Esophageal stricture prevention post endoscopic sub-mucosal dissection

Running title- Prophylaxis for esophageal stricture

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CONFLICT OF INTEREST

None of the authors has any conflicts of interest or financial relationship with the company that produces or distributes the device described in the review article.

SOURCE OF FUNDS

No grant or funding source was involved in writing up the review article
ABSTRACT

Advancement in diagnostic modalities and improvement in surveillance programs for Barrett esophagus has resulted in increase in incidence of superficial esophageal cancers (SEC). SEC, due to their limited metastatic potential are amenable to non-invasive treatment modalities. Endoscopic ultrasound (EUS), endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD) are few new modalities that gastroenterologist have used in last decade to diagnose and treat SEC. Esophageal stricture (ES) is a very common complication and a major cause of morbidity post ESD. In past few years there here has been a tremendous effort to reduce the incidence of ES among patients undergoing ESD. Steroids have shown most consistent results over time with minimum complications. Although, the preferred mode of delivery still remains debatable with both systemic and local therapy having its own pros and cons for specific subgroup of patients. Newer modalities like esophageal stents, autologous cell sheet transplantation, polyglycolic acid and tranilast have shown promising results but the depth of experience is still limited. We have summarized case reports, prospective single center studies and randomized controlled trials describing the various methods aiming to reduce the incidence of ES post ESD. Indications, techniques, outcomes, limitations and complications reported are discussed.

KEY WORDS

Esophageal cancer; Esophageal stricture; Endoscopic sub-mucosal dissection

INTRODUCTION

13,570 men and 3,410 women in the United States are expected to have a new diagnosis of esophageal cancer (EC) in the current year. Although, EC accounts for only 1% of newly diagnosed cancers in the United States, it is much more prevalent in Iran, northern China, India and southern Africa. Based on National Cancer Institute’s Surveillance, Epidemiology and End
Results (SEER) database, the 5-year survival rate for localized, regional and distant EC is 40%, 21% and 4% respectively.\textsuperscript{2}

With advancement in diagnostic technology and active surveillance programs for patients with Barrett esophagus, more cases of EC are being diagnosed in their early stage. Superficial esophageal cancers (SEC) is a term used to represent esophageal cancers limited to mucosa with minimum metastatic potential and thus amenable to non-surgical treatment options. Endoscopic modality has evolved as the preferred diagnostic and therapeutic treatment choice for these SEC. Endoscopic ultrasound (EUS) offers an accuracy of 85% in diagnosing SEC.\textsuperscript{3}

Endoscopic mucosal resection (EMR) is an alternative modality to stage SEC. In last decade, there has been a gradual shift of focus from EMR to endoscopic sub-mucosal dissection (ESD) for SEC. ESD allows en bloc resection of the lesion irrespective of it’s size and is associated with lower recurrence rate as compared to EMR which essentially involves piecemeal resection of lesions more than 2 cm in size.\textsuperscript{4}

Esophageal stricture (ES) has been reported to be the most common complication post ESD.\textsuperscript{5} Histologic depth and circumferential extension of the EC are independent risk factors for post operative ES.\textsuperscript{6} There has been a constant effort to minimize the rate of ES post ESD. In this review article, we have summarized case reports, prospective single center studies and randomized controlled trials describing the various methods aiming to reduce the ES post ESD. Indications, techniques, outcomes, limitations and complications reported are discussed.

**MAIN TEXT**

**Materials and methods:**

An extensive English language literature search was done till May, 2015; using Pubmed, Medline, Google to identify the peer reviewed original and review articles using key words—esophageal cancer, endoscopic sub-mucosal dissection and esophageal stricture prophylaxis. Human only articles were selected. The references of pertinent studies were manually searched to identify additional relevant studies. The indication, procedural details, technical success rates,
clinical outcomes, complications and limitations were considered as part of inclusion criteria. Search results yielded case report, prospective single center studies and a few randomized controlled trials.

Results:

12 original articles were considered appropriate to be included in the review article. Ten studies were from Japan, which included two prospective studies, which used a historical population as the control group,\textsuperscript{7,8} seven single center prospective studies,\textsuperscript{9-15} and one retrospective study.\textsuperscript{16} One prospective randomized controlled study from China\textsuperscript{17} and one case report from Korea\textsuperscript{18} were also included in the review. All studies have been summarized in Table 1.

Discussion:

Indications:
Patients with superficial or early esophageal cancer who were considered appropriate for undergoing endoscopic sub-mucosal dissection were included by the authors of all the studies. All selected patients had an expected post ESD mucosal defect of more than half of the esophageal circumference.\textsuperscript{7-18} There is a strong correlation between the extent of mucosal defect and the incidence of esophageal stricture post ESD. There was a wide variation in the extent of mucosal defect among the subjects from each study. The procedure details for the endoscopic sub-mucosal dissection and the resultant size of mucosal defect for subjects across all studies has been summarized in table 2.

Subjects with evidence of lymph node metastases, active synchronous cancer, multiple esophageal cancers, prior radiation therapy/ adjuvant chemotherapy or surgery for esophageal cancer, coexisting severe comorbidities like uncontrolled diabetes mellitus, liver cirrhosis and active corticosteroid or anticoagulant use were excluded from study group by the respective authors.\textsuperscript{7-18}
Type of intervention with technical aspect:
Authors have reported a wide variety of modalities- local steroid injection, topical steroid gel application, oral steroids, preemptive scheduled EBD, combination of EBD and Tranilast, transplantation of autologous cell sheets, Poly-glycolic acid (PGA) sheets, and stents to prevent ES formation post ESD.

Steroids- oral, injection or gel application-

Hashimoto et al. in his prospective study described the prophylactic use of triamcinolone acetonide (TA) injection (10 mg/ml) in an effort to prevent ES post ESD. The author used a 25 G needle to inject steroid in aliquots of 0.2 ml, 1 cm apart in a semi-circular fashion into the area of mucosal defect. Similarly, Hanoaka et al. used 25 G needle to inject lower concentration TA (5 mg/ml) in ulcer bed submucosa in 0.5- 1.0 ml increments. The author did used a different pattern, starting from the ulcer margin and then followed it by linear injections from distal to proximal side of the ulcer margin. Special precautions were taken to avoid intramuscular steroid injection. Mori et al. in his randomized prospective study compared the steroid injection therapy against steroid gel application. In the steroid injection arm, the author administered 0.2 ml TA injections (10mg/ml) into the ulcer floor at 8 mm intervals which was followed by 5 minute (min) session of endoscopic balloon dilation (EBD). In the other arm, TA gel (10 ml mixed with 7.5 ml of endolubri jelly) was applied from distal to proximal end of ulcer with spraying tube via endoscope, which was followed by similar 5 min session of EBD. In another study by Takahashi et al., 0.5 ml aliquots of TA (10 mg/ml) were injected at the ulcer base using 25 G needle. TA was administered, starting from distal edge repeating evenly at points 10 mm apart till the proximal edge is received. In the case report by Lee et al., which involved near circumferential mucosal defect, author administered a higher concentration of TA (20 mg/ml) in aliquots of 0.5 ml, which were distributed evenly across ulcer at 8 sites.

Overall, all authors used TA as the preferred steroid agent both for injection and gel application. Authors did used different concentrations of TA and had there own specific pattern of administering it into the ulcer base, essentially with the aim of achieving uniform distribution.
across the mucosal defect. Some authors reported variation in the total steroid dose administered based on the ulcer bed size,\(^7,^9\) whereas other reported using a fixed amount irrespective of the size.\(^8\) Most authors also placed an extra effort to avoid injury to muscular layer at time of administration, as that might hamper the healing process. Oral steroid was tried in two studies and was compared against the subjects undergoing scheduled preemptive EBD to prevent ES post ESD.\(^{14,16}\) In both studies, prednisolone was the drug of choice and was given to subjects on day 3, post ESD. The regimen started with a dose of 30 mg daily and was tapered gradually every week for a total duration of 8 weeks. The subjects ended up getting approximately 1000 mg of prednisolone over the 8-week duration. Oral steroids have a potential role in ES prevention post ESD. More information is needed to choose among the type, dose, route and duration of steroid, as the preferred modality for ES prophylaxis.

*Endoscopic balloon dilation (EBD)-*

Endoscopic dilation with either a bougie or a dilator is the preferred treatment for the esophageal stricture. Few authors have extrapolated this concept to use scheduled EBD to prevent ES post ESD.\(^{14-16}\) In all three studies, EBD was done using a CRE balloon dilator, twice a week, for 4\(^{15}\) to 8 weeks,\(^{14,16}\) starting within few days of ESD. Uno et al. described using 2 to 3 progressively larger diameter dilators per session, with the aim of not going beyond 3 mm dilation at a time.\(^{15}\) Yamaguchi et al. used a dilator, designed to deliver three different pressure controlled diameter at three distinct points.\(^{16}\) Clinical clues like mucosal tear or bleeding were also used to individualize the EBD session treatment for each subject. All studies have compared the efficacy of a second agent to the group getting EBD alone.

*Transplantation of autologous cell sheets-*

Ohki et al. reported their unique experience of using patients own cells to heal the mucosal defect post ESD, thus preventing esophageal stricture.\(^{11}\) The author cultured the epithelial cells
from the patient’s own buccal mucosa. These autologous oral mucosal epithelial sheets on a support membrane were transferred to the esophageal mucosal defect using the endoscopic forceps. Each sheet was 23.4 mm in diameter and the number of sheets used to cover the ulcer base varied from 2- 8 depending on size of mucosal defect.

*Poly-glycolic acid sheets*- 

PGA is an absorbable suture stiffener. It has potential to prevent scarring and contraction post surgical intervention. Mucosal defect covered with fibrin glue and PGA sheet known as MCFP technique has been applied in many fields of surgery and appears to be safe.19-21 Lizuka et al. described their experience with PGA sheets in preventing ES post ESD. Essentially the technique involves covering of ulcer base with PGA sheets with assistance of fibrinogen and thrombin solution spray.12 Sakaguchi et al. also used the PGA sheets and fibrin glue in an effort to prevent ES post ESD.13 The author used a modified version of clip and pull method to deploy the PGA sheets. The size and number of PGA sheets used to cover the mucosal defect varied across the two studies.

*Tranilast*- 

Tranilast (N-[3,4-dimethoxycinnamoyl]-anthranilic acid) is an anti-allergic drug with anti-tumor action and new evolving role in managing fibrotic pathologies.22 Uno et al. did a pilot study to determine the efficacy of tranilast in preventing ES post ESD.15 Because of lack of data on the effective dose and route of administration, the author used a empiric oral daily dose of 300 mg, divided in three doses to be taken with meals for all the subjects in addition to EBD session.

*Stents*- 

Wen et al. reported the first randomized trial comparing the efficacy of esophageal stent in preventing ES post ESD.17 The author used a metal stent composed of high elastic stainless steel
covered with high intensity medical silicone membrane. Stent was placed via guide wire and endoscope and was removed after a duration of 8 weeks. The length (25 to 180 mm) and diameter (15 to 18 mm) of stent was selected based on the size of mucosal defect.

The technical details of all the above described procedures have been summarized in table 1.

**Timing and frequency of intervention:**
There is no consensus on the timing and the duration of the prophylactic intervention. Speaking physiologically, earlier the intervention, more efficacious it should be in preventing the ES by molding the healing esophageal ulcer at appropriate time. The duration of intervention on the other hand should be guided by the time required for epithelialization of the ulcer bed.

Majority of the authors planned their intervention to prevent ES on the day of ESD. Hashimoto et al. administered the TA injection on day 3rd, 7th and 10th post ESD. Mori et al. in his randomized study comparing TA injection to gel application also planned the intervention on day 5th, 8th, 12th and 15th post ESD. Scheduled preemptive EBD session were planned to start on day 3, post ESD, and were continued at a frequency of twice a week for next 8 weeks. Oral steroid were also started from day 3, post ESD and were continued for next 8 weeks on a tapering regimen. Tranilast was started within first few days of ESD and was continued on a daily basis for next 8 weeks.

More studies are required to form a consensus and help guide future interventions.

**Monitoring and Follow up:**
All patients were followed clinically, post intervention to evaluate for any symptoms of dysphagia. All subjects were scheduled to undergo either an upper endoscopy for direct visualization of the esophageal mucosa or indirect tests like barium contrast esophagogram to evaluate the contour and anatomy of the esophagus. The timing of the follow up or the diagnostic test was pre-decided as per the individual study design unless patient clinically started to show any signs of dysphagia which resulted in earlier diagnostic intervention. Also,
different authors have used different parameters to define the esophageal stricture for their respective studies. Table 3 provides a summary of follow up intervals, diagnostic tests and parameters for defining ES for each study.

**Outcome:**
The ideal way to measure the efficacy of the above mentioned interventions is to compare the incidence of esophageal stricture post ESD. Another indirect measure is to compare the number of required sessions of endoscopic balloon dilation for each group of subjects.

**Esophageal stricture**-

Hashimoto et al. in their study showed a ES rate of 19% (4/21) in the study arm receiving TA injection as compared to 75% (15/20) in the control group. A similar trend was shown by Hanoaka et al. for the ES rate post TA injection therapy (10% (3/30) in the study arm versus 66% (19/29) in the control group). The two studies did differ in the timing and frequency of TA injection post ESD as described above. Although both of these studies showed a significant reduction in ES incidence post TA injection but the control group that the author had used to compare is a historical population group and therefore the inference from these results could not be generalized. The randomized controlled trial by Takahashi et al. comparing TA injection with no therapy helps us to answer this question more accurately. The ES rate for the TA study arm was 62.5% (10/16) which is still pretty high but lower than that of control group- 87.5% (14/16). So, we can safely conclude that TA injection therapy does prevents stricture prevention post ESD but not in all. Lee et al. in their case report reported 100% success in preventing ES post ESD with prophylactic TA injection therapy. This case also had near whole circumferential esophageal mucosal defect, thus a higher potential for ES. The success with TA therapy in preventing ES in this case is strongly suggestive of its strong efficacy. The question
that still remains unanswered is why the results are not uniform—is it because of procedure
technique or subject’s individual characteristics.

Mori et al. in their randomized controlled study, did head to head comparison between steroid
injection therapy + EBD versus steroid gel application + EBD. No significant difference was
observed in the ES rate across the two arms. The author did reported that the requirement of
technical expertise and the total procedure time for the gel application study arm (6.87 minutes)
was lower (although not statistically significant) than that of injection group (total procedure
time- 7.33 minutes). Also, the gel application provides an alternative way of stricture
prevention among subjects on oral anticoagulation or antiplatelet medications, as it obviates
the need of needle injection thus lowering the bleeding risk.

Two studies illustrated the efficacy of oral steroids in preventing ES post ESD. In a small
prospective study by Isomoto et al. the study arm (4 subjects) getting oral prednisolone
developed stricture in only 50% of the population as compared to 100% among the subjects (all
3) undergoing scheduled EBD post ESD. A similar trend was shown in a larger prospective
study be Yamaguchi et al.. Out of 19 subjects who received oral prednisolone, only one
developed ES (5.3%) post ESD, as compared to the other arm, which received preemptive EBD
(31.8%, 7 out of 21). The study results had the same trend for patients with either
semicircular (more than three quarters of circumference) or circular (full circumference)
mucosal defect post ESD. Oral steroid regimen is an interesting alternative to the injection/
gel administration. It does not require any invasive test (EGD), thus decreasing the treatment
cost and also provides a uniform distribution of steroid over larger esophageal mucosal defects.

Oral steroids also obviate the concern for procedure related complications as seen with
injection treatment, but do come with the concern for possible systemic side effects. Based on
our limited experience till now, none of the subjects in either of the studies had any adverse
effect attributable to the steroid therapy.

The study by Ohki et al. demonstrated that autologous cell sheet transplantation was
successfully in preventing ES formation in 8 out of 9 subjects. The only failure {11.1% (1/9)}
was the subject with full circumferential mucosal defect. Although the study was small but
results were promising. There are no studies comparing autologous cell sheet transplantation with the steroid therapy/ EBD in preventing ES post ESD. Results from the study by Lizuka et al. were suggestive of success of MCFP in preventing ES post ESD.\textsuperscript{12} 6 weeks post ESD, only 1 subject out of 13 (7.7%) developed ES. 2 more subjects reported to have dysphagia post ESD but did not had ES on evaluation. Another study by Sakaguchi et al.\textsuperscript{13} also used PGA and fibrin glue as means of preventing ES post ESD but the results were not consistent with that of Lizuka et al.. 3 out of 8 subjects (37.5%) developed ES. Mean time to stricture occurrence was $28 \pm 7$ days. More experience with PGA is needed to conclude where we stand with their role in ES prevention post ESD.

Unko et al. in his pilot randomized study illustrated the efficacy of tranilast in preventing ES post ESD.\textsuperscript{15} Both study arms underwent scheduled EBD sessions. Addition of tranilast decreased the incidence of ES post ESD almost by half (33.8% as compared to 68.8% in the control arm).\textsuperscript{15} Wen et al. did a randomized study comparing the role of metal stents in preventing ES post ESD.\textsuperscript{17} The intervention arm had a ES rate of 18.2% (2/11) as compared to the control arm of 72.7% (8/11). The results are strongly suggestive of efficacy of metal stents in preventing ES post ESD.

\textit{Endoscopic balloon dilation-}

Steroids have anti-inflammatory effect and modulate wound healing by decreasing collagen production.\textsuperscript{23} Steroids are supposed not only to decrease the ES rate but may also modify the response to dilation therapy for strictures. The mean number of EBD sessions required among subjects who have received prophylactic TA injection post ESD was 1.7 (range- 0 to 15), much lower when compared to the historical control group (mean- 6.6 and range from 0 to 20) in the study by Hashimoto et al.\textsuperscript{7} A similar trend was seen in the study by Hanoaka et al. across the TA injection study (number of EBD sessions- range of 0 to 2) and the historical control group (number of EBD sessions- range of 0 to 15).\textsuperscript{8} In the randomized study by Takahashi et al. the mean number of EBD sessions (6.1 ± 6.2) and the mean duration of dilation therapy (3.5 ± 4.0 months) for the study arm (TA injection) were much lower than that of the control arm (mean
number of EBD sessions- 12.5 ± 10.0; mean duration of dilation therapy- 6.1 ± 5.0 months).\textsuperscript{10} Isomoto et al. and Yamaguchi et al. showed a statistically significant (p value < 0.05 and < 0.0001 respectively) decrease in mean number of EBD sessions required with the oral prednisolone as compared to the EBD control group.\textsuperscript{14,16} The trend was consistent across all subjects irrespective of the size of mucosal defect.\textsuperscript{16} All these results are consistent with the fact that steroids do modulate the wound healing and thus can alter the response of ES to EBD therapy.

In the head to head randomized trial between TA injection + EBD and TA gel + EBD treatment, the mean number of EBD sessions post day 20 was 4.27 for the injection group which was significantly higher (p value < 0.05) than 1.6 for the gel group.\textsuperscript{3} Clearly, the balance tilts in favor of steroid gel application despite the absence of significant difference between the ES rate across the two study arms.

In the study by Ohki et al. only one subject developed ES post autologous cell sheet transplantation.\textsuperscript{11} The subject had full circumferential mucosal defect and required 21 EBD sessions to relieve stenosis.

In the study by Lizuka et al. only one patient developed ES post MCFP and required 5 EBD sessions to relieve stenosis.\textsuperscript{12} In another study involving the use of PGA to prevent ES post ESD, the mean number of EBD sessions required were 0.8 ± 1.2.

Uno et al. experience with tranilast showed promising results in a long follow up study. The median number of additional EBD sessions required by the study arm by the end of 48 weeks was zero as compared to 4 for the control arm (p value < 0.0138).\textsuperscript{15}

In the randomized controlled study by Wen et al. comparing the efficacy of metallic esophageal stent in preventing ES post ESD, the mean number of bougie dilations required were 0.45 (range- 0 to 3) for the stent arm as compared to 3.9 (range- 0 to 17) for the arm without the stent.\textsuperscript{17}

The experience with autologous cell sheet transplants, poly-glycolic acid sheets, tranilast and esophageal stents is still in baby steps and it is hard to draw any conclusions. The results have shown promise for the future and more studies are awaited to get more decisive answers.
**Adverse events:**

Any intervention comes with its possible complication. Although most of the interventions discussed here were relatively benign, few complications have been reported. Overall, bleeding and perforation were two common complications reported by the authors.

**Bleeding and perforation**

In the study by Hanoaka et al., among the study arm, which received the TA injection, 2 subjects (7%) developed complications. One patient presented with black tarry stools, 8 days post ESD which was attributed to esophageal source and required endoscopic hemostasis. Another patient developed deep sub-mucosal tear without perforation, during stricture evaluation 2 months post ESD. The subject was successfully managed conservatively. In the study by Mori et al. the study arm getting TA injection reported esophageal bleeding within first 2 weeks post ESD, which required endoscopic hemostasis as compared to 0% complication rate in the steroid gel intervention arm. Both of these subjects were on oral anti-coagulation. Steroid gel application offers an alternative to injection therapy especially among patients at higher bleeding risk like those on oral anti-coagulants and anti-platelets. Takahashi et al. in his study reported esophageal perforation for one subject in each of the study arms. The perforation was attributed to the EBD session and not to the TA injection therapy. The intervention arm was reported to have one perforation for 97 EBD sessions in total, whereas the control arm had one perforation for 200 EBD sessions. Uno et al. also reported one case of perforation secondary to additional EBD session (6.25%), successfully managed in a conservative manner. Another way to represent it is that one out of 98 additional EBD sessions resulted in perforation (1.02%). In contrast to the above two studies, where the esophageal perforation was attributed to the therapeutic additional EBD session for the already formed ES, Yamaguchi et al. reported one case of pneumo-mediastinum secondary to the scheduled preemptive EBD (1 out of 22 subjects, 4.5%). The subject improved with conservative management. In the study by Lizuka et al. one subject (out of 15) developed esophageal bleeding post ESD which was managed conservatively and no blood transfusion was required.
Miscellaneous-

Ohki et al. in their study reported that 4 out of 9 subjects developed high-grade fever, but it self resolved without any intervention.\textsuperscript{11} Wen et al. reported that in the intervention arm (esophageal metal stent), one subject developed chest pain which self resolved without any intervention and another subject developed transient bleed at the time of stent removal which also self resolved requiring no intervention.\textsuperscript{17}

The ESD and intervention itself are not the only underlying factors predisposing to the complications, but patient factors and EBD sessions also play an important role. Nonetheless, the frequency of reported complications in each of the respective studies is low and most of them were managed conservatively without any intervention.

CONCLUSION

Esophageal stricture is the most common complication post ESD and is the most common cause of morbidity among patients with esophageal cancer status post ESD. There is a paradigm shift in the management of ES in last few years, with the focus being shifted from the treatment to the prophylaxis. Both local and systemic prophylactic steroid use for prevention of ES post ESD has shown the most consistent and promising results with minimum complications. Experience with autologous cell sheet transplants, poly-glycolic acid sheets, tranilast and esophageal metal stents in preventing ES formation post ESD is promising but still relatively new. Further experience with current treatment options, development of novel strategies and refinement of endoscopic technique in delivering the targeted intervention will help expand the field of preventive care in future. Preliminary reports appear promising but larger multi-centric prospective studies with longer follow up and head to head comparison trials with current treatment options are needed in future to develop consensus guidelines.’

ACKNOWLEDGEMENT
Jain D contributed to literature search, data collection, compilation of results and writing up the manuscript. Singhal S contributed to literature search and editing of the manuscript.

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Table legends:
1. Table 1- Descriptive summary of all the studies- intervention, results and complications
2. Table 2- Procedure details of endoscopic sub-mucosal dissection and resultant mucosal defect size across subjects for each study
3. Table 3- Follow up intervals, diagnostic tests and stricture definition used across different studies