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Research Article

Sublingual Nitroglycerine Spray Facilitates Efficient Submucosal Tunneling during Per Oral Endoscopic Myotomy—A Nonrandomized Trial

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J Digest Endosc

Abstract

Introduction In the last one decade, per oral endoscopic myotomy (POEM) has been found to be an effective minimally invasive approach for the treatment of esophageal achalasia cardia and was lately shown to be noninferior to laparoscopic Heller's myotomy in a randomized controlled trial.

Here we describe a new method of using sublingual nitroglycerine spray during submucosal tunneling to facilitate the procedure.

Materials and Methods This study includes a cohort of 50 patients who were diagnosed with achalasia cardia on high-resolution esophageal manometry. Out of the 50 patients, 27 patients were administered two metered doses of sublingual nitroglycerine spray during submucosal tunneling across the gastroesophageal junction (GEJ), and 23 patients were not administered nitroglycerine. This process was nonrandomized; patients were assigned sublingual nitroglycerine using alternating sequence enrollment number.

Results All the procedures were technically feasible and successful without any major complications. Eckhardt's scores of all patients normalized after the procedure. The mean submucosal tunneling time and mean time across GEJ were 36.8 ± 7.9, 14.2 ± 2.9 in intervention group (sublingual nitroglycerine), and 50.2 ± 8.9 and 23.0 ± 3.6 minutes in nonintervention group, respectively. Time for each procedure was significantly less ($p < 0.05$) in patients who were given sublingual nitroglycerine. Mucosal injury and bleeding during procedure were not significantly different in the two groups.

Conclusions This POEM technique with the use of sublingual nitroglycerine spray is simple and renders POEM easier and less time consuming.

Keywords
- achalasia cardia
- POEM
- sublingual nitroglycerine
- submucosal tunneling

Introduction

Natural orifice transluminal endoscopic surgery has always been an inspiring concept for endoscopists.[1] Achalasia cardia is a primary motility disorder of the esophagus characterized by absence of normal peristalsis and failure of swallow-induced relaxation of the lower esophageal sphincter (LES). Disruption of the LES to relieve outflow obstruction forms the basis of currently available treatment options. Different modalities of treatment including pharmacological agents,

DOI https://doi.org/10.1055/s-0044-1782496.
ISSN 0976-5042.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

pneumatic balloon dilatation (PBD), and laparoscopic Heller's myotomy (LHM) have been developed over time for treatment of achalasia cardia. The current form of per oral endoscopic myotomy (POEM) was developed by Inoue in 2008 as an endoscopic treatment for achalasia cardia that is an effective and less invasive measure.[2,3]

POEM is technically demanding and time consuming. Creation of a submucosal tunnel and extending distally to about 2 to 4 cm into gastric side is an integral step for successful procedure. This requires accurate delineation of submucosal tissue and precise identification of mucosal, submucosal, and muscular layers. In addition, because of the nature of the pathology of achalasia, the working space near gastroesophageal junction (GEJ) is often limited because of close approximation of muscle layer and contralateral mucosa. Repeated injection of saline mixed with indigo carmine, adequate lateral dissection in tunneling, and stretching of submucosal fibers by cap have been described to ease tunneling across GEJ.

Nitrates have been shown to reduce LES pressure on high-resolution esophageal manometry.[4] Hence, nitrates can be used to reduce LES pressure, during submucosal tunneling to mitigate the narrowing caused by tight LES. Hereby we are describing a new method of nitroglycerine sublingual spray during submucosal tunneling to facilitate the procedure.

Materials and Methods

This was a prospective nonrandomized study that includes the cohort of 50 patients who were diagnosed with achalasia cardia on high-resolution manometry from January 2021 to July 2022. Ethical approval was taken from institutional review committee. Patients were assigned in to two groups: intervention group (sublingual nitroglycerine spray) and nonintervention group alternatively based on enrollment number for POEM. Eight patients with type 3 achalasia cardia, five patients with sigmoid esophagus, three patients with prior balloon dilatation patients, one patient with post-Heller ineffective esophageal motility, one patient with coronary artery disease with history of coronary artery bypass graft, and one with esophageal diverticulum were excluded.

Symptoms were noted and Eckhardt's score was calculated before and 3 months after the procedure. Standard diagnostic upper gastrointestinal endoscopy and high-resolution manometry were performed in all patients before the procedure. Patients were diagnosed and classified according to Chicago 4.0 classification.

Primary outcomes were total submucosal tunneling time and tunneling time across GEJ. Secondary outcomes were development of mucosal injury and bleeding during submucosal tunneling.

Statistical analysis was done by SPSS version 24, and comparison of data was done by independent *t*-test, chi-squared test, Fisher's exact test, and Mann–Whitney U test. For all statistical analysis, *p*-value less than 0.05 was considered significant.

Procedure

All patients were taken under general anesthesia for the procedure, which was performed by a single endoscopist. Intravenous antibiotics were administered before the procedure. High-definition gastroscopes (GIF-H190; Olympus, Tokyo, Japan or EG 530 WR Fujinon, Tokyo, Japan) with an integrated water jet channel fitted with a transparent distal attachment (DH-28GR, Fujifilm / D-201-11804, Olympus) were used. Carbon dioxide insufflation was done throughout the procedure. First, a submucosal bleb was created in the midesophagus 8 to 12 cm above GEJ using saline and 0.25% indigo carmine solution on posterior esophageal wall in all patients. A 2-cm longitudinal mucosal incision was created with a triangular tip (TT) knife (KD 640L Olympus) in retrograde direction using Endocut at 50W on effect 2 (ERBE, Tubingen, Germany). The endoscope was then negotiated into the submucosal space and the TT knife was used to dissect the submucosal fibers using forced coagulation mode at 50W on effect 2. Repeated jet injection of saline mixed with indigo carmine was done to expand the submucosal space and intervening large vessels were coagulated using coagulation forceps (COAGRASPER, FD-411QR; Olympus) in soft coagulation mode at 60W on effect 4.

Patients in intervention group were administered two 400 µg metered doses of sublingual nitroglycerine spray after initial priming of five sprays as the tunnel became narrow near the GEJ. The endoscope was carefully oriented so as to ensure the mucosal layer was not injured during dissection as the submucosal tunnel was extended, passing the LES and 2 cm into the proximal stomach. Subsequently myotomy of the inner circular muscle bundles was performed starting 2 cm distal to the mucosal entry point. The sharp tip of the TT knife was used to catch circular muscle bundles, lift them toward the tunnel, followed by cutting with coagulation current at 50W on effect 2. For final closure of the mucosal entry site, hemostatic clips (EZ-CLIP, HX-610-090L; DF Olympus) were applied.

At the end of the procedure, scope was inserted into the natural esophageal lumen to confirm its smooth passage through the GEJ. Subjective parameters like spontaneous expansion of submucosal space, ease of tunneling, and time taken to cross GEJ were taken into account after nitroglycerine spray. Recording of the procedure was done through endoclinic 2 software.

Total submucosal tunneling time and time across GEJ (time to make submucosal tunnel across GEJ) were calculated through endoclinic software. Tunnel length was calculated from distal margin of mucosal incision to end of tunnel.

Results

A total of 50 patients of achalasia cardia were included in the study, 27 patients in intervention group, and 23 in nonintervention group. There were no significant differences in age and gender across the two groups (►**Table 1**). Of the 27 patients in intervention group, 18 patients were type 2 and 9 were type 1 achalasia cardia. Out of 23 patients in

Table 1 Demographic, manometry, Eckhardt's score, intraoperative findings, and complications of patients who underwent POEM

		Intervention group	Nonintervention group	*p*-Value
Gender	Male	15	13	0.945
	Female	12	10	
Age (mean) in years		36.4 ± 9.4	33.3 ± 7.0	0.191
Type of achalasia				
Type 1		9	7	
Type 2		18	16	0.826
Mean IRP (mm Hg)		35.5 ± 5.3	34.9 ± 5.4	0.687
Mean tunnel length (cm)		11.0 ± 0.9	11.2 ± 0.9	0.490
Mean submucosal tunnelling time (min)		36.8 ± 7.9	50.2 ± 8.9	< 0.05
Mean time across GE junction (min)		14.2 ± 2.9	23.0 ± 3.6	< 0.05
Complications	Bleeding	2	6	0.071
	Pleural effusion	1	1	0.904
	Mucosal injury	2	3	0.509
Eckhardt's score	Preprocedure	8.96 ± 0.85	8.95 ± 0.76	0.977
	Postprocedure	1.4 ± 0.7	1.7 ± 0.6	0.142

Abbreviations: GE, gastroesophageal; IRP, integrated relaxation pressure; POEM, per oral endoscopic myotomy.

nonintervention group, 16 patients had type 2 and 7 had type 1 achalasia cardia ($p = 0.82$). Mean integrated relaxation pressure in intervention group was 35.5 ± 5.3 and 34.9 ± 5.4 mm Hg in nonintervention group ($p = 0.68$). All these parameters were not significantly different among both groups. Demographic and procedural details are listed in ►**Table 1**.

The mean Eckhardt's scores before and after procedure were not significantly different among both the groups. The mean submucosal tunneling time was significantly less ($p < 0.05$) in intervention group. Similarly mean time taken across GEJ was significantly less with sublingual nitroglycerin ($p < 0.05$; ►**Table 1**).

Spontaneous expansion of tunnels across GEJ were noted after sublingual nitroglycerin spray (►**Fig. 1A, B**).

All the procedures were technically successful without any long-term complications. There was minimal mucosal injury (type 1) in three patients (intervention group 1 and nonintervention 2) that were left alone without any consequence.

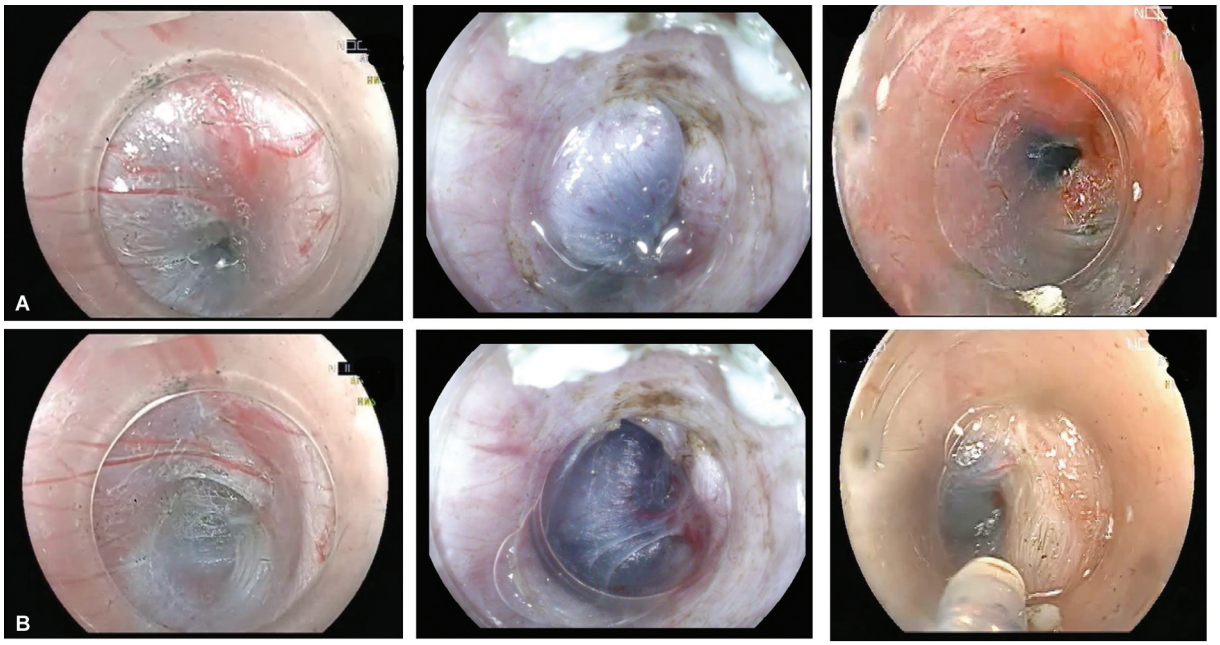

Fig. 1 (A) Narrowed submucosal tunnel at gastroesophageal (GE) junction before sublingual nitroglycerine spray. (B) Expansion of submucosal tunnel at GE junction after sublingual nitroglycerine.

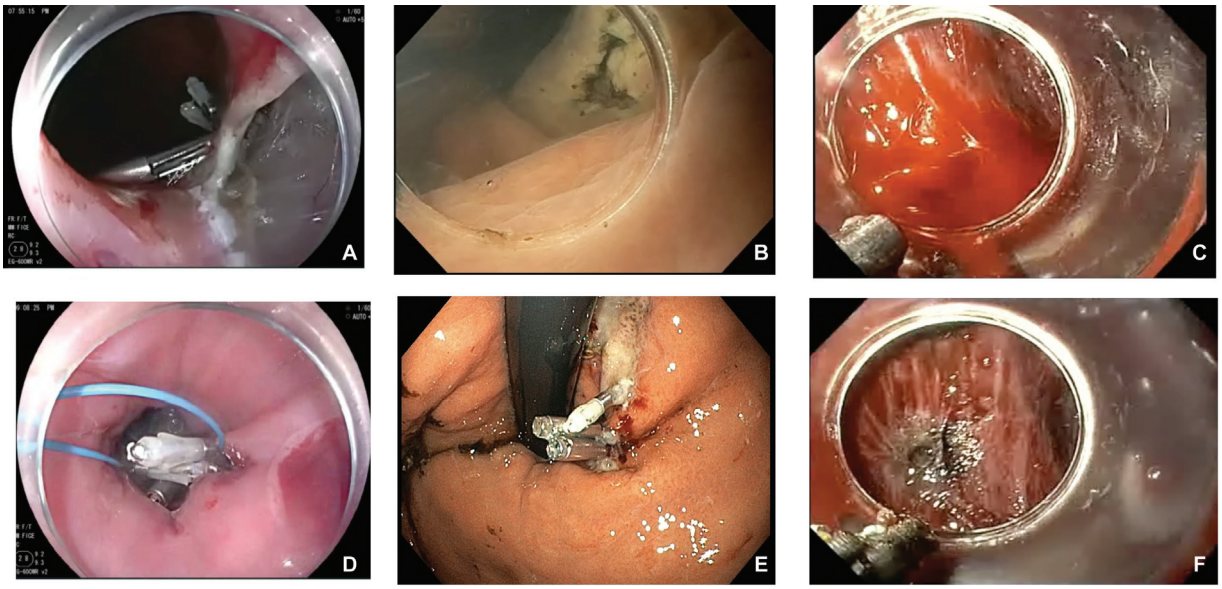

Fig. 2 Complications during per oral endoscopic myotomy. (**A**) Esophageal mucosal injury (type 2). (**B**) Gastric mucosal injury (type 2). (**C**) Bleeding during submucosal tunneling. (**D**) Closure of deep esophageal mucosal injury by loop and clip method. (**E**) Closure of deep gastric mucosal injury by hemostatic clips. (**F**) Control of bleeding during submucosal tunneling.

Two patients developed type 2 mucosal injury (►**Fig. 2A, B**), one in each intervention group 1 (gastric) and nonintervention group II (esophageal).

Type 2 esophageal mucosal injury in noninterventional arm was noticed after myotomy. Initial closure was attempted with hemostatic clips but due to scalded surrounding mucosa defect size increased (2A). Then subsequently closure was achieved with loop and clips method. Endoloop (3 cm) was fixed at margins of defect by multiple hemostatic clips and loop was tightened by polyloop ligating device (HX-400U-30 Olympus) and then released (►**Fig. 2D**).

Type 2 gastric mucosal injury in noninterventional group (►**Fig. 2B**) was managed by clipping (F**ig. 2E**).

Bleeding was noticed in eight patients (intervention group 2 and nonintervention group 6) during the procedure (►**Fig. 2C**), which was controlled easily (►**Fig. 2F**).

Two patients developed minimal pleural effusion, one in both group, which resolved with conservative management. There was no significant difference in complications among the two groups. None of the patients had hypotension during procedure or any event of delayed bleeding.

Esophagogram was obtained in all patients on postoperative day 1 and no leaks were identified in any patient. All patients were able to commence liquid diet on postoperative day 1 and solid meals 1 week later. Dysphagia resolved in all patients.

Discussion

Achalasia cardia is a progressive irreversible primary esophageal motility disorder. Most of the cases are idiopathic; however, cases secondary to Chagas disease and herpes virus are also reported.[5,6] Pharmacological treatment with agents like calcium channel blockers and botulinum toxin injection has been used for the treatment but they have low long-term success rates and few poorly tolerated side effects.[6,7] Surgical treatment of choice is LHM with partial fundoplication. Endoscopic treatment with PBD is less durable than LHM and these patients often require reintervention.[8] Introduction of POEM by Dr. Inoue in 2008 is a new technique for the treatment of achalasia cardia. The successful outcome of achalasia by POEM procedure has been measured primarily by two parameters, pressure of the LES, and Eckhardt's score.[9] A systematic review done in 2015 showed success rate of 93%, with very low incidence of any major complications.[10] Clinical success rate of POEM depends on adequacy of myotomy toward gastric end of the submucosal tunnel.[11] POEM appears equally effective in controlling symptoms when compared to LHM. POEM has advantages of shorter duration of anesthesia, decreased procedure time, and length of hospital stay, but has higher rate of gastroesophageal reflux.[12]

Nitrates have been shown to reduce LES pressure on high-resolution esophageal manometry.[4] In pilot study, Amyl Nitrite was used in two patients of achalasia cardia to ease tunneling across GEJ by Majidah et al,[13] and they demonstrated that the diameter of the LES increased by more than 3 mm in patients with idiopathic achalasia in response to amyl nitrite. Similarly, in our study spontaneous expansion of LES was noticed after the use of sublingual nitroglycerine (►**Fig. 1A, B**). However, we have not measured diameter of LES after expansion. Our study also showed that use of sublingual nitroglycerine spray during tunneling at GEJ significantly decreased total submucosal tunneling time and time across GEJ, without any significant difference in complication rates (►**Table 1**).

All procedures were successful and without any significant difference in clinical improvement of symptoms and Eckhardt's score. In our experience, tunneling across GEJ was difficult during learning curve, which was rendered easier

and less time taking with use of sublingual nitroglycerine. No major complications occurred in our study and all minor were managed successfully. Limitations of study were small sample size, exclusion of type 3 achalasia patients, and lack of randomization.

Conclusions

This modified POEM technique with the use of sublingual nitroglycerine spray is simple and renders POEM easier. Relaxation of GEJ by sublingual nitroglycerine spray expedites submucosal tunneling across GEJ. Novice can adopt this modified POEM technique in initial cases during learning curve. Further randomized and multicentric studies are needed to confirm our finding, which may affect change in clinical practice.

Financial Disclosure
None.

Conflict of Interest
None declared.

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