Effects of medical adhesives in prevention of complications after endoscopic submucosal dissection

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Abstract

AIM: To evaluate the use of medical adhesive spray in endoscopic submucosal dissection (ESD).

METHODS: Patients who underwent ESD between January 2009 and June 2012 (n = 173) were enrolled in the prospective randomized study. Two patients undergoing surgery due to severe intraoperative hemorrhage and failed hemostasis were excluded, and the remaining 171 patients were randomly divided into two groups: group A (medical adhesive group, n = 89) and group B (control group, n = 82). In group A, a medical adhesive spray was evenly applied after routine electrocoagulation and hemostasis using hemostatic clip after ESD. Patients in group B only treated with routine wound management. Intraoperative and postoperative data were collected and compared.

RESULTS: In all 171 patients, ESD was successfully completed. There was no significant difference in the average treatment time between groups A and B (59.4 min vs 55.0 min, respectively). The average length of hospital stay was significantly different between group A and B (8.89 d vs 9.90 d, respectively). The incidence of intraoperative perforation was 10.1% in group A and 9.8% in group B, and was not significantly different between the two groups. In all cases, perforations were successfully managed endoscopically and with conservative treatment. The incidence of postoperative delayed bleeding in group A was significantly lower than that in group B (0.00% vs 4.88%, respectively).

CONCLUSION: ESD is an effective minimally invasive treatment for gastrointestinal precancerous lesions or early-stage gastrointestinal cancer. Medical adhesive spray is effective in preventing delayed bleeding after ESD, and can thus reduce the average length of hospital stay.

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Key words: Endoscopic submucosal dissection; Medical adhesive; Early-stage gastrointestinal cancer; Postoperative delayed bleeding; Intraoperative hemorrhage

Core tip: This is the first report to use medical adhesive after endoscopic submucosal dissection (ESD), and results were exciting. Application of medical adhesive spray can prevent complications of ESD, especially the delayed bleeding, consequently reducing the average length of hospital stay, and avoiding additional health care expenditures.

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INTRODUCTION

In endoscopic submucosal dissection (ESD), special instrument and other ancillary equipment are used to resect and strip gastrointestinal precancerous lesions and early-stage cancer on the basis of endoscopic mucosal resection (EMR). ESD has been widely performed in clinical practice due to its advantages of complete resection and reduced recurrence rates. However, compared to EMR, ESD is associated with a high incidence of complications such as perforation and bleeding, which has limited the utility of ESD. Currently, ESD is only performed at some institutions in China. Medical adhesives (spray type) have been widely used in surgery and for the treatment of gastric varices because of their adhesive, reinforcement, and leak proofing functions. However, there has been no report of their use in gastrointestinal (GI) endoscopy. This study investigated the use of medical spray adhesives for the prevention of complications in patients undergoing ESD.

MATERIALS AND METHODS

Patients

Patients who underwent ESD at the department of digestive endoscopy of our hospital between January 2009 and June 2012 (n = 173) were enrolled. Two patients undergoing surgery due to severe intraoperative hemorrhage and inability to achieve adequate hemostasis were excluded. The remaining 171 patients completed the ESD treatment and were included in the analysis. There were 75 males and 96 females with an average age of 57.21 ± 12.22 years (range, 18-82 years). There were 37 cases of esophageal lesions, 110 cases of gastric lesions, and 24 cases of colorectal lesions diagnosed by routine endoscopy. This study investigated the use of medical spray adhesives for the prevention of complications in patients undergoing ESD.

Instruments and adhesives

An Olympus GIF-Q260J electronic gastroscope and CF-Q260 colonoscopy system were used. In addition, an NM-4L-1 injection needle, triangle-tip knife, FD-1U-1 hot biopsy forceps, snare, Puko hemostatic clip, HX-610-135 hemostatic clip, and ERBE ICC-200 high-frequency electric cutting device were also employed. The medical adhesive (Compont Medical Adhesive) is a spray-type adhesive and the primary ingredient is butyl α-cyanoacrylate. During ESD, a transparent cap was added at the end of the lens and carbon dioxide insufflation was adopted.

ESD

After conventional therapeutic steps, patients were randomly divided into group A (medical adhesive group, n = 89) and group B (control group, n = 82) according to a computer-generated random number table. There was no significant difference in age, gender, or lesion type between the two groups (Table 1). Patients receiving anticoagulant drugs such as aspirin underwent ESD 5-7 d after drug withdrawal.

All patients underwent the following operations under intubation anesthesia or intravenous anesthesia: (1) Staining: During endoscopy, the lesions were identified and stained with methylene blue. After staining, the lesion boundary was obvious; (2) Marking: A needle knife or argon plasma coagulation (APC) was used to mark at the lesion edges; (3) Injection: An epinephrine/saline solution (1:10000) containing a small amount of methylene blue was injected submucosally at multiple places lateral to the marked points at the lesion edges; (4) Pre-cut: A needle knife was used to cut open the mucosa at the marked points at the lesion edges; (5) Cut: The TT knife was used to make a circular incision on the lesion edge along the marker; (6) Stripping: The TT knife was used to cut open the submucosa layer by layer, and the lesion was peeled off. For the muscularis propria lesions, the lesions were completely stripped from the nearby tissue after the lesion was exposed. In some cases, when the lesion was almost completely peeled off, the snare was used to trap the lesion root so that the lesion could be resected completely; and (7) Wound treatment: After resection of the lesion, small visible blood vessels were treated with argon plasma coagulation (APC) or hot biopsy forceps. The perforated wound surface was closed with metal hemostatic clips. In addition, medical adhesive was sprayed onto the wound surface via a spray catheter in group A patients.

Patients with severe intraoperative bleeding or perforation who were unable to undergo endoscopic treatment received surgical treatment. All the patients receiving ESD were maintained non per os (NPO) postoperatively and received a nasogastric tube and low flow suction. Antacids and necessary hemostatic drugs (Ethamsylate, PAMBA) were administered, together with the prophylactic antibiotics. Abdominal signs such as abdominal pain and distension were monitored closely. Endoscopy was repeated 1, 3, and 6 mo after surgery to examine wound healing, residual lesions, and recurrence.

The postoperative abdominal signs, recurrence, length of hospital stay, and incidence of complications including delayed bleeding, perforation and infection were compared between the two groups.

Statistical analysis

Categorical data were analyzed using the χ² test, and quantitative data were analyzed using the t test. SPSS 10.0 statistical software was used for analysis and the significance level α was set at 0.05.

RESULTS

A total of 173 patients underwent ESD treatment. There
were two patients with muscularis propria lesions with a diameter of 4 or 5 cm, respectively, protruding toward the abdominal cavity. During ESD, the bleeding was difficult to control and these two patients received surgical treatment. The lesions were completely stripped off in the remaining 171 patients. Patient clinical data are shown in Table 1.

The average duration of ESD (from submucosal injection to complete stripping of lesions) was 59.44 min (range, 36-150 min) in group A and 55.00 min (range, 35-140 min) in group B and the difference was not statistically significant. The average length of hospital stay was 8.89 d (range, 6-15 d) in group A and 9.90 d (range, 5-21 d) in group B and the difference was statistically significant. In group B, four patients experienced delayed bleeding and were hospitalized for 19, 19, 20, and 21 d, respectively. Excluding those patients, the average length of hospital stay in group B was 9.40 d (ranged, 5-15 d), which was not significantly different compared with group A (Table 2).

All the 171 patients treated with ESD, with the exception of two patients who were lost to follow-up after treatment, underwent repeat endoscopy 1, 3, 6, and 12 mo after treatment. To date, no recurrence has been noted.

During ESD, bleeding (< 40 mL) occurred in all patients, and hemostasis was successful after electrocoagulation, APC, and application of the hemostatic clip. No delayed bleeding occurred in group A (0.00%, 0/89), whereas delayed bleeding occurred in four patients in group B (4.88%, 4/82), which was significantly different from that in group A. In group B, one patient with an esophageal lesion, two patients with gastric lesions, and one patient with colon lesions experienced bleeding 3, 5, 10 and 7 d after surgery. One patient had symptoms of shock including progressive drop in blood pressure and cold sweats, and the vital signs became stable after transfusion and active medical treatment. Gastric endoscopy and colonoscopy revealed active bleeding at the location of the ESD. After norepinephrine saline flush, APC, application of hemostatic clips, and the endoscopic application of medical spray adhesive, hemostasis was successful. No patients underwent surgical intervention for the control of bleeding.

Perforation occurred in nine of 89 (10.1%) patients in group A. Of these patients, one had an esophageal lesion, seven had gastric lesions, and one patient had colon lesions. Perforation occurred in 8 (9.8%) of 82 patients in group B. Of these patients, two had esophageal lesions and six had gastric lesions. The incidence of perforation was not significantly different between the two groups. Among the nine patients who experienced perforation in group A, seven patients had muscularis propria lesions, one patient had ulcer scars, and the remaining patient had non-ulcer scar lesions. All of the eight patients who experienced perforation in group B had muscularis propria lesions, and none had ulcer scar formation or non-ulcer scar lesions. The diameter of perforation ranged from 0.2 to 2.0 cm, and the wound surface was clipped using hemostatic clips in all the cases. Abdominal paracentesis was performed to release gas in patients with obvious abdominal distension. All perforations resolved after fasting, placement of an indwelling nasogastric tube and gastrointestinal decompression in patients who received gastric procedures, absolute bed rest, and treatment with antibiotics. No patient underwent surgical treatment.

After ESD, 12 patients in group A and 10 patients in group B experienced varying degrees of abdominal distension and abdominal pain, and the incidence was 13.5% and 12.2%, respectively (P > 0.05). Eight of the 12 patients with abdominal distension and abdominal pain in group A experienced intraoperative perforation, and the remaining four patients had no intraoperative perforation. Six of the 10 patients with abdominal distension and abdominal pain in group B experienced intraoperative perforation, and the remaining four patients did not. The symptoms resolved in all patients within 1-3 d after conservative treatment including gastrointestinal decompression, fasting, antacids, and antibiotics. Anal pain during defecation occurred in two patients (2.25%) in group A and 8-10 d after treatment, which was followed by the discharge of solid medical adhesive. A summary of complications is presented in Table 3.

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Table 1  Patient clinical data

|                | All patients (n = 171) | Group A (medical adhesive group) (n = 89) | Group B (control group) (n = 82) | P value |
|----------------|------------------------|------------------------------------------|---------------------------------|---------|
| Age (yr)       | 57.21 ± 12.22          | 56.47 ± 13.02                            | 58.01 ± 11.31                  | NS      |
| Gender (male/female) | 75/96                | 39/50                                    | 36/46                          | NS      |
| Lesion location |                        |                                          |                                |         |
| Esophageal     | 37                     | 21                                       | 16                             | NS      |
| Gastric        | 110                    | 58                                       | 52                             | NS      |
| Colorectal     | 24                     | 10                                       | 14                             | NS      |
| Depth of lesion|                        |                                          |                                |         |
| Mucosa or submucosa | 50                    | 23                                       | 27                             | NS      |
| Muscularis propria | 121                  | 66                                       | 55                             | NS      |

Data are expressed as mean ± SD. NS: Not significant.

Table 2  Comparison of treatment duration and length of hospital stay

|                | Group A (medical adhesive group) | Group B (control group) | P value |
|----------------|----------------------------------|-------------------------|---------|
| Average duration of ESD treatment (min) | 59.44 ± 18.46                | 55.00 ± 21.00           | 0.143   |
| Average length of hospital stay (d)    | 8.89 ± 2.33                   | 9.90 ± 3.30             | 0.021   |
| Average length of hospital stay when patients with delayed bleeding were excluded (d) | 8.89 ± 2.33 | 9.40 ± 2.47 | 0.172 |

Data are expressed as mean ± SD. ESD: Endoscopic submucosal dissection.
Table 3 Complications

|                          | Group A (medical adhesive group) | Group B (control group) | P value |
|--------------------------|----------------------------------|-------------------------|---------|
| Incidence of delayed bleeding | 0.00%                           | 4.88%                   | 0.035   |
| Incidence of perforation  | 10.10%                          | 9.80%                   | 0.938   |
| Location of perforation (n) |                                 |                         |         |
| Esophageal                | 1                               | 2                       |         |
| Gastric                   | 7                               | 6                       |         |
| Colorectal                | 1                               | 0                       |         |
| Perforated lesions        |                                 |                         |         |
| Muscularis propria        | 7                               | 8                       |         |
| Scar formation            | 1                               | 0                       |         |
| Non-scar forming lesion   | 1                               | 0                       |         |
| Incidence of abdominal distension | 13.50%                        | 12.20%                   | 0.802   |
| With perforation          | 8                               | 6                       |         |
| Without perforation       | 4                               | 4                       |         |
| Difficulty excreting adhesive | 2.25%                          | 0.00%                   |         |

### DISCUSSION

ESD is a technique that uses special instruments and other equipment to resect and strip gastrointestinal precancerous lesions and early-stage tumors on the basis of EMR. ESD can be used for the one-time complete resection of lesions with a diameter greater than 2 cm, and the high en bloc resection rate can reduce residual lesions and the chances of recurrence, thus achieving a radical cure.[8,9]. The indications for ESD are still controversial; however, some scholars believe that as long as there is no lymphatic and blood vessel invasion or metastasis, the lesion can be resected using ESD regardless of lesion location and size.[1]. With improvement in the management of endoscopic complications, the depth of lesions treated with ESD has gradually increased and ESD has been used to treat some muscularis propria lesions and stromal tumors. Some authors have even proposed a concept of ESE.[11,12]. However, the incidence of major complications with ESD, including bleeding and perforation, is still relatively high which has limited the generalization of ESD to a larger extent.

The main ingredient of the medical adhesive used in this study is butyl α-cyanoacrylate. As an adhesive with special biomedical function, it has biomedical functions in addition to the common gluing function and mechanical function. It has been confirmed that butyl α-cyanoacrylate is non-toxic to the human body and not mutagenic, teratogenic, or carcinogenic, and will not cause an irritant reaction. Medical adhesives are widely used in surgery, and can rapidly solidify in the presence of anionic substances such as tissue fluid and blood. The adhesive used has a similar strength as tissues, and therefore is not likely to fall off during extension and flexion movement. The adhesive strength is greater than the physiological strength of human body; therefore, its tissue adhesive function is reliable.[12,13]

Manner et al[10] reported an incidence of delayed bleeding after ESD of 6.5%, and Sugimoto et al[11] in a multi-center study reported an incidence of 3.7%. In our study, the incidence of delayed bleeding in the control group was 4.88%, similar to that previously reported. However, no delayed bleeding occurred in the medical adhesive group, and this was significantly different from the incidence in the control group.

Ono et al[12] reported a perforation rate of 5% among 906 patients who were treated with ESD. Sugimoto et al[13] reported a perforation rate of 10.3% in patients with scar lesions and 3.5% in patients without scar lesions. In our study, the perforation rates in groups A and B were 10.1% and 9.8%, and the difference was not statistically different. The incidence of perforation in our study was slightly higher than that in the report by Ono et al[12], but it was similar to the incidence of perforation in patients with scar lesions in the study by Sugimoto et al[13]. We analyzed the depth of the perforated lesions, and found that among the 17 cases of perforation in the two groups, there were 15 cases of muscularis propria lesions, one case of scar formation, and one case of a non-scar forming lesion. Therefore, the relatively high incidence of perforation in our study was due to relatively deep lesions. Generally, perforation was managed successfully with conservative treatment including fasting and antibiotics.[13]

As for other complications of ESD, 12 patients in group A (medical adhesive group) and 10 patients in group B (control group) experienced varying degrees of abdominal distension, and the incidence was 13.5% (12/89) and 12.2% (10/82), respectively, and was not different between the groups. Anal pain during defecation occurred in two patients in group A 8-10 d after treatment, which was followed by discharge of solid medical adhesive. Medical adhesive was not used in group B, so no difficulty in excreting the medical adhesive occurred.

The average duration of ESD in group A was 59.44 min (range, 36-150 min) and in group B was 55.00 min (range, 35-140 min) and the times were not statistically different. However, the average treatment time in group A was slightly more than that in group B, and we believe this is because of the extra time needed to apply the medical adhesive. Our results are consistent with a treatment time of 35-180 min reported by Sano et al[14]. With improvement of techniques and accumulation of experience, the operation time will be gradually shortened, while treating larger and deeper lesions may increase the operation time.

The average length of hospital stay was 8.89 d (range, 6-15 d) in group A and 9.90 d (range, 5-21 d) in group B, and the differences were statistically significant. In group B, four patients experienced delayed bleeding and were hospitalized for 19, 19, 20 and 21 d, respectively. Excluding those patients, the average length of hospital stay in group B was 9.40 d (ranged, 5-15 d), and this was not significantly different compared with group A, indicating that delayed bleeding may significantly increase the length of hospital stay.

In summary, application of spray-type medical adhe-
sive may cause difficulty in excreting the medical adhesive in a few patients, but it does not affect the overall therapeutic effects and prognosis. Use of a spray-type medical adhesive can prevent complications of ESD, especially delayed bleeding. Application of a spray-type medical adhesive can reduce the average length of hospital stay, thereby avoiding additional health care expenditures.

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**COMMENTS**

**Background**

Endoscopic submucosal dissection (ESD) is an effective minimally invasive treatment for gastrointestinal precancerous lesions or early-stage gastrointestinal cancer. Medical adhesive spray can be effective in preventing delayed bleeding after ESD, and can thus reduce the average length of hospital stay.

**Research frontiers**

ESD is associated with a high incidence of complications such as perforation and bleeding, which has limited the utility of ESD. Medical adhesives (spray type) have been widely adopted in surgery and for the treatment of gastric varices because of their adhesive, reinforcement, and leak proofing functions.

**Innovations and breakthroughs**

This is the first report to use medical adhesive after ESD, and results were exciting. Use of a spray-type medical adhesive can prevent complications of ESD, especially delayed bleeding. Application of a spray-type medical adhesive can reduce the average length of hospital stay, thereby avoiding additional health care expenditures.

**Applications**

Medical adhesive spray can be effective in preventing delayed bleeding after ESD, and can thus reduce the average length of hospital stay.

**Terminology**

ESD is an effective minimally invasive treatment for gastrointestinal precancerous lesions or early-stage gastrointestinal cancer.

**Peer review**

This is a good prospective randomized study in which authors analyzed the effect of medical adhesive spray in preventing delayed bleeding after ESD. The results are interesting and suggest that the use of medical adhesive spray may be a useful therapeutic approach in the prevention of delayed bleeding after ESD.