

EFFECT THE USE OF MITOMYCINE C IN LARYNGEAL SURGERY,

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Abstract

Objective: to study the effect of use of topical mitomycin C (MMC) on the larynx. And whether there is any difference in the outcome if it was used in the larynx as compared to its use in the nose.

Patients and method: This is a retrospective study of twelve patients with the diagnosis of laryngeal stenosis that were managed at king Abdulaziz University hospital between April 2002 and November 2006. All of the patients underwent microlaryngoscopy and laser dilatation of the stenosis, followed by topical application of MMC. The outcome of the first surgical intervention was evaluated and compared to the outcome of the first surgical intervention and use of MMC in choanal atresia (CA) cases according to our previously reported data.

Results: Five (42%) out of 12 patients with laryngeal stenosis improved following the first microlaryngoscopy, laser dilatation and application of MMC compared to 9 (69%) out of 13 patients who underwent endoscopic dilatation of CA and application of MMC.

Conclusion; According to our data there was more benefit of the use of MMC in the cases of CA as compared to the larynx. However, the observed difference was not statistically significant.

Key words; mitomycin, subglottic stenosis, laryngeal web, choanal atresia.

Introduction:

Mitomycin C (MMC) has been used as adjunct to the surgical management of choanal atresia (CA) and laryngeal and tracheal stenosis with a varying degree of success. Scar formation and re-stenosis remain the main causes of failure in the surgical management of airway stenosis.¹ Numerous randomized prospective animal studies^{2,3} have shown convincing results for the use of MMC in the prevention of glottic and subglottic stenosis (SGS) in the post-operative period. Human studies have also demonstrated the efficacy and safety of topical MMC (0.4 mg/ml) in the treatment of airway stenosis.^{4, 5}

MMC has been recommended as an adjunct to CA surgery after observing improved patency and a decreased need for dilatation, stenting and revision surgery.⁶ Bradford et al⁷ showed a statistically significant outcome with use of MMC compared to control for CA surgeries. On the other hand, According to our previous study on use of MMC for CA cases; there was no statistically significant improvement with the use of MMC.¹³

MMC is an anti-metabolite produced by *Streptomyces caespitosus*.⁴ It possesses both anti-neoplastic and anti-proliferative properties. Its anti-neoplastic property is derived from its ability to crosslink DNA and inhibit RNA and protein synthesis which is used for this purpose primarily in the treatment of gastrointestinal malignancies. Furthermore, MMC has been shown to inhibit fibroblast proliferation both in vivo and vitro.^{8, 9} Hence its clinical use as a modulator of wound healing response. The exact mechanism by which it exerts its anti-fibroblastic activity is unknown, though there is evidence to suggest that it may be mediated by apoptosis which is a gene directed process causing cell death. It has successfully been used by ophthalmologists to prevent re-stenosis in Glaucoma surgery, Dacrocystorhinostomy, Optic nerve sheath fenestration and Pterygium recurrence.^{10, 11} The rationale of the use of MMC is to inhibit fibroblast proliferation during the post-operative phase without damaging mucosa and epithelial growth.¹²

In this study an attempt was made to study the effect of the use of MMC on the outcome of endoscopic laryngeal surgery. Also by comparing the outcome of this drug on the larynx to its effect on the nose by utilizing our data of the use of MMC for CA surgery which was reported before.¹³

Materials and Methods:

We identified fourteen patients who underwent microlaryngoscopic treatment along with topical application of MMC for their diagnosis of laryngeal airway obstruction at the King Abdulaziz University Hospital in Riyadh, Saudi Arabia from April 2002 to November 2006.

Use of MMC consisted of topical application of the drug after microscopic laser dilatation of SGS, or division of laryngeal web (L.WEB). MMC was used in a concentration of 0.4mg/ml for a period of 4 minutes, followed by irrigation of the application site with 15cc of saline.

Myer and Cotton¹⁴ grading of SGS was used to indicate the severity of SGS; grade I (up to 50%) stenosis, grade II (51-70%), grade III (71-99%) and grade IV with no detectable lumen. The percentage of the glottic chink affected by the glottic web was also estimated.

For each patient we reviewed the medical records and recorded clinical details such as age, sex, diagnosis, history of past surgery for their complaints, date of first surgery with MMC, outcome of this first surgery (whether Improved or Not improved), type of revision surgery done (with or without topical application of MMC), the follow up duration in months, final outcome of surgery and complications of the surgery or MMC.

We defined Improvement following surgery, as patient having satisfactory airway with no further symptoms of airway obstruction and patent airway on endoscopy, also involved decanulation if tracheotomy was used, without the need for revision surgery. Those who had Not-improved were operated upon again with or without topical application of MMC and were followed up following revision surgery and their final outcome was recorded.

In this study we compared the outcome of the use of MMC in the larynx to our previously reported prospective controlled study about the use of MMC for CA cases. There we used the same MMC concentration and for the same period of application time in 13 of CA cases who underwent endoscopic repair of CA, and in 7 CA case MMC was not used (table 1).

The initial outcome after the first microlaryngoscopic surgery and use of MMC, was compared to our outcome of use of MMC on CA after the first endoscopic intervention according to our previously reported results.

Chi-Square test was used to compare categorical variables. A p-value of less than 0.05 indicated a statistical significance. For all statistical tests, we used the statistical Package for Social Sciences version 11.5 software.

Result:

The study consisted of 14 patients with laryngeal obstruction. Seven patients (50%) with sub-glottic stenosis (SGS), 5 patients (34%) with laryngeal web (L.WEB), 1 patient (7%) with posterior commissure scar (PC SCAR), 1 patient (7%) with sub-glottic stenosis and laryngeal web (SGS+L.WEB).

Age in this group ranged between 18 months and 18 years (Mean age=100.71 months). In this group there were 12 male patients and 2 female patients (Male: Female = 6:1). These patients were followed up after surgery for a duration ranging from 2 months to 48 months (Mean=14.12 months). Of these 14 patients, 2 patients were lost to follow up and will be excluded from our study.

Five patients (42%) improved following the first surgery, 7 patients (58%) did not improve (table 2). Six of those who failed the first intervention had revision microlaryngoscopic surgery without MMC and 1 had revision microlaryngoscopic surgery with MMC application (Table 2). At the end of follow up 5 patients with revision surgery improved, 1 patient did not improve and 1 patient was lost to follow-up. There was no complication seen in this group.

Comparing the improvement rate with the use of MMC after the first endoscopic intervention in the larynx (42%) to that of the use of MMC in CA after the first endoscopic surgery (69%) (Table 3), showed that the use of MMC on CA was associated with better outcome, however this difference was not statistically significant $p= 0.45$.

Discussion:

Kunitomo and Mori¹⁰ in 1963 presented the first clinical use of MMC in the prevention and treatment of scar formation in pterygium surgery. Since then there have been many studies about the efficacy of MMC and others on its complications on the airway.¹⁵ Perepelitsyn et al⁵ study showed a statistically significant difference when comparing the outcome of laryngeal & tracheal stenosis surgery of the MMC group with those of CO2 laser group and with the CO2 laser with steroid injection group. Rahbar et al¹ demonstrated that topical application of MMC can be beneficial in modulation of wound healing and in decreasing scar formation in treatment of airway stenosis.

According to our previously reported data about the use of MMC on CA, there was some improvement in use of MMC as compared to control cases (table 1), however that improvement was not statistically significant, $p= 0.230$.¹³

Our primary aim in this study was to observe if there was any significant benefit with respect to use of topical MMC in Laryngeal surgeries, and whether the effect of MMC in the larynx is similar to its effect in the nose. In our study we found that there was no significant difference of the effect of MMC with respect to site of topical application, whether for CA in the nose or for endolaryngeal procedure. Accordingly it is difficult to support the effectiveness of MMC to prevent scarring in the larynx.

Laryngotracheal stenosis remains a challenge to any otorhinolaryngologist due to scar formation and re-stenosis. Modulation of wound healing process to prevent excess scar formation can play a major role in improving the success rate and decreasing the need for further surgery. The goal of any treatment is the restoration of an adequate airway, provision of

a competent larynx for protection against aspiration and the achievement of a satisfactory voice.

Endoscopic management of laryngeal and tracheal lesions has undergone tremendous advancement in the past 2 decades. The development of microlaryngoscopy, adaptation of the microscope, use of CO₂ Laser, as well as use of microdebrider have significantly changed the outcome.^{16, 17}

Despite the advancements in endoscopic surgical techniques and the better understanding of the wound healing process as well as with the introduction of mucosa preserving laser surgery such as the micro-trap door flap technique¹⁸ and radial incision and dilation¹⁹, there is still a high degree of scar formation and re-stenosis. The review of literature shows a wide range of success by many authors ranging from 44% to 66%^{8, 9} in Endoscopic treatment of airway stenosis.

Regardless of the surgical technique used, there is always further injury to the airway mucosa which causes release of plasma proteins, blood cells and platelets, which react with tissue factors to form a fibrin-fibronectin clot.²⁰ This serves as a matrix for the migration of capillaries, fibroblasts and inflammatory cells. Fibroblasts synthesize collagen, glycosaminoglycans and fibronectin to form granulation tissue. Over time there is collagen maturation, capillary resorption and myofibroblast contraction causing scar formation.

CA is a congenital uncommon condition characterized by the obstruction of posterior nasal apertures and was first described in 1755 by Johann Roederer. The incidence is estimated to be 1 in 5000-7000 live births.²¹ Recent reports show mixed – bony and membranous to comprise as much as 70% of the cases.²² Associated congenital anomalies are found in up to 50% of the cases.

Any attempt to study these rare but challenging conditions is thronged with difficulties because of many factors which could include small sample size, previous treatments, multiple etiologies and chronicity.

Conclusion:

This retrospective study was undertaken with the primary aim of studying the effect of use of topical MMC on the larynx. And whether there was any difference in the outcome if it was used in the larynx as compared to its use in the nose. According to our data there was more benefit of the use of MMC in the cases of CA as compared to the larynx. However, the observed difference was not statistically significant.

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Table-1

	MITOMYCIN USED	MITOMYCIN NOT USED
Success	9 (69%)	4 (57%)
Failure	4 (31%)	3 (43%)

Table 1: comparing the success rate in mitomycin and non-mitomycin cases of CA according to our previous reported study.

t. No.	DIAGNOSIS	H/O PAST SURGERY	Pre-Op Grade/ %age	Outcome after 1 st intervention	REVISION SURGERY: (WM)WITH MITOMYCIN, (W/O.M)WITHOUT MITOMYCIN	F/U DURATION (month)	Post-Op Grade/ %age	FINAL OUTCOME I/NI	COMPLICATION
1	SGS	N	SGS-3	NI	WM	24	SGS-1	I	N
2	SGS+L.WEB	N	SGS-2 L.WEB- 20%	NI	W/O.M		SGS-1 L.WEB- normal	Lost to follow up	
3	SGS	Y	SGS-2	I		7	SGS-1	I	N
4	SGS	Y	SGS-1	I		48	normal	I	N
5	L.WEB	N	50%	NI	W/O.M	23	30%	I	N
6	PC SCAR	N	40%	NI	W/O.M	9	30%	NI	B/L VC PALSY
7	SGS	N	SGS-2	NI	W/O.M	4	SGS-1	I	N
8	SGS	Y	SGS-3	NI	W/O.M	2	SGS-1	I	N
9	L.WEB	N	30%	NI	W/O.M	11	20%	I	N
10	SGS	N	SGS-3	I		2	SGS-1	I	N
11	L.WEB	N	50%	I		2	20%	I	N
12	SGS	Y	SGS-2	I		25	normal	I	N

Table 2 shows the laryngeal cases, their diagnosis, H/O past surgery (N-No, Y-Yes), preoperative and post operative grade of narrowing, outcome after surgery (I-Improved, NI-Not-improved), revision surgery (WM-With MMC, W/O.M-Without MMC), follow-up duration in months & complication.

	CA	Laryngeal stenosis	p-VALUE
AGE (MEAN)	40.25	100.71	0.014 – SIGNIFICANT
SEX (Male : Female)	4 : 9	12 : 2	0.008437 – SIGNIFICANT
FOLLOW UP DURATION (MEAN)	20.3	14.12	0.318 – NOT SIGNIFICANT
OUTCOME AFTER 1ST SURGERY (I/NI)	9/4	5/7	0.45 – NOT SIGNIFICANT

Table 3 compares the Groups with respect to their mean age, ratio of male and female patients, mean follow-up duration and outcome after 1st surgery (I-Improved, NI-Not-Improved).