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Original article

Causes of unsatisfactory results of the use of mitomycin-C in endoscopic endonasal dacryocystorhinostomy

E.L. Atkova [a]; A.A. Fedorov [a]; A.O. Root [a]; S.D. Iartsev [b]; N.N. Krakhovetsky [a]; V.D. Yartsev [a,*]

Abstract

Purpose: To study the antifibrotic effectiveness of mitomycin-C in the tissues of the ostium site after it application for endonasal endoscopic dacryocystorhinostomy.
Material and methods: The study included 45 patients (48 cases) with primary obstruction of the nasolacrimal duct. All patients underwent endoscopic endonasal dacryocystorhinostomy (EEDCR). At the final stage of the operation, a swab with MMC was placed in the region of the formed ostium at a concentration of 0.2 mg/ml for 3 min. An ostium was not intubated. After that, biopsies of the mucous of the nasal cavity and lacrimal sac were performed to study the morphological changes that occur in the tissues overtime, as well as to calculate the concentration of the drug in the tissues.
Results: According to the chemical analysis, the concentration of MMC immediately after application was 0.626 ± 0.176 μg/g; after 30 min the concentration of the drug was reduced to 0.23 ± 0.06 μg/g; a day after the operation the drug was not found in the tissue samples. Morphological study established that the repair processes occurring in the mucosa of the nasal cavity and the lacrimal sac after EEDCR are similar to the reparative processes without the use of MMC. The effectiveness of surgical treatment: ''positive results'' - 77.1% of cases, ''relapses'' - 22.9% of cases.
Conclusions: Application of MMC for prevention of excessive scarring after EEDCR is impractical as it is not possible to achieve antifibrotic concentration of the drug at dacryocystorhinostomy ostium site using this method.

Keywords: Dacryocystorhinostomy, Mitomycin-C, Fibrosis, High-performance liquid chromatography-mass spectrometry

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Introduction

Mitomycin-C (MMC) is an alkylating antibiotic used in dacryology for prevention of excessive scarring of the area of the formed ostium after dacryocystorhinostomy. *In vitro* study showed its inhibitory effect on the proliferation of fibroblasts. However, clinical effectiveness of its application has remained controversial until now.

Mitomycin-C (MMC) is used in dacryology since 1998 for the prevention of excessive scarring of the region of the formed ostium after dacryocystorhinostomy.[20]

The mechanism of action of the drug includes inhibition of the synthesis of DNA, cellular RNA and protein, which leads to suppression of collagen synthesis by fibroblasts.[2,9,10,12,19,20]

In 2013 Ali et al. conducted a fundamental study that determined the optimal concentration suppressing the

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[a] Eye Diseases Research Institute, Rossolimo St., 11 a, 119021 Moscow, Russia
[b] Frumkin Institute of Physical Chemistry and Electrochemistry of the Russian Academy of Sciences, Leninskii Prosp., 31k4, 101000 Moscow, Russia

* Corresponding author.
e-mail addresses: evg.atkova@mail.ru (E.L. Atkova), info@eyeacademy.ru (A.A. Fedorov), anna.root@mail.ru, a.root@niigb.ru (A.O. Root), yartsew1@yandex.ru (S.D. Iartsev), krahovetskiynn@mail.ru (N.N. Krakhovetsky), yartsew@ya.ru, v.yartsev@niigb.ru (V.D. Yartsev).

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growth of fibroblasts and not causing their apoptosis (0.2–0.3 mg/ml) and optimal exposure (3 min).[2] In their further studies, the authors, using electron microscopy, studied the biopsy material of the nasal mucosa after endonasal dacryocystorhinostomy with application of MMC at concentration of 0.2 mg/ml and 3 min exposure. It was proved that the application of the drug causes ultrastructural changes affecting epithelium, vessels and fibroblasts.[1]

To date, enough information has been accumulated about the possibility of using MMC as an antifibrotic agent, confirmed by *in vitro* studies.[2,10] However, its clinical effectiveness remains controversial.

We study the antifibrotic effectiveness of mitomycin-C in the tissues of the ostium site after it application for endonasal endoscopic dacryocystorhinostomy.

Material and methods

The study included 45 patients (48 cases) with primary obstruction of the nasolacrimal duct, at the age of 63 ± 15 years. The study was conducted after the approval of the local ethics committee. Nature of the forthcoming study was explained to the patients and they provided informed consent.

The study did not include patients with traumatic lesions of the lacrimal passages and their secondary changes, previous surgical interventions on the lacrimal pathways, diseases of the nasal cavity and paranasal sinuses that required treatment. A standard ophthalmological and dacryological examination were performed. Complaints for lacrimation were assessed on the *Munk* scale.[15] The patients underwent lacrimal meniscometry with an optical coherent tomograph RTVue-100-2 (*Optovue*, USA) with the definition of the conditional depth of the lacrimal meniscus according to the procedure described by us earlier.[5] Endoscopy of the nasal cavity was performed. In all cases computed tomography with topical contrast enhancement of lacrimal passages was performed with GE Optima CT 660 (*General Electric*, USA).

Endoscopic endonasal dacryocystorhinostomy (EEDCR) was performed by forming an ostium at the level of the lacrimal canaliculi orifice, the medial wall of the lacrimal sac was excised along the perimeter of the bone ''window''. Fragment of the mucous of the nasal cavity was resected till the edge of the ostium. No intubation was performed. All patients at the final stage of the operation underwent application of MMC with a swab treated with 2 ml of MMC at a concentration of 0.2 mg/ml for 3 min at the ostium site. After the removal of the swab the lacrimal passages were rinsed with physiological saline (Fig. 1).

Fifteen patients (15 cases) had histological examination of the mucous of the nasal cavity and lacrimal sac on the second, fifth, tenth, fourteenth, twenty first, twenty-eighth and sixtieth days (according to the physiological laws of wound healing).

Study protocol: a biopsy of the nasal mucosa from the ostium region was performed endonasally under the control of a 30-degree optic with a diameter of 2.7 mm (*Karl Storz*, Germany) after anemization of the nasal cavity with lidocaine and epinephrine and local infiltration anesthesia with an articaine solution with epinephrine 1:100,000 - 1.7 ml (Ultracaine D-C Fort, *Sanofi Aventis*, France), each time from various areas. The resulting samples were placed in a fixing solution (10% neutral formalin) for 24 h, washed in running water, dehydrated in an upward concentration alcohol, clarified in xylene and encased in paraffin. Serial transverse sections with 4–6 μm thickness were prepared on a rotational Historange microtome 2218 (*LKB*, Sweden), stained with toluidine blue, or hematoxylin and eosin. The resulting histological specimens were examined on a Leica DM-2500 photomicroscope (*Leica*, Germany). The images were photographed with a digital camera DFC320 (*Leica*, Germany), followed by image analysis using the ImageScope Color software (*Aperio Technologies*, USA).

In 14 patients (15 cases) concentration of MMC in the mucosa of the nasal cavity was studied immediately after the administration of the drug, after 30 min, and also on the 1st day after the surgery.

Study protocol: the biopsy was performed in a manner similar to that described above. Before the chemical analysis, the samples were placed in 1 ml of deionized water, and then weighed on a precision scale (*Sartorius AG*, Germany) within 0.001 g precision and held in an ultrasonic bath WiseClean (*Daihan Scientific*, Korea) for 15 min. Samples were stored for no more than a day at a temperature of 5° C. The concentration of the drug in the resulting solution was determined, and concentration of MMC was found in the initial tissue sam-

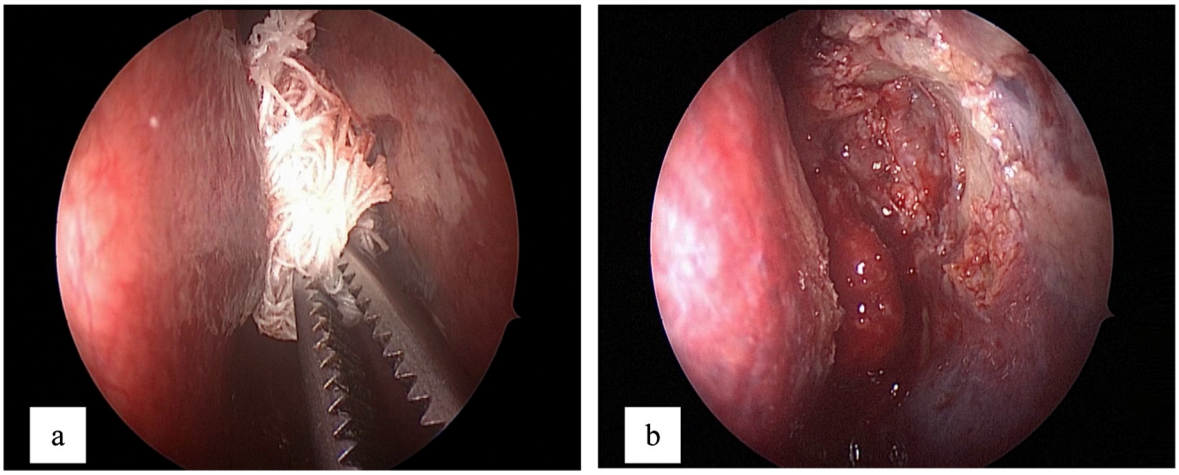

Figure 1. The stage of EEDCR. Endoscopic view. (a) Installation of a swab with mitomycin-C in the area of the operation; (b) endoscopic view after removal of a swab.

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