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Применение митомицина-С при эндоскопической эндоназальной дакриоцисториностомии

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Митомицин-С (ММС) является наиболее часто используемым препаратом для профилактики избыточного рубцевания области дакриостомы после эндоскопической эндоназальной дакриоцисториностомии (ЭЭДЦР). Большинство исследователей используют его в виде аппликаций на завершающем этапе операции, однако эффективность такого способа применения остается дискутабельной. **Цель** работы — оценить эффективность нового, инъекционного, способа применения митомицина-С при ЭЭДЦР. **Материал и методы.** В исследование вошли 86 пациентов (95 случаев) (средний возраст 63±9 года) с первичной обструкцией носослезного протока. Всем больным была выполнена ЭЭДЦР по методике P. Wormald. Далее пациенты были разделены на 2 группы. В 1-й группе выполняли инъекции ММС в слизистую оболочку полости носа и слезного мешка, во 2-й — аппликацию ММС по общепринятой методике. Для изучения концентрации препарата в тканях у пациентов 1-й группы осуществляли биопсию слизистой оболочки полости носа и слезного мешка. Для изучения системной абсорбции препарата проводили забор крови у пациентов обеих групп в различные временные интервалы. Клиническую эффективность оценивали в среднем через 14±5 мес после операции. **Результаты.** Концентрация ММС в тканях области дакриостомы у пациентов 1-й группы сразу после его введения составляла 390±10 мкг/г, через 30 мин — 120±20 мкг/г. Через сутки после операции препарат в тканях не выявлен. Ни в одном из образцов крови ММС обнаружен не был. Положительные результаты в 1-й группе составили 97,9% случаев, во 2-й — 87,2%. **Заключение.** Инъекционный способ применения ММС на заключительном этапе ЭЭДЦР показал клиническую эффективность и безопасность и может быть рекомендован к применению в клинике.

Ключевые слова: *митомицин-С, эндоскопическая эндоназальная дакриоцисториностомия, рубцевание, высокоэффективная жидкостная хроматография-масс-спектрометрия.*

Mitomycin C after endoscopic endonasal dacryocystorhinostomy

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Mitomycin-C (MMC) is the most frequently used agent for prevention of excessive scarring at the osteotomy site after endoscopic endonasal dacryocystorhinostomy (EEDCR), which, however, being applied during the final stage of the surgery, shows questionable effectiveness. **Aim** — to evaluate the effectiveness of a new administration route of mitomycin C in EEDCR. **Material and methods.** The study included 86 patients (95 cases) in the age range of 62.3±9 years with primary acquired nasolacrimal duct obstruction. All patients underwent P.J. Wormald modification of EEDCR and were further divided into 2 groups. In group 1, MMC was injected into the nasal cavity and lacrimal sac mucosa, while in group 2 it was applied locally according to the standard procedure. To measure tissue concentrations of MMC, mucosal biopsies were taken in patients of Group 1. Systemic absorption of MMC was studied through blood samples in both groups. Clinical efficacy was assessed in 14±5 months after surgery. **Results.** Immediately after injection, the average tissue concentration of mitomicyn C in patients of Group 1, was 390±10 μg/g and 30 minutes later — 120±20 μg/g. No mitomycin C was found in Day 1 tissue samples and in any of the blood samples. Positive clinical results were reported in 97.9% of cases from Group 1 and in 87.2% of cases from Group 2. **Conclusion.** The method of injecting MMC during the final stage of EEDCR has proved clinically effective and safe and can be recommended for use in clinical practice.

Keywords: *mitomycin C, endoscopic endonasal dacryocystorhinostomy, scar formation, high-performance liquid chromatography-mass spectrometry.*

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According to a number of researchers, excessive scarring of a well-formed dacryostoma (also known as anastomosis) after endoscopic endonasal dacryocystorhinostomy (EEDCR) is one of the primary causes of negative surgery outcomes [1—3].

The most studied drug used for prevention of excessive scarring in the anastomosis site is Mitomycin C (MMC) – a cytostatic drug with antifibrotic effect [4]. Most researchers applied MMC topically on the final stage of the surgery [5—8]. Some authors described it as effective [9—12], others – as non-influential on the surgery outcome [6, 13—15].

In one of our other studies [16], liquid chromatography–mass spectrometry (LC-MC) helped prove that when applied topically the drug does not achieve necessary antifibrotic concentration in the tissues of the anastomosis area established by *in vitro* research [17]. Consequently, a demand for a new delivery method of the drug to the tissues of the anastomosis area has emerged.

The purpose of this study is to evaluate the effectiveness of a new MMC application method – injection – in patients with EEDCR.

Material and methods

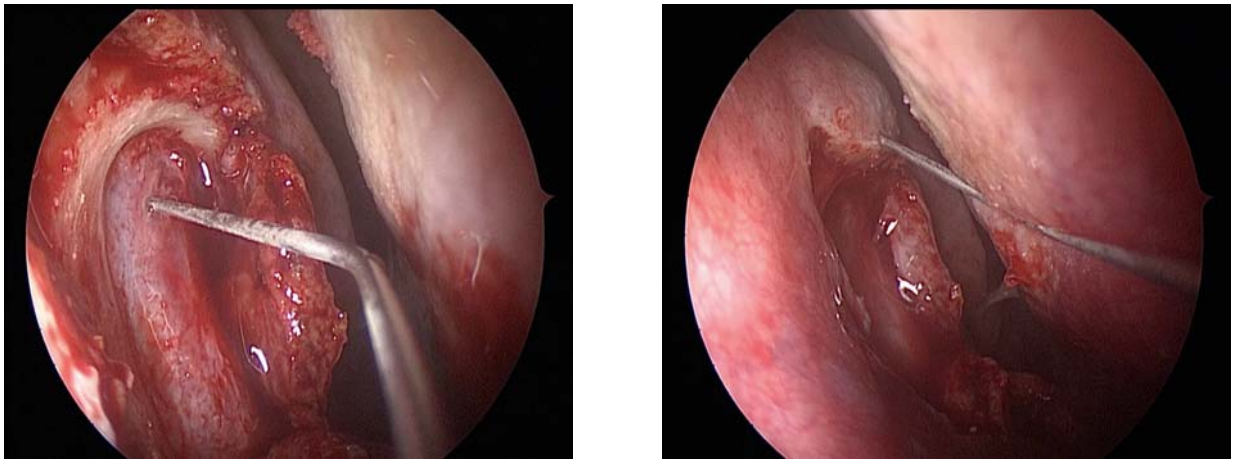
The study included 86 patients (95 cases) aged 28 to 75 years (mean age 63±9) with primary acquired nasolacrimal duct obstruction. The study was approved by local Ethics Committee and informed consent for examination and treatment was obtained from all the patients.

The study excluded patients with traumatic injuries of the lacrimal passages (LP) and its secondary changes, patients that had previously received surgical treatment for dacryologic conditions, as well as patients with various nasal cavity disorders.

All patients underwent standard ophthalmological and dacryological examination. Complaints of lacrimation were graded according to Munk's epiphora scale [18]. Additionally, the patients underwent lacrimal meniscometry with assessment of the conditional depth of the lacrimal meniscus performed on optical coherence tomography scanner RTVue-100-2 (Optovue, USA) according to the procedure described earlier [19], as well as standard endoscopy of the nasal cavity and multispiral computed tomography with LP straining performed with tomography scanner GE Optima CT 660 (General Electric, USA).

EEDCR was performed according to method described by P. Wormald [20] that involves formation of anastomosis on the level of lacrimal canaliculi orifice. The patients were then divided into two groups. The first group included 45 patients (48 cases) that had the drug injected prior to excision of medial wall of the lacrimal sac according to the authors' proposed method: 0.2 mg/ml MMC was injected into 6 different points (0.1 mL into each) of the lacrimal sac wall along the perimeter of the bone "window" using syringe and needle with curved tip. Next, the lacrimal sac was excised and its medial wall removed (without flap formation). A fragment of the nasal cavity mucosa was resected up to the posterior border of the anastomosis. After that, MMC of the same concentration and dosage was injected into 6 points of the nasal cavity mucosa around the formed dacryostoma (patent RU2610557 dd. 13.01.2016) **(Figure 1)**.

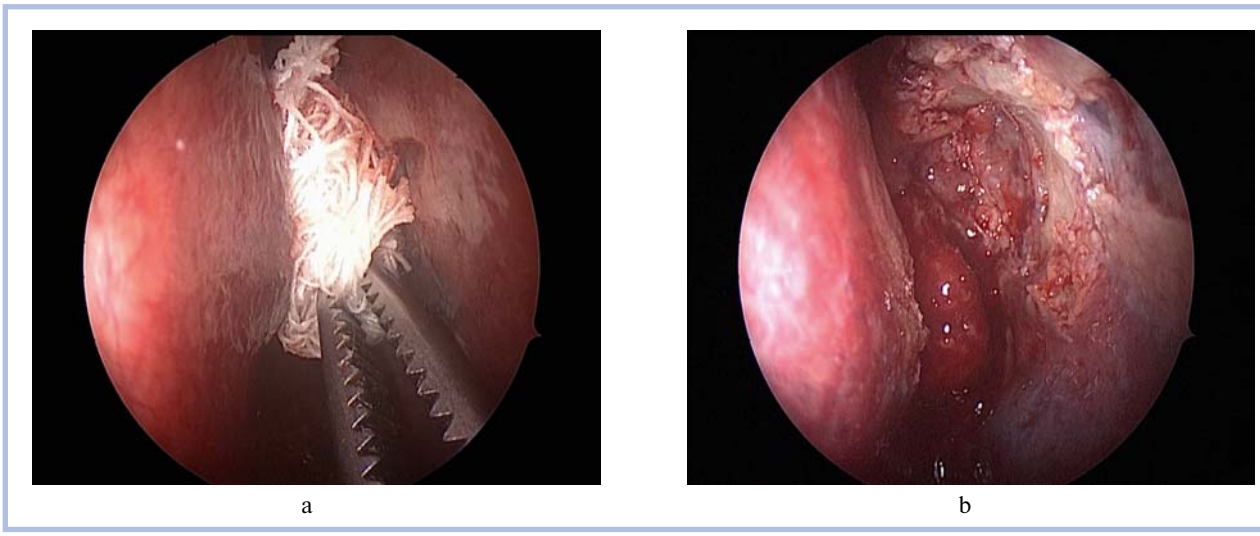
The second group included 41 patients (47 cases) who had MMC applied during the final stage of the surgery by placing a turunda (gauze swab) prepared with 2 mL of the 0.2 mg/mL solution in the dacryostoma site for 3 minutes. The surgery concluded with flushing of the



a b

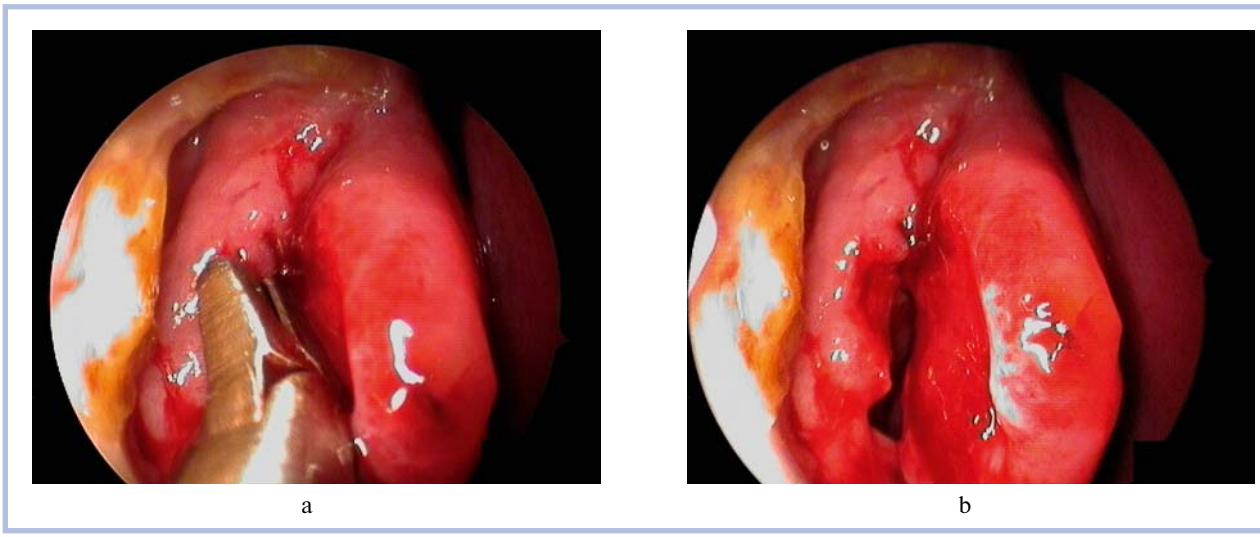
Figure 1. **A stage of EEDCR. Endoscopic view.**

a – injection of MMC into the mucous membrane of lacrimal sac; b – injection of MMC into the mucous membrane of nasal cavity.



a b

Figure 2. **A stage of EEDCR. Endoscopic view.**
a – placing a turunda with MMC into the anastomosis site. b – the view after removing the turunda.



a b

Figure 3. **Taking biopsy from the anastomosis site. Endoscopic view.**
a – a stage of taking biopsy from the anastomosis site. b – the view after taking the biopsy.

LP and swabbing dacryostoma and middle nasal passage areas using a turunda **(Figure 2)**.

Biopsy of nasal mucosa and lacrimal sac was performed in order to determine concentration of MMC in the tissues in 12 patients (15 cases) of the first group. Each of them underwent 4 biopsies by the procedure described earlier [16] **(Figure 3)**. The first biopsy was performed prior to the drug injection (control sample), the second – immediately after the drug injection, the third biopsy was done 30 after the injection, and the fourth biopsy – 24 hours after the drug injection.

Prior to analyzing the obtained samples were put into 1 mL of deionized water, then weighted on 0.001 g accuracy precision scales (Sartorius AG, Germany), and held in ultrasound bath WiseClean (Daihan Scientific, South Korea) for 15 minutes. The samples were stored at 5°C, for 24 hours at most. MMC concentration in the original sample was determined by measuring its concentration in the solution and relating it to the mass of the tissue sample.

In-situ studying of MMC concentration was performed by LC-MC method using liquid chromatograph Agilent 1260 (Agilent, U.S.A.) and mass-spectrometry detector Maxis Impact (Bruker, Germany) with electrospray ionization, quadrupole and time-of-flight analyzer mass analyzers. Zorbax SB-C18 column with dimensions of 150x2.1x0.005 mm was used for separation in isocratic elution mode with 100% acetonitrile (JT Baker, Nether-

lands); speed during the mobile phase was 0.25 mL/min. The analysis took 2.1 min in total.

In order to study systemic MMC absorption, 10 patients (10 cases) from the first group had 3 mL blood samples taken from peripheral vein using evacuated blood collection receptacle with ethylenediaminetetraacetic acid (EDTA) (MK RUSTECH, Russia). Each patient had five samples taken. The first sampling was done before MMC injection (control sample), the second sampling – immediately after the injection, the third – 30 minutes after the injection, the fourth – 1 hour after the injection; the last sampling took place 2 hours after the injection. The samples were prepared for analysis using centrifuge CH80-25 (Armed, Russia) spinning at 3000 rpm for 15 minutes. The resulting serum was then frozen at -20°C and transported to the laboratory utilizing coolant agents.

Quantitative measurement of MMC in blood samples was performed by LC-MC method using high-efficiency liquid chromatograph Agilent 1260 (Agilent Technologies, U.S.A.) equipped with gradient pump, degasser, autosampler, photodiode-matrix detector and tandem mass-selective detector Agilent 6460 (Agilent Technologies, U.S.A.). The data was processed using Agilent MassHunter software version B.06.00 (Agilent Technologies, U.S.A.).

The following criteria were used to evaluate the results of surgical treatment:

"Recovery":

1. Munk epiphora score 0.
2. Absence of purulent discharge.
3. Depth of lacrimal meniscus is decreased.
4. Positive dye disappearance nasal test.
5. Passable LP during irrigation.
6. Presence of a formed dacryostoma during endoscopy of the nasal cavity.

"Improvement":

1. Munk epiphora score 0–2.
2. Absence of purulent discharge.
3. Depth of lacrimal meniscus is maintained or decreased.
4. Positive or delayed dye disappearance nasal tests.
5. Liquid passes into the nasal cavity only upon pressure on the syringe plunger or as a thin jet.
6. Presence of a formed dacryostoma during endoscopy of the nasal cavity.

"Relapse":

1. Munk epiphora score 3–4.
2. Purulent discharge from LP.
3. Depth of lacrimal meniscus is increased.
4. Negative dye disappearance nasal test.
5. Obstructed LP during irrigation.
6. Presence of a cicatricially deformed dacryostoma during endoscopy of the nasal cavity.

Recovery and *Improvement* were considered positive results; disease's *Relapse* was the negative result.

Patients were followed up for 9 to 24 (14±5) months after surgery.

Statistical analysis was done using Microsoft Office 2013 and SOFA Statistics 1.4.4 software.

Results

Concentration of MMC in the original tissue samples amounted to 390±10 μg/g immediately after the injection, at 30 minutes after the injection it decreased to 120±20 μg/g, and 24 hours later MMC was absent from the tissue samples.

When analyzing MMC concentration in blood, the drug was not detected in any of the samples (assay sensitivity of 0.3 ng/mL).

Clinical outcomes of the surgical treatment can be seen in the **Table**.

As can be seen, 97.9% of the first group had positive results after the surgery, while 2.1% had negative. In the second group, positive results were observed in 87.2% of patients, negative – in 12.8%.

The first group had 38 (79.2%) recovery outcomes, improvement – in 9 (8.7%) of cases, relapse was observed in 1 (2.1%) patient.

In the second group, 25 (53.2%) of cases were recorded as recovered, 16 (34%) patients had improvement outcome, and relapse was noted in 6 (12.8%) cases.

Post-operative follow-up revealed the following complications: in the first group – granulations in the dacryostoma area (3 cases; 6.25%), synechiae between the leading edge of middle turbinate and the lateral wall of nasal cavity in the dacryostoma area (2 cases; 4.2%). In the second group, similar complications were observed in 7 (14.9%) and 8 (17%) cases correspondingly.

Discussion

While a considerable amount of dacryologists still uses MMC routinely in their practice, its effectiveness is still debatable [5]. Until recently, the maximum concentration for most effective and safe usage of the drug remained undetermined. In 2013, M. Ali et al. conducted a study on cell culture of nasal mucosa fibroblasts and found effective cytostatic MMC concentration to be 0.2–0.5 mg/mL [17]. T. Prasannaraj et al. [14], S. Tirakunwichcha et al. [6] applied the drug in that concentration topically but could not confirm its clinical effectiveness. They also noted that some of the studies supporting high effectiveness of MMC for antifibrotic action was conducted on unstandardized clinical material and with unrepresentative sample selections. For example, some researchers used MMC in primary surgeries, some – in revision surgeries [8, 22], others along with MMC performed intubation of formed anastomosis with silicone implants [15, 22]. Maximum follow-up period also varied – from 6 to 18 months [8, 23]. Considering that *in vitro* studies had confirmed antifibrotic efficacy of the drug, but the clinical effect could not be obtained by all researchers, it can be assumed that with topical applica-

Клинические результаты проведенного хирургического лечения

Признак	1st group		2nd group	
	before surgery	after surgery	before surgery	after surgery
Munk, score	2–4 median 4	0–4 median 0	2–4 median 4	0–4 median 1
Purulent discharge:				
presence	48 (100%)	1 (2,1%)	47 (100%)	6 (12,5%)
absence	—	47 (97,9%)	—	41 (87,2%)
Depth of lacrimal meniscus, μm	425±172	263±130	390±180	268±135
Dye disappearance nasal test, cases, %				
positive	—	47 (97,9%)	—	41 (87,2%)
negative	48 (100%)	1 (2,1%)	47 (100%)	6 (12,5%)
LP irrigation, cases, %:				
unobstructed	—	38 (79,2%)	—	25 (53,2%)
as a thin jet	—	9 (8,7%)	—	16 (34%)
unpassable	48 (100%)	1 (2,1%)	47 (100%)	6 (12,8%)
Endorhinoscopy of the nasal cavity, cases, %:				
epithelial lining	—	47 (97,9%)	—	41 (87,2%)
cicatricial deformity	—	1 (2,1%)	—	6 (12,5%)

tion of MMC the required concentration has not been achieved.

Our previous study [16] aimed at calculating MMC concentration in the tissues of dacryostoma area for topical application method showed that maximum concentration of the drug in examined tissues was 0.626±0.176 μg/g, which is about 300 times lower than 0.2–0.5 mg/mL – the concentration figure acquired by M. Ali et al. [17] with confirmed antifibrotic effect.

M. Ali et al. [17] and D. Hu et al. [24] have proved in an *in vivo* test that with increasing MMC concentration and application duration, it starts manifesting its *cytotoxic* effect; thus, higher concentrations of the drug when applied with a turunda and longer exposing duration are unviable. Despite the theoretical possibility of achieving the required concentration in the tissues, it is apparent that it would damage the cells closer to surface and induce tissue necrosis. Moreover, increasing the concentration and time of exposure of the drug is bearing the risk of increased systemic absorption leading not only to local, but also to general adverse effects.

Based on the above, increased concentration of the drug in the tissues of dacryostoma area can be concluded to be reasonable only with improved method of delivering MMC to tissue.

One such method was proposed by S. Kamal et al. [25]. On the final stage of dacryocystorhinostomy (DCR) (110 cases) the authors injected 0.1 mL MMC in the concentration of 0.2 mg/mL into 4 points of nasal mucosa (anterior, posterior, top and bottom) around the formed dacryostoma. The surgery then was concluded by intubating the dacryostoma with a silicone implant. This method of MMC injection in DCR showed good results in 97.3% cases 6 months after the surgery.

However, as we came to believe, that method is not without flaws. It is known that reparation processes take place not only in the nasal mucous membrane, but also in the mucous membrane of the lacrimal sac, which was confirmed in our previous pathohystological studies [26]. The authors of the method described above only conducted antifibrotic measures in the nasal cavity, not affecting the lacrimal sac. Furthermore, they intubated dacryostoma with a silicone implant in the end of the surgery, which is associated with undesirable long-term retention, as well as with a number of possible complications, particularly granulation and infection (including resistant activators associated with biofilms [27]) that can lead to relapse of dacryocystitis [28].

When applying MMC according to the method described earlier in the article – injecting it into mucous membranes of the nasal cavity and lacrimal sac – the need to intubate dacryostoma disappears, as confirmed by the current study. Despite the increase of injected drug volume to 1.2 mL with unchanged concentration of 0.2 mg/mL, a chemical examination showed absence of the drug from blood, which allows an assumption that systemic complications will not occur after injection of MMC in the mentioned volume and concentrations.

Concentration of the drug (385±10 μg/g) in the tissues is within the range of cytostatic MMC concentration determined in an *in vivio* experiment [17]. **Figure 4** features a diagram of concentration against time: marked red are minimum and maximum cytostatic concentrations, blue – concentration acquired with injection method, green – concentration achieved in 3 minutes. It explains the antifibrotic effect at minimum cytostatic action of MMC in the tissues of dacryostoma.

The clinical results of this study are comparable to the results of S. Kamal et al. [25], but our method does not require intubation of the formed anastomosis with a lacrimal implant. No systemic or local complications such as necrosis, inflammation and secondary infection associated with MMC injection were observed with our method. The complications that occurred were intrana-

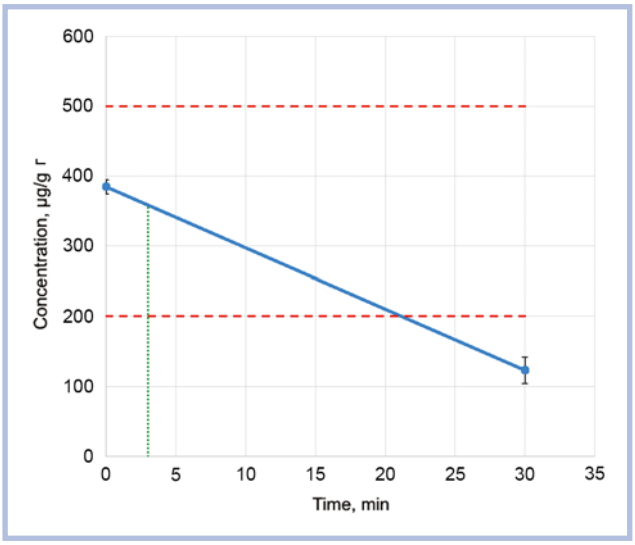


Figure 4. **Concentration of MMC (µg/g) for achieving cytostatic effect.**

See explanation in the text.

sal synechiae (4.2% of cases) and granulation (6.25% of cases), which are not considered severe and indicate the need for regular post-surgery monitoring.

Conclusion

Injection of MMC into the mucous membrane of the nasal cavity and lacrimal sac has proved to be clinically effective and safe when applied during the final stage of EEDCR for prevention of excessive scarring at the anastomosis site. The conducted pharmacokinetic study showed that the required cytostatic concentration was successfully achieved in the tissues of dacryostoma area when using the newly developed injection method. The method can be recommended for use in clinical practice.

Author contributions:

Study conception and design: E.A., A.R.

Acquisition and processing of data: A.R., N.K., V.Y., S.Y., A.P., I.S.

Statistical analysis: A.R., N.K., V.Y.

Drafting of manuscript: E.A., A.R., S.Y., G.R.

Critical revision: V.Y., A.P., I.S.

The authors declare that there are no conflicts of interest.

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