

The Adjunctive Role of application of Mitomycin C intraoperatively with posterior transverse laser cordotomy in treatment of bilateral abductor vocal fold paralysis

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Abstract

Bilateral abductor vocal fold paralysis (BAVFP) is a common complication following thyroidectomy. In those patients whose airway is compromised by the paralyzed vocal folds, tracheostomy is emergently indicated, which is, though life-saving, a stigmatizing mishap with significant impact on quality of life. A significant proportion of afflicted patients recover recurrent laryngeal nerve function 6-12 months after the onset, and thus may get rid of the tracheostomy. However, patients who do not recover vocal fold mobility always seek to become independent of the tracheostomy tube. Dennis and Kashima (1989) have devised Posterior Transverse CO₂ Laser Cordotomy (PTLC) in order to relieve the obstruction at the posterior glottis. Variable results for this procedure have been reported. Granulation tissue with subsequent scar formation may be a cause for the varying results. Mitomycin C (MMC), an anti-mitotic chemotherapeutic agent has been shown to reduce granulation and scar tissue formation in multiple studies using animal models in which airway scarring is induced. MMC has also shown significant prevention of re-stenosis following surgical correction of laryngotracheal stenosis. We report, for the first time, a case-control series of 23 patients with post-thyroidectomy BAVFP who have undergone PTLC. The study group (12) had MMC adjuvant application during PTLC. Thirteen patients had a tracheostomy prior to inclusion. Three outcomes of the intervention were compared in the study and control groups: decannulation rate (for tracheostomized patients), dyspnea symptom scale (DSS) change for non-tracheostomized patients, and voice quality. DSS was the only outcome that showed a statistically significant difference between the study and control groups.

Key words: Mitomycin C, abductor vocal fold paralysis, posterior laser cordotomy.

Introduction

Bilateral abductor vocal fold paralysis (BAVFP) is a rare but life-threatening condition which may require an emergency tracheotomy procedure (1). The aim of all surgical techniques used in the treatment of vocal fold paralysis is to restore a lumen sufficient to guarantee adequate breathing through the natural airway, without the patient having to permanently maintain the tracheotomy tube, while preserving acceptable phonatory quality and without impairing swallowing (2). Posterior transverse laser cordotomy (PTLC) was first described by Dennis and Kashima as a technique for providing an airway at the posterior glottis without pre-operative tracheotomy; they reported it as a successful method with satisfactory functional results (1). Scarring, stenosis, and adhesion are problems in otolaryngological surgery that can lead to impaired organ function and structural distortion. Previous studies have described methods to modulate the wound healing process and to reduce undesirable excessive scarring. Cryosurgery, dye laser, or drugs such as steroids and 5-fluorouracil have been used to reduce scars, but final results are not always satisfactory (3). Since 1998, a great deal of attention has been focused on the use of topical mitomycin C (MMC) as an

adjuvant to reduce re-stenosis after endoscopic laser management for bilateral vocal fold abductor paralysis (4). Mitomycin-C is an antineoplastic antibiotic that acts as an alkylating agent by inhibiting DNA and protein synthesis. It can inhibit cell division, protein synthesis, and fibroblast proliferation (5). The key steps in the initiation of scar formation are fibroblast proliferation and collagen formation secondary to mucosal injury. MMC has been demonstrated to have antifibroblastic activity in vitro and in vivo (6).

The purpose of this prospective study is to investigate the role of intraoperative local applications of topical mitomycin-C in prevention and treatment of glottic restenosis and recurrence of obstruction after posterior transverse laser cordotomy for patients with post thyroidectomy bilateral vocal fold paralysis, and also evaluate the quality of voice and respiration in those patients in comparison to those without application of mitomycin

Material

Twenty three patients with impaired airway due to bilateral abductor vocal fold paralysis consecutively treated with endoscopic posterior transverse CO₂ laser cordotomy (PTLC) at Ain Shams University Hospitals, ENT department, Cairo, Egypt, from January 2002 to

November 2007. Their age ranged from 27 years to 53 years (mean age = 40 years), 7 males and 16 females. The procedure was done after the elapse of one year from the onset of vocal fold paralysis.

Inclusion and exclusion criteria:

The study included post-thyroidectomy patients with bilateral abductor vocal fold paralysis, complaining of dyspnea and stridor, Recurrent cases subjected to any previous corrective surgical procedures were excluded from the study.

All patients had an informed consent for the procedure of a unilateral posterior transverse CO2 laser cordotomy with special emphasis on two main postoperative sequelae which are: 1) The possibility of failure of decanulation for the tracheostomized patients with the liability for revision surgery or the need to be tracheostomized in those without tracheostomy, 2) The decreased quality of voice.

Thirteen patients of the study population were tracheostomized, as they had respiratory distress at a variable period dating since their thyroid surgery (from the first postoperative day – 2.5 months after thyroid surgery).

Methods

All cases gave a past history of total thyroidectomy followed by respiratory distress. Six cases of them had papillary thyroid carcinoma and had completed their treatment with radioactive iodine, with no evidence of recurrence at time of cordotomy. The rest of the cases were not aware about the nature of their thyroid gland disease.

Laryngeal photography was done for all the patients preoperatively to verify and document the diagnosis. Postoperative photography was done to assess the result of our corrective procedure.

We divided the patients into 4 groups: 1st & 3rd groups included 12 patients, who were subjected to PTLC and topical Mitomycin application; and 2nd & 4th groups included 11 patients, who were subjected to PTLC only. Patients in the 1st and 2nd groups were tracheostomised (13 in number), while patients in the 3rd and 4th groups were not tracheostomised (10 in number).

General anesthesia using endotracheal intubation of small size 5 – 5.5 for non tracheostomized patients (n=10) and through the tracheostomy tubes for the rest of the patients (n=13).

The laryngoscope was introduced and suspended exposing adequately the posterior segment of the vocal folds. The operating microscope was adjusted at a magnification of 16X with a 400-mm lens.

The CO2 laser was adjusted at a power setting of 4W in a super-pulsed mode (0.25 mm- 0.3 mm spot size). Using the micromanipulator, the laser beam was applied just anterior to the vocal process of the arytenoid

(probed by spatula).

A transverse cut was made by the CO2 laser at this level along the whole thickness and depth of the vocal fold laterally limited by the appearance of the inner endochondrium of the thyroid cartilage. The laser plume was continuously sucked for clear visualization of the laser cut. The resulting charring was continuously swabbed using normal saline soaked neurosurgical cottonoids.

In the 1st & 3rd group; following laser cordotomy, a neurosurgical cottonoid soaked in MMC (0.4 mg/cc) was placed at the site of the cut wound for a period of 4 minutes, and then the site of the wound was re-swabbed several times with normal saline.

For the non tracheostomized patients, removal of the endotracheal tube was done and respiratory status was assessed in order to decide the need for immediate post-operative tracheostomy tube or not. Postoperative prophylactic antibiotics and antireflux measures were applied to all patients.

Each patient was subjected to the following technique (7): All the patients were subjected to a follow up schedule based on a weekly post-operative indirect telescopic examination of the larynx for 2 months post-operatively. Follow-up has ranged from 6 months to 36 months.

Laryngeal photography was done at a period of 2 and 6 months post-operatively for the assessment of the posteriorly created glottic chink, state of epithelialization at the site of cordotomy, presence of any granulations or fibrous adhesions or variable degree of re-stenosis.

Airway assessment

Subjective analysis; severity of dyspnea was evaluated in the preoperative (before tracheostomy or cordotomy) and postoperative periods by means of a five level symptom scale (as non, mild, moderate, severe, and very severe), according to the limitation in daily activity and level of respiratory difficulty (table 1) (1).

Dyspnoea level	Stage	Symptoms
None	1	None
Mild	2	Dyspnoea with no limitation of daily activity
Moderate	3	Dyspnoea with mild limitation of daily activity, no stridor
Severe	4	Dyspnoea with significant limitation of daily activity, with stridor
Very severe	5	Respiratory difficulty requiring tracheotomy

Table (1): Dyspnoea symptom scale

Voice assessment: This was performed before surgery, 1 month after surgery and after decanulation, according

	Mitomycin application	Need of tracheostomy	-	Dyspnoea scale		Complication developed	Need of 2nd session	Time of decannulation
				Pre-operative	Post-operative			
Group 1	+ve	+ve	1	5	2			after 1 month
			2	5	2			after 1 month
			3	5	2			after 5 weeks
			4	5	2			after 2 months
			5	5	2			after 1 month
			6	5	3			after 4 months
			7	5	2			after 3 months
Group 2	-ve	+ve	8	5	2	granulations	+ at 6thm	after 4 months
			9	5	3	-	+at 4th m	after 10 months
			10	4	2	granulations	+ at 8th m	after 4 months
			11	4	3	restenosis	+ at 6th m	after 8 months
			12	5	4	granulations		failed
			13	5	3	-		after 1 year
Group 3	+ve	-ve	14	3	2			
			15	3	2			
			16	4	2			
			17	3	2			
			18	3	3	Not improved	+ at 4m	
Group 4	-ve	-ve	19	3	2	Tracheostomized	+ at 5 m	After 8 months
			20	3	4	Granulation		
			21	3	4	restenosis	+ at 9 m	After 1 year
			22	3	3	granulations		
			23	3	2	oedema	+ at 4 m	

Table (2): Patients' data and postoperative follow up results of the 4 groups.

N.B. The dyspnea grading was evaluated for every patient before any intervention (either tracheostomy or cordotomy) and after cordotomy with the closure of the stoma if still present (before 2nd session or decannulation).

to the Ain Shams protocol of voice assessment (8).

It included:

A) Auditory perceptual assessment (APA): This is done during patient interviewing using a 5-points scale (0 - 4) for determining the items overall grade of dysphonia (G), and character of voice including: strained (S), leaky (L), breathy (B) and rough (irregular) (8) [0 for normal, 4 for severe].

Overall grade: a comprehensive evaluation of the voice taking into account all factors such as strain, leakiness, breathiness and roughness.

B) Acoustic analysis of voice: This was done using the Multi-Dimensional Voice Program (MDVP model 4305) from KAY Elemetrics Corporation). The analysis sample was a sustained phonation of the vowel /a/ and a mid-vowel segment was selected for analysis. The following parameters were measured:

1. Average fundamental frequency (F0) in Hz.
2. Jitter percent (Jitt %).
3. Shimmer percent (shim %).
4. Noise to Harmonic ratio (NHR).

Results:

The patients' data and postoperative follow up results

were summarized in table 2.

None of the non tracheostomized patients required immediate post-operative tracheostomy depending on their O2 saturation level on air for a period of 30 minutes after extubation, but 2 patients from the 4th group were grade IV dyspnea scale. They needed tracheostomy at 5, 9ms, due to development of granulation and restenosis that need 2nd session (Figure 3).

MMC application	Dyspnea grade			
	DG 2	DG 3	DG 4	Total
+ve	4	4	3	11
-ve	10	2	0	12
Total	14	6	3	23

Table (3): Comparison between groups with application of mitomycin with PTLC versus those with PTLC only regarding postoperative dyspnea grade $\chi^2= 6.206$, degrees of freedom, 2; $p= 0.04491$

	Group 1&3 (12 pts) (with mitomycin)	Group 2&4 (11 pts) (without mitomycin)
Complication developed	Not improved (1)	Granulation (5) Restenosis (2) Oedema (1)
Need of 2nd session	1 case	7 cases
Time of decanulation	1- 4 months	4 months - 1year One failed

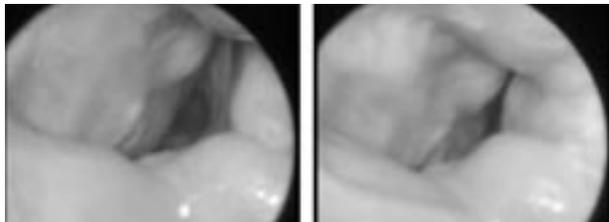
Table (4): Differences in complications, need for 2nd session, and time of decanulation between the various groups.

	F0	Jitter %	Shimmer %	NHR	MPT
MMC +ve (n=12)	T=0.157, p=0.4377	T=0.235, p=0.4070	T=0.078, p=0.4687	T=2.401, p=0.0082	T=3.059, p=0.0011
MMC -ve (n=11)	T=1.867, p=0.0309	T = 0.178, p=0.4294	T = 0.178, p=0.4294	T = 2.490, p=0.0064	T = 2.934, p=0.0017

Table (5): Comparison of preoperative and postoperative voice parameters in both MMC+ and MMC- groups using Wilcoxon's matched pairs signed ranks test: (F0 = Fundamental frequency, NHR= Noise-to-Harmonic Ratio, MPT= Maximum Phonation Time)

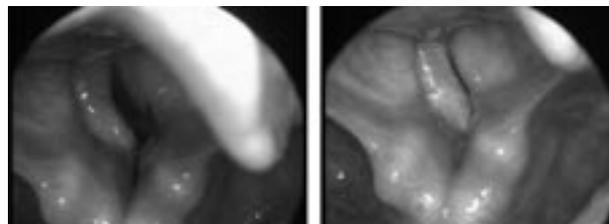
Voice parameter	z statistic (corrected for ties)	p value
F0	0.0615	0.4755
Jitter %	0.0923	0.4632
Shimmer %	0.0	0.5
NHR	0.4308	0.3333
MPT	0.0615	0.4755

Table (6): Comparison of postoperative voice parameters in MMC+ and MMC- groups using Mann-Whitney U test: (F0 = Fundamental frequency, NHR= Noise-to-Harmonic Ratio, MPT= Maximum Phonation Time)



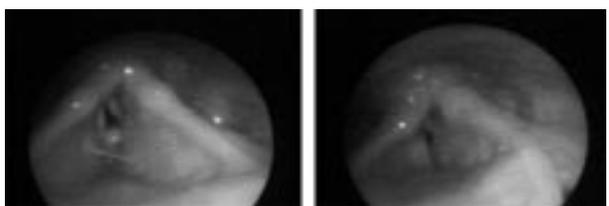
02:06:17 (5:1) - Respiration 02:07:16 (5:1) - Phonation

Fig 1: showed postoperative photography of one pt from group 1 during respiration and phonation.



00:07:20 (4:1) - Respiration 00:13:24 (4:1) - Phonation

Fig 2: showed postoperative photography of a pt from group 3 during respiration and phonation



00:33:08 (3:1) - Respiration 01:09:06 (3:1) - Phonation

Fig3: showed postoperative photography of a pt from group 4 during respiration and phonation, showed granulation at site of PTLC

Discussion

Bilateral abductor vocal fold paralysis (BAVFP) is a clinical situation that occurs as a result of bilateral paralysis of the recurrent laryngeal nerves, the condition is a major complication of thyroidectomy. The major problem in BAVFP patients is dyspnea, which may require emergency intervention; therefore, the goal of surgery is to provide sufficient glottis opening while protecting glottal functions as much as possible. Tracheotomy still remains the most effective surgical intervention for providing airway patency, but because of its drawbacks, various surgical techniques for the glottis have been described (1).

Since Kashima and Dennis proposed the CO2 laser surgical posterior cordotomy" (PTLC) in 1989, A numbers of similar and modified approaches have been published in the surgical literature. In addition, Dennis & Kashima recommended limiting partial cordotomy to the dorsal glottis in order to maximally preserve the functionally important vibrating anterior part of the vocal folds (9).

The procedure is effective and easily repeatable in cases of recurrence and its complications are rare. Laccourreye recently reported a 92% decannulation rate with this approach in 25 patients (10).

Dursun and Gökcan (2006) reported an immediate relief of dyspnea in all patients (22 pts) after posterior transverse cordotomy, with significant changes in patients' postoperative scores, which was shown in the authors' series by significant improvement in FEV1/ FVC ratios (1).

PTLC may lead to the formation of granulation tissue, the most common cause of revision surgery. Revision rates in the literature are between 19-66% (1). In our series was (45% due to granulation tissue formation) , and 18 % due to restenosis in the patients for whom PTLC only was done, that required 2nd session within 4-8 months, with delayed, but successful decanulation within 4-12 months in 91%, and failure only in one patient (9%).

According to Dursun and Gökcan 2006, granulation tissue and oedema are part of the normal wound healing process, which generally resolve by 3 postoperative months, but in our series the granulation tissue didn't resolve spontaneously till 6 ms so we did 2nd session in the 2nd &4th groups.

Regardless of the surgical techniques, there is further injury to the airway mucosa that leads to fibroblast proliferation and collagen formation, which are the key for scar formation. Modulation of the wound healing response to prevent excessive scar formation can play a

major role in increasing the success of surgical treatment and reducing the need for further surgery (11). The use of topical mitomycin-C has been shown to decrease granulation tissue formation after endoscopic laser surgery and prevention of subsequent restenosis and scar formation in the larynx (12).

Topical application of mitomycin C appears to be a useful adjunct in reducing cicatricial scarring of the airways. Human and animal studies have demonstrated the efficacy and safety of mitomycin C topically in the treatment of airway stenosis at concentrations ranging from 0.4 mg/mL to 10 mg/mL, although no reports of mitomycin C toxicity have been reported in the otolaryngology literature (4).

In this study, we have found that Mitomycin C can be beneficial as an adjuvant for endoscopic CO₂ laser cordotomy in cases with BAVFP, as 92 % of our patients in group 1 & 3 had statistically significant improvement of their airway (P value = 0.04), and only one patient that needs 2nd session (8%), and hence it decreases the need for further surgery and increases the success rate of endoscopic PTLC, with rapid decanulation (1-4 months with mean 7 weeks) in comparison to those groups for whom PTLC only was done, as 63% of them needed 2nd session and decanulation was delayed from 4-12ms postoperatively.

One of the most important disadvantages of PTLC is postoperative loss of phonation, which returns to an acceptable level over time. When quality of speech is evaluated objectively, an improvement in acoustical and aerodynamic parameters has been noted over 6 postoperative months (13).

But we informed our pts that their voice quality would worsen to some degree after the operation, in exchange for relief of dyspnea without a tracheostomy.

In our study, all values showed non-significant difference between the pre- and post surgery states in the 4 groups except the overall grade of dysphonia as judged perceptually. The overall grade of dysphonia showed a significant deterioration after surgery by a mean difference of 0.9 on a 5-points scale. The breathy character was apparent in the after-surgery ratings of the patients' voice though not reaching significant figures. Also, there was no statistical difference as regard the postoperative change of voice in patients for whom Mitomycin used versus those without usage of Mitomycin.

In spite of perceptually judged overall deterioration of the grade of dysphonia, yet the patients themselves in the 4 groups did not account on the presence of an

appreciable change of voice when seen one month after surgery or after decanulation. The increase of the perceptual grade of dysphonia may be accounted for by the appearance of a mean value for the breathy character of 1.1 in comparison to 0 mean value before surgery in the 4 groups. This grade of a "breathy" character of voice (which was statistically non-significant) is considered minimal after an operative intervention which is supposed to increase the phonatory gap.

References

1. Dursun G and Gökcan MK: Aerodynamic, acoustic and functional results of posterior transverse laser cordotomy for bilateral abductor vocal fold paralysis. *J Laryngol Otol* 2006; 120(4): 282-288
2. Saetti R, Silvestrini M, Galiotto M, Derosas F, Narne S. Contact laser surgery in treatment of vocal fold paralysis. *Acta Otorhinolaryngol Ital.* 2003; 23(1): 33-37.
3. Manuskiatti W and Fitzpatrick R E. Treatment of Keloid and hypertrophic sternotomy scars: comparison among intralesional steroids, 5-Fluorouracil, and 585-nm flash lamp-pumped pulsed-dye laser treatment. *Arch. Dermatol* 2002; 138: 1149-1155.
4. Hueman E M and Simpson C B: Airway complications from topical mitomycin C. *Otolaryngol Head Neck Surg* 2005; 133 (6): 831-835.
5. Rahbar R, Valdez T, Shapshay S. Preliminary results of intraoperative mitomycin-C in the treatment and prevention of glottic and subglottic stenosis. *J Voice* 2000; 14 (2): 282- 286.
6. Unal M: The successful management of congenital laryngeal web with endoscopic lysis and topical mitomycin C. *Int. J. pediatric Otorhinolaryngol* 2004; 68: 231-235.
7. Dennis DP, Kashima H. Carbon dioxide laser posterior cordectomy for treatment of bilateral vocal cord paralysis. *Ann Otol Rhinol Laryngol* 1989; 98(12 Pt 1): 930-934.
8. Kotby MN, El-Sady SR, Bassiouny SE, Abou Rass YA, Hegazi MA. Efficacy of the Accent Method of voice therapy. *J Voice* 1991; 5:316-320.
9. Olthoff A, Zeiss D, Laskawi R, Kruse E, Steiner W. Laser microsurgical bilateral posterior cordotomy for the treatment of bilateral vocal fold paralysis. *Ann Otol Rhinol Laryngol* 2005; 114(8): 599-604.
10. Laccourreye O, Paz Escovar MI, Gerhardt J, et al. CO₂ laser endoscopic posterior partial transverse cordotomy for bilateral paralysis of the vocal fold. *Laryngoscope* 1999; 109(3):415-418.
11. Rahbar R, Shapshay SM, Healy GB, Massachusetts B. Mitomycin effects on laryngeal and tracheal stenosis, Benefits and complications. *Ann Otol Rhino Laryngol* 2001; 110: 1-5.
12. Spector JE, Werkhaven JA, Spector NC, Huang S, Page RN, Baranowski B et al. Preservation of function and histologic appearance in injured glottis with topical Mitomycin C. *Laryngoscope* 1999; 109: 1125-1129.
13. Hans S, Vaissiere J, Crevier-Buchman L, Laccourreye O, Brasnu D. aerodynamic and acoustic parameters in CO₂ Laser posterior transverse cordotomy for bilateral vocal fold paralysis. *Acta otolaryngol* 2000; 120: 330-335.