Recent Advancement in Otorhinolaryngology - Mitomycin-C

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Abstract:
Mitomycin-C is a chemotherapeutic drug that acts by inhibiting DNA synthesis. Its use and application in ENT has been increasing in recent years because of its mandatory effects on wound healing. Current applications include Tracheal Stenosis, nasal synechia, endoscopic dacryocystorhinostomy surgeries and allergic disease. This article reviews the current trends and uses of mitomycin-C in the eye and its related complications.

Key Words:
Mitomycin-C, ENT diseases, Synechia, Stenosis

1. Introduction:
Mitomycin-C (MMC) is an anti-neoplastic/antibiotic agent isolated from soil bacterium Streptomyces caespitosus. It is used intravenously to treat upper gastro-intestinal tumors, anal cancer, breast cancer and bladder tumors. Mitomycin C has also been used topically rather than intravenously in several areas like bladder cancers and intra-peritoneal tumors. It is now well known that a single instillation of this agent within 6 hours of bladder tumor resection can prevent recurrence. In esophageal and tracheal Stenosis application of MMC onto the mucosa immediately following dilatation will decrease restenosis by decreasing the production of fibroblasts and scar tissue.

Its use and application in ENT has been increasing in recent years because of its modulatory effects on wound healing.

2. Pharmacology and mechanism of action:
It is an anti-metabolite with anti-proliferative effect on cells showing the highest rate of mitosis by inhibiting DNA synthesis and interferes with RNA transcription and protein synthesis. DNA is inhibited by cross linking at the N position of Adenine and at 06 and N position of Guanine. The cell cycle is most affected during the late G-I and early S-phase. The chemical formula is C15H18N4O5.

3. Drug Reconstitution and Pharmacokinetics:
The drug is available in a vial (2mg/ml). It is further reconstituted with normal saline (5ml) to make 0.4mg/ml or in 10ml to make 0.2mg/ml. the drug should be stored under refrigeration after reconstitution to preserve its potency and under these conditions; it is potent for a period of two weeks only. MMC is delivered in solubilized form.

4. Clinical uses of Mitomycin C in Otorhinolaryngology:
   a) Nasal synechia
   b) Nasopharyngeal carcinoma
   c) Tracheal Stenosis
   d) 4-Keloids head and neck region
   e) After Myringotomy
   f) FESS in Chronic Rhino sinusitis
   g) Endoscopic DCR
   h) Pharygo-oesophageal stricture
   i) Vocal cord paralysis

   a) Nasal Synechia:
   Synechia is the most frequent complication after sinus surgery and has been reported in up to 36% of cases. Several types of materials have been used to reduce the incidence of synechia, including Mitomycin C (MMC).
Postoperative synechia is the most frequently reported complication in the literature, found in between 11% and 36% of the cases. Revision surgery is required in 1% to 2% of the cases. When only revision surgery is considered, the incidence rate ascends to 56%\textsuperscript{2}. A review on 182 FESS patients revealed that the only findings related to little clinical improvement were fibrosis in medial antrostomies and in the ethmoidal region\textsuperscript{1}.

Mitomycin C was not effective in preventing postoperative synechiae in patients submitted to functional endoscopic sinus surgery.

Mitomycin C was effective in preventing postoperative total synechiae in patients submitted to functional endoscopic sinus surgery.

Studies with larger populations, higher dosages, and longer time of exposure are required.

b) Nasopharyngeal Carcinoma

Mitomycin C (MMC) is a classic chemotherapeutics which exhibits effective anti-tumour effects against a variety of solid tumours by inducing apoptosis and reducing drug resistance \textsuperscript{7,8}. Notably, the inhibitory effects of MMC against NPC cells have been reported previously \textsuperscript{9}. Combination therapy with various drugs is a common strategy in cancer treatment to obtain an additive or synergistic effect and to reduce the potential toxicity. So far, numerous MMC-containing combinations. Remedies have been reported with encouraging clinical effects \textsuperscript{10,11}.

combined chemotherapy and antibody targeted therapy to show that MMC and anti-LMP1 Fab combination exhibited synergistic effects to inhibit NPC tumor growth in vivo with high efficacy and much less toxicity associated with MMC. The anti-tumour effects appear to be mediated via the induction of apoptosis and the inhibition of VEGF expression. This novel combination therapy represents a promising strategy for the treatment of NPC.

c) Laryngeal Stenosis:

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 cannot be identified.\textsuperscript{12} After any of the afore-mentioned damage to the mucosa, the following inflammatory process activates fibroblasts to participate in wound healing. Fibroblasts synthesize several factors, such as transforming growth factor \beta1 and basic fibroblast growth factor, that stimulate the production of extracellular matrix components, leading to scar formation and contraction at the stenosis site.\textsuperscript{13,14} 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.\textsuperscript{12} 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.\textsuperscript{12,13} However, a high rate of restenosis ranging from 40% to 70% has been reported after the endoscopic treatment of tracheal stenosis,\textsuperscript{15–18} urging a need for therapies aimed to obtain better results. Treatments studied to reduce recurrences include steroids, 5-fluorouracil,
halofuginone, tamoxifen, and mitomycin-C (MMC).18

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.19

d) Keloid:

Keloids were described by Egyptian surgeons around 1700 BC21. Baron Jean-Louis Alibert (1768–1837) identified the keloid as an entity in 1806. He called them cancroïde, later changing the name to chéloïde to avoid confusion with cancer. The word is derived from the Greek χηλή, chele, meaning "hoof", here in the sense of "crab pincers", and the suffix -oid, meaning "like". Persons of any age can develop a keloid. Children under 11 are less likely to develop keloids, even from ear piercing. We know that certain dark-skinned races are more prone to the development of keloids. For instance, the occurrence of keloids in black patients is between 4% and 16%.22 Keloids may also develop from Pseudofolliculitis barbae. The tendency to form keloids is speculated to be hereditary. Keloids can tend to appear to grow over time without even piercing the skin, almost acting out a slow tumorous growth; the reason for this is unknown. The ratio of type I collagen to type III collagen is elevated.22 Histologically, keloids are fibrotic tumors characterized by a collection of atypical fibroblasts with excessive deposition of extracellular matrix components, especially collagen, fibronectin, elastin, and proteoglycans.23,24 Generally, they contain relatively acellular centers and thick, abundant collagen bundles that form nodules in the deep dermal portion of the lesion. Keloids present a therapeutic challenge that must be addressed, as these lesions can cause significant pain, pruritus (itching), and physical disfigurement.25,26 Topical Mitomycin C application for keloids after surgical excision showed success rate of 95% without any toxic side effects or complications which is in line with previous study by C.E. Stewart et al.20 Combination of surgical excision with topical mitomycin-C application is highly safe and effective in treating head and neck keloids in contrast to other modalities which have either a high recurrence rate or are invasive.

e) After Myringotomy:

Mitomycin C (MMC) is an antineoplastic agent of the antibiotic subgroup, which is produced by a fungus called Streptomyces caespitosus.

It blocks DNA and RNA replication by interfering in the G1 and S phases at the late stages of the cell cycle. Local application of MMC to the margins of perforations after myringotomy is reported to delay perforation closure.27,28

The aim of this study was to investigate the effects of locally applied MMC on the duration of TM healing and on the expression of bFGF, TGF-β1, and KGF-1 after perforations induced by myringotomy.

f) FESS In Chronic Rhinosinusitis:

Mitomycin-C (MMC): MMC is an alkylating antineoplastic antibiotic that prevents replication of fibroblasts and epithelial cells, in otolaryngology MMC is currently under inquiry for the prevention of laryngotracheal stenosis, as an adjunct to FESS to prevent closure of the maxillarsinus antrostomy.29 MMC operates by disrupting base paring of DNA molecules in the G-1 phase of cell cycle, and inhibits formation of RNA and protein synthesis- this way inhibits proliferation of fibroblasts. Additional function is inhibition of apoptosis in fibroblasts and blockage of
angiogenesis. Topical applications of MMC over last decade extended to fields of plastic surgery and rhinology especially endoscopic sinus surgery (ESS) and acryocystorhinostomy (DCR).\textsuperscript{30,31} The concentration of MMC ranged from to 1.5 ml 0.3 mg/ml to 0.6 mg/ml, whereas dose applied ranged from 0.5 ml and duration of topical MMC application was 5 minutes in majority (7 out of 9) of studies, 4 minutes in 2 studies. Application method was in the way of soaked cotton pledgets 5 in 9 studies, ribbon gauze in 2 studies and Merocel pack in 1 study. No studies report any adverse effects or systemic toxicity of topical MMC applied for 5 minutes and in maximum concentrations-0.6 mg/ ml and maximum dose of 1.5 ml. Years of experiences from ophthalmologists shown that MMC in concentration of 0.4 mg/ml for 5 minutes appears to be very safe.

The aim of the study was to determine whether topical application of Mitomycin-C at the conclusion of FESS decreases the incidence of postoperative adhesion formation.

g) Endoscopic Dacryocystorhinostomy

The most important cause of failure of DCR surgery is fibrosis occurring under the flaps near the osteotomy sites. MMC inthese cases tends to suppress fibrous proliferationand scar formation. Intra-operative MMC application is effective in increasing the success rate of DCR surgery and no significant complications resulted from its use\textsuperscript{32}.

The non-patency rate in the MMC group is 4.5% compared to 11.4% in the conventional group. A piece of cotton soaked with 0.2mg/ml MMC is applied to the osteotomy site for 30 minutes intra-operatively is effective in maintaining a larger osteotomy size and also improves success rates over the traditional DCR procedure\textsuperscript{33}.

Dose: 0.02 to 0.04% for 5-30 minutes.

h). Pharyngoesophageal stricture

To assess the role of mitomycin C (MMC) in the management of Pharyngoesophageal stricture after total laryngopharyngectomy and free flap reconstruction. Five patients since 1998 underwent evaluation and treatment for pharyngoesophageal stricture after totallaryngopharyngectomy and free flap reconstruction. The method of reconstruction included four tubed radial forearm free flaps and one jejunal free flap.\textit{(Laryngoscope 2003 Sep;113(9):1499-502 Donald J Annino, Laura A Goguen)}

5. Conclusion:

The use of topical Mitomycin C in Otorhinolaryngology it is increasing in every subspecialty but risk benefit ratio should be considered, keeping in mind its complications. The dose and duration of application of MMC depends on surgery in which it is being used but is still controversial. Trials with longer follow up are required to establish safety and efficacy of drug.

6. References:


