento endoscópico;
Mitomicina C tópica

Mitomicina C tópica endotraqueal como terapia complementaria al tratamiento endoscópico de la estenosis laringotraqueal fibrótico-cicatricial recurrente

Resumen
Objetivo: Describir la preparación de mitomicina C tópica endotraqueal y los resultados clínicos de 4 pacientes tratados de forma coadyuvante con mitomicina C tópica para estenosis laringotraqueales (ELT) graves y recurrentes.

*Corresponding author.
E-mail address: soldelsur@libero.it (S. Cortés de Miguel).

1130-6343/$ - see front matter

Método: Revisión bibliográfica para determinar la concentración y forma de elaboración de mitomicina C para uso tópico endotraqueal. Revisión de las historias clínicas.
Resultados: Se determina una concentración de 0,4 mg/ml mitomicina C tópica en el tratamiento de las estenosis laringotraqueales. En los casos tratados se aplicó la solución de 0,4 mg/ml en la zona estenosada tras fotorresección con láser y dilatación con broncoscopio. Tres pacientes se encuentran asintomáticos desde el punto de vista respiratorio y en uno, ha fracasado el tratamiento.
Conclusiones: El tratamiento ELT es complejo debido al continuo desarrollo de tejido de granulación y fibrosis como consecuencia de lesiones de la vía aérea. La mitomicina C tópica, por sus potentes efectos antifibróticos, parece ser el agente coadyuvante idóneo.

Introduction

Laryngotracheal stenosis (LTS) is a disabling and potentially fatal disease that consists of a progressive and permanent decline in the calibre of the laryngotracheal lumen that can be congenital or acquired. This partial or complete narrowing of the upper airway produces difficulty in breathing, affects phonation, and can even compromise the swallowing process. Acquired laryngotracheal stenosis are much more frequent than congenital stenosis, due particularly to the use of endotracheal intubation. This has resulted in a significant increase in intralaryngeal and tracheal trauma, which after cicatrisation and development of stenosis, disables the patient from adequately developing social and work-related activities. Its incidence is hard to calculate but it may range between 5% and 20% of intubated or tracheotomised patients, according to various studies.[1,2]

Currently, there are different types of therapeutic options for the management of laryngotracheal stenosis, which must be individualised based on the severity of the case. The goal is to avoid radical surgery and use less invasive techniques, such as rigid bronchoscopic dilatation, tracheal prostheses, and laser photoresection. However, no therapeutic option is 100% effective and all of them may cause additional damage to the airway mucosa, leading to the development of restenosis, due to the development of new fibrotic and cicatricial tissue.[1,2] This kind of lesion progresses with an intense inflammatory response due to both the initial lesion and the subsequent treatment, causing excessive formation of granulation and fibrotic tissue. Therefore, in recent years, alternative procedures have been proposed focused on modulating the host inflammatory response to the initial lesion.[3] An example of this is the use of topical mitomycin C based on its inhibitory action on fibroblastic activity. Several studies in humans[3,4] and animals[5] report the utility of topical mitomycin C for severe subglottic tracheal stenosis that recur after different treatments (concentrations ranging from 0.4 mg/ml to 10 mg/ml).[6]

The aim of this study is to describe the preparation of mitomycin C for topical endotracheal use and to report the clinical results in four patients that used it as an adjuvant treatment for severe and recurrent laryngotracheal stenosis in the Pneumology Department of our hospital.

Method

A literature review was conducted to determine the concentration and method of preparation of mitomycin C for topical endotracheal use. The Pneumology Department of our hospital requested approval for "Compassionate Use" of this medication from the Spanish Ministry of Health, since this is not an approved indication for this medication in Spain. Four patients in whom conventional therapies had repeatedly failed were treated with the concentration. It was administered as an adjuvant antifibrotic treatment, through topical application to the stenosed area after laser photoresection and dilatation with rigid bronchoscopy.

Mitomycin C is commercially available in Spain as an antineoplastic agent. It is an antitumour antibiotic that is activated in the tissue, acting as an alkylating agent that disrupts DNA in cancerous cells and inhibiting mitosis in a large variety of cell lines, including fibroblasts. Among its indications is the treatment of various neoplasias.[7]

The four patients with laryngotracheal stenosis in our study are described below:

Case 1: A 59-year-old woman with post-intubation subglottic tracheal fibrotic cicatricial stenosis. Since 2006, she had been treated with several endoscopic and prosthesis implantation procedures, but finally the prosthesis was removed in March 2007 due to several episodes of migration. In the spring of 2008, the patient presented with dyspnoea and stridor, and she was found on endoscopy to have restenosis. For that, topical mitomycin C treatment was requested as an adjuvant treatment to a new rigid bronchoscopy, laser incisions, and mechanical dilatations, to prevent residual fibrosis and avoid cicatricial re-occlusion.

Case 2: A 56-year-old woman diagnosed with fibrotic cicatricial subglottic tracheal stenosis of idiopathic origin. Since March 2007 she had been treated on three occasions with laser photoresection, rigid

bronchoscopic dilatations, and placement of a Dumon tracheal prosthesis, which then had to be removed because of migration. In November 2008 a relapse occurred that required endoscopic treatment and topical mitomycin C was requested for application in the stenotic area following dilatation as an antifibrotic complementary treatment.

Case 3: A 22-year-old man affected by a complex fibrotic cicatricial tracheal stenosis after intubation due to a traffic accident. He was treated on several occasions with bronchial laser and Dumon tracheal endoprosthesis in March 2003. In October 2008 the prosthesis was removed. In February 2009 a recurrence of the stenosis was confirmed by endoscopy, thus meeting criteria for new endoscopic treatment with topical mitomycin C as an antifibrotic adjuvant treatment.

Case 4: A 38-year-old man with subglottic tracheal stenosis due to intubation after coma secondary to an open cerebral haemorrhage. He was treated in February 2009 with radial laser incisions and dilatation of the stenotic area with rigid bronchoscopy. In May 2009 a new endoscopic treatment for restenosis was performed, which was associated with the application of topical mitomycin C. The patient did not achieve the expected results and in June 2009, after the stenosis recurred, a new treatment was performed with endoscopic dilatation and Dumon tracheal endoprosthesis placement.

Results

Several studies have demonstrated the safety and efficacy of topical mitomycin C at a concentration of 0.4 mg/ml for the treatment of LTS.[3,4,8,9]

To achieve this concentration, a vial containing 10 mg of mitomycin C is diluted with 25 ml of saline solution using aseptic technique. Once diluted, the product is a clear bluish-purple solution. This dilution is loaded in two 12 ml syringes and put in a photo-protected bag. The mitomycin C solution at a concentration of 0.4 mg/ml is thus obtained, which is stable for 24 hours at ambient temperature.[10] However, a study in 2002 that evaluated the activity of mitomycin C through the microagar diffusion technique revealed that mitomycin C in a phosphate buffer solution at 0.4mg/ml can be kept at +4 ºC for a maximum of 3 months without significant loss of activity.[11]

In the treated cases, the 0.4 mg/ml solution was applied to the stenosed area after laser photoresection and bronchoscopic dilatation.

To evaluate the success or failure of the therapy, the presence or absence of respiratory symptoms (dyspnoea), as well as the presence or absence of restenosis on subsequent endoscopies were assessed as variables after 6 months. The first three patients described above were asymptomatic from a respiratory standpoint after the evaluation period and had near-normal calibre of the laryngotracheal complex on endoscopy. In the fourth patient, treatment failed due to restenosis.

Discussion

Treatment of LTS remains a challenge, due to the continuous development of fibrosis and granulation tissue as a consequence of an airway lesion. Topical mitomycin C, due to its potent antifibrotic effects, seems to be an ideal adjuvant treatment, given that it can be applied directly to the site of the lesion at a relatively high concentration with minimal systemic effects.[12]

Most of the published literature supports de use of topical mitomycin C to improve the outcomes of therapeutic measures to treat laryngotracheal stenosis. The studies, taken together, are quite variable in terms of design, the selected surgical outcomes, mitomycin C dosing, and method of application. This heterogeneity suggests that the use of mitomycin C is, in part, still unknown, and standardisation of the criteria is needed to evaluate trials to prove clinical efficacy, the optimal method of application, and adequate dosing of mitomycin C.[13]

The main barrier to assessing the result of this complementary treatment is the lack of a known pattern of progression following stenosis treatment. Therefore, there are currently no known criteria for predicting recurrence or non-recurrence. Consequently, we cannot evaluate the negative result that occurred in Case 4. According to the experience of the Pneumology Department of our hospital, in some patients there is no recurrence after the first endoscopic treatment. However, in other patients there are multiple recurrences, sometimes occurring after a few weeks and sometimes occurring more than twelve weeks later, even in the same patient. Therefore, in our opinion, long follow up periods are required to evaluate its efficacy.

Conflict of interest

The authors affirm that they have no conflict of interest.

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