



Application Research of Sodium Hyaluronate in Endoscopic Submucosal Tunnel Resection (STER) for Esophageal Cancer

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DOI: 10.32629/jcmr.v4i4.1468

Abstract: Objective: This study aims to evaluate the efficacy and safety of submucosal injection using a mixture containing sodium hyaluronate in submucosal tunneling endoscopic resection (STER) for esophageal submucosal tumors (SMTs). Methods: A total of 42 patients with SMTs participated in this study from January 2020 to October 2023. The patients were randomly divided into the experimental group (n=21) and the control group (n=21). The experimental group received a mixture of 5ml sodium hyaluronate injection (50mg) + 25ml fructose sodium chloride injection + 0.1ml methylene blue injection as submucosal injection. The control group received 30ml fructose sodium chloride injection + 0.1ml methylene blue injection. Submucosal injection started 5cm proximal to the SMT in the esophagus using the mixture until effective mucosal elevation for subsequent STER surgery. Results: There was no statistically significant difference in the average diameter of resected specimens between the experimental group (1.9±1.3 cm) and the control group (2.0±1.1cm, P>0.05). The average operation time in the experimental group (70.05±9.93 min) was significantly shorter than the control group (96.29±12.15 min, P<0.05). The average submucosal injection volume in the experimental group (13.52±2.77ml) was significantly lower than the control group (26.38±3.47ml, P<0.05). In cases with bleeding <5ml, the experimental group had 18 cases (86%), while the control group had 4 cases (19%); in cases with bleeding >5ml, the experimental group had 3 cases (14%), and the control group had 17 cases (81%), showing a statistically significant difference (P<0.05). Conclusion: Submucosal injection using a mixture containing sodium hyaluronate for STER surgery not only exhibits excellent efficacy but also high safety.

Keywords: Submucosal injection solution; Sodium hyaluronate; Therapeutic efficacy

Submucosal tumors (SMTs) in the gastrointestinal tract refer to tumor-like elevations with a normal mucosal covering. SMTs are usually incidentally discovered during endoscopic examinations. SMTs in the esophagus are commonly smooth muscle tumors or stromal tumors. When SMTs originate from the muscularis propria (MP) layer, have a larger diameter, or are stromal tumors, there is a higher likelihood of malignant transformation [1,2].

In recent years, Submucosal Tunneling Endoscopic Resection (STER) has been widely used domestically and internationally for removing submucosal tumors (SMTs) originating from the intrinsic muscular layer of the digestive tract, demonstrating its safety and efficacy [3,4,5]. Since upper gastrointestinal SMTs require STER under general anesthesia and tracheal intubation, especially for esophageal SMTs where the operative space is limited, and the outer wall of the esophagus is adjacent to vital organs such as the mediastinum and lungs, reducing the surgical duration can lower the risk of surgery-related complications. A clear surgical field is critical in reducing the surgical duration, making optimal exposure of the surgical field particularly important. The STER technique involves initially establishing a submucosal tunnel (whereby an injection of submucosal fluid is followed by incising the mucosa with an endoscopic knife to create an entry, inserting an endoscope into the submucosal layer, and then using the knife to continuously dissect the submucosal tissues to form the submucosal tunnel). An effective and long-lasting liquid cushion formed by submucosal injection medication is a crucial requirement for the smooth establishment of the tunnel and is also an important factor in ensuring a clear and exposed surgical field. Sodium hyaluronate is a physiological active substance, a high molecular weight viscous polysaccharide. It possesses high viscosity and elasticity, making it one of the components used in endoscopic submucosal injection drugs. Its safety and effectiveness have been proven in Endoscopic Submucosal Dissection (ESD) of the digestive tract [6]. This study explores the application of sodium hyaluronate in esophageal STER, aiming to provide clinical evidence for finding a more optimal submucosal injection fluid. The following report details the outcomes.

1. Materials and Methods

1.1 Clinical Data

From January 2020 to October 2023, 42 cases of submucosal tumors (SMT) in the esophagus were detected during

endoscopic examinations at the Digestive Endoscopy Center of the First Affiliated Hospital of Hainan Medical University. Patients underwent complete endoscopic ultrasound examinations confirming that all 42 cases of esophageal SMT originated from the muscularis propria (MP) layer. They underwent thorough preoperative assessments, meeting the indications for Submucosal Tunneling Endoscopic Resection (STER), and signed informed consent forms before the surgery. In our study, the criteria for inclusion in STER were as follows:

- (1) Esophageal SMT fully covered by the mucosa;
- (2) Confirmed by CT and/or Endoscopic Ultrasound (EUS) that SMT originates from the Muscularis Propria (MP) layer;

- (3) Transverse diameter of the esophageal SMT does not exceed 3.5 cm (≤ 3.5 cm);

- (4) Patients over 18 years old;

- (5) Absence of signs of metastasis or invasion outside the digestive tract;

- (6) EUS evaluation indicates no high-risk features of malignant tumors in the SMT. Exclusion criteria are as follows:

- (1) SMT located less than 3-5 cm from the esophageal inlet, with insufficient space for tunneling;

- (2) Presence of metastasis and/or invasion outside the digestive tract;

- (3) SMT deemed high-risk for surgery, for example, SMT with abundant blood supply;

- (4) Pregnant women;

- (5) Patients with severe cardiopulmonary diseases intolerant to general anesthesia, and patients with coagulation disorders (international normalized ratio > 1.5 and/or platelet count $< 50 \times 10^9$).

Patients were divided into two groups according to a random number table using a randomized controlled principle: the experimental group consisted of 21 cases, where a mixture of 5ml of sodium hyaluronate injection (50mg) + 25ml of fructose sodium chloride injection + 0.1ml of methylene blue injection was used as the submucosal injection solution; the control group also had 21 cases, employing a mixture of 30ml of fructose sodium chloride injection + 0.1ml of methylene blue injection as the submucosal injection solution.

1.2 Method

1.2.1 Instruments and Medications

Olympus CF-Q260J therapeutic gastroscope, Dual knife, transparent hood, hemostatic forceps, disposable submucosal injection needle, ERBE VIO 200D treatment unit; carbon dioxide insufflator; sodium hyaluronate injection (2.5ml/vial, 10mg/ml, Alzhi, produced by Nippon Soda Co., Ltd.), methylene blue injection, fructose sodium chloride injection, etc.

1.2.2 Preoperative Examination and Preparation

Routine preoperative tests include assessment of cardiopulmonary function, coagulation function, complete blood count, liver and kidney function, and general patient evaluation to exclude surgical contraindications. Patients are advised to fast for 12 hours and abstain from liquids for 6 hours prior to the procedure. Before surgery, patients undergo general anesthesia and tracheal intubation performed by an anesthesiologist. Close monitoring of the patient's respiration, blood pressure, pulse, and blood oxygen saturation is carried out.

1.2.3 Endoscopic Procedure: Steps of STER procedure

- (1) Under general anesthesia with tracheal intubation, the patient is positioned on the left side. Carbon dioxide insufflation is employed for all procedures.
- (2) The endoscope is inserted into the esophagus to locate the SMT and ensure accurate positioning.
- (3) Injection of submucosal fluid is done to raise the mucosa. A longitudinal incision of 2cm is made on the oral side of the SMT, creating the submucosal tunnel.
- (4) The tunnel is extended approximately 2cm on the anal side of the SMT. Using the Dual knife under direct endoscopic visualization, the tumor is progressively dissected until completely excised, followed by managing the surgical wound.
- (5) Closure of the tunnel entrance is performed using a clip. The excised tissue is sent for pathological examination. During the procedure, a disposable submucosal injection needle, along with a 10ml syringe for rapid drug injection, is utilized. The mixed solution used for submucosal injection can be incrementally added multiple times until adequate elevation of the mucosa is achieved.

1.2.4 Postoperative Observation and Management

Postoperatively, monitor the patient's heart rate, blood pressure, and oxygen saturation. Intravenous proton pump inhibitors (PPIs) and hemostatic medications may be administered as needed. For surgeries with extended duration, larger lesion sizes, or larger surgical wounds, antibiotics may be added postoperatively to prevent infection. Monitor for signs such as absence of fever, chest discomfort, dyspnea, subcutaneous emphysema, melena, or, if necessary, perform a chest X-ray to exclude pneumothorax or mediastinal emphysema, which may indicate surgery-related complications. Following 48-72

hours of continuous fasting post-surgery without signs of complications, the patient may be allowed a clear liquid diet.

1.2.5 Postoperative Follow-up

All patients will undergo gastroscopy at 3, 6, and 12 months postoperatively, followed by annual examinations thereafter, to observe wound healing progress and monitor for tumor recurrence.

1.2.6 Observation Metrics

Record lesion size, surgical duration, volume of submucosal injection solution, intraoperative bleeding volume, and perforation incidence in both the experimental and control groups.

1.2.7 Statistical Analysis

Data will be processed using SPSS 26.0 statistical software. Categorical data will be presented as counts or percentages, and intergroup comparisons will be performed using the χ^2 test. Continuous variables will be expressed as mean \pm standard deviation ($x \pm s$), and intergroup comparisons will be conducted using independent samples t-tests, with significance set at $P < 0.05$.

2. Results

2.1 General Characteristics

In this study, a total of 42 cases underwent STER for esophageal SMT. Among the 21 cases in the experimental group, there were 11 males and 10 females, with a mean age of (43.2 \pm 10.9) years and an average lesion diameter of (1.9 \pm 1.3) cm. In the control group of 21 cases, there were 9 males and 12 females, with a mean age of (43.7 \pm 11.5) years and an average lesion diameter of (2.0 \pm 1.1) cm. There were no statistically significant differences between the two groups in terms of gender distribution ($P=0.537$), age ($P=0.075$), or lesion diameter ($P=0.587$).

2.2 Comparison of Various Observation Indicators between the Two Groups

(1) The operation time from the incision of the tunnel to the complete completion of the entire STER procedure, including tumor lesion resection and closure with titanium clips, ranged from 52 to 120 minutes. The average operation time in the experimental group was (70.05 \pm 9.93) minutes, which was significantly lower than that in the control group with an average operation time of (96.29 \pm 12.15) minutes ($P < 0.001$), as shown in Table 1.

(2) The average volume of submucosal injection fluid in the experimental group was (13.52 \pm 2.77) ml, significantly lower than that in the control group which was (26.38 \pm 3.47) ml ($P < 0.001$), as shown in Table 2.

(3) In the experimental group, 18 cases (86%) had intraoperative bleeding of <5 ml, and 3 cases (14%) had >5 ml bleeding. In the control group, 4 cases (19%) had intraoperative bleeding of <5 ml, and 17 cases (81%) had >5 ml bleeding. The difference was statistically significant ($P < 0.001$). The intraoperative bleeding in the experimental group was significantly lower than in the control group, with only 14% experiencing >5 ml bleeding, which was notably lower compared to the control group (81%). The difference in intraoperative bleeding between the two groups was statistically significant ($\chi^2=18.709$, $P < 0.001$), as shown in Table 3. No recurrence of bleeding occurred after endoscopic hemostasis.

Table 1. Comparison of Average Operation Time in Two Groups of STER (Mean \pm Standard Deviation, min)

Group	n	Average Value	t-value	P-value
Experimental Group	21	70.05 \pm 9.93	-7.66	< 0.001
Control Group	21	96.29 \pm 12.15		

Table 2. Comparison of Submucosal Injection Fluid Volume in Two Groups (Mean \pm Standard Deviation, ml)

Group	n	Average Value	t-value	P-value
Experimental Group	21	13.52 \pm 2.77	-13.27	< 0.001
Control Group	21	26.38 \pm 3.47		

Table 3. Comparison of Intraoperative Bleeding Amount in Two Groups (χ^2 , cases)

Group	Blood Loss	Number of Cases	Proportion	χ^2	P-value
Experimental Group	< 5 ml	18	86%	18.71	< 0.001
Experimental Group	> 5 ml	3	14%		
Control Group	< 5 ml	4	19%		
Control Group	> 5 ml	17	81%		

2.3 Pathological Results

Postoperative pathology diagnosed 40 cases as leiomyoma and 2 cases as stromal tumors. All were completely excised in a single procedure.

2.4 Postoperative Observations

There were no instances of delayed bleeding or perforation post-STER. The hospitalization period for all STER cases ranged from 5 to 7 days. Postoperative follow-up examinations revealed good healing of the surgical site without local tumor recurrence or metastasis.

3. Discussion

In recent years, there has been a growing body of research on STER, confirming its safety and efficacy. STER is considered the optimal method for the removal of SMTs originating from the muscularis propria, exhibiting high rates of complete resection and maintaining mucosal integrity [7, 8]. The establishment of a tunnel not only helps preserve mucosal integrity but also reduces the risk of complications such as gastrointestinal perforation, postoperative infections, fistulas, and strictures [9]. During the implementation of STER, the establishment of the submucosal tunnel is an extremely critical and necessary step for the success of the procedure. Therefore, the smooth and rapid creation of the submucosal tunnel can effectively expose the surgical field, shorten the operation duration, and reduce complications. The use of a mixed liquid drug for submucosal injection forms a fluid cushion in the submucosal layer, aiding in the separation between the mucosal and muscular layers. This process is advantageous for the electric knife in dissecting the submucosal layer and establishing the tunnel. Adequate submucosal fluid cushion maintenance for an adequate duration provides the operator with a clear operative field, facilitating the smooth establishment of the submucosal tunnel. This helps reduce surgical difficulty, shortens the operation duration, prevents damage to muscular tissue, and decreases the occurrence of surgery-related complications such as bleeding and perforation. As esophageal STER necessitates procedures under general anesthesia with endotracheal intubation and the use of a carbon dioxide pump for insufflation, reducing the operation time can also lessen the retention of carbon dioxide in the body, thereby decreasing the adverse effects of hypercapnia.

As endoscopic submucosal dissection (ESD) has become widely used for the resection of early gastrointestinal tumors, various solutions have been employed for submucosal injection. Similar to ESD, submucosal injection solutions used in STER often include mixtures of glycerin fructose sodium chloride injection and methylene blue injection. However, these solutions are easily absorbed after submucosal injection and have a short duration of maintenance (as observed in this study to be sustained for 5 minutes). This short duration is clearly disadvantageous for the establishment of the submucosal tunnel during STER. Sodium hyaluronate is a single-chain high-molecular-weight viscoelastic polysaccharide composed of repeating units of glucuronic acid and N-acetylglucosamine disaccharides. Its aqueous solution behaves as a non-Newtonian fluid and is widely distributed in various tissues of the body, with higher concentrations found in ocular vitreous, synovial fluid, skin, and other areas [10]. It exhibits excellent viscoelasticity, lubrication, buffering, scavenging of free radicals, and anti-inflammatory properties, contributing to its extensive use in ophthalmology, dermatology, orthopedics, and cosmetics due to its unique properties [11,12]. In the field of endoscopic diagnostic and therapeutic techniques, the excellent viscoelasticity of sodium hyaluronate is utilized. This study demonstrates that the average dosage in the experimental group (13.52 ± 2.77 ml) and the mean duration of the surgical procedure (70.05 ± 9.93 min) were both lower compared to the control group. Additionally, intraoperative bleeding was lower in the experimental group. This suggests that the use of sodium hyaluronate in combination with fructose and methylene blue for submucosal injection during STER enables the injected solution to maintain a longer duration. It also leads to better submucosal elevation, reducing the need for repeated injections and drug dosage during the procedure. Furthermore, it facilitates the creation of a submucosal tunnel, resulting in clear exposure of the surgical field, shorter operation times, and decreased risks of surgery-related complications.

In summary, our research suggests that choosing hyaluronic acid as the submucosal injection drug in STER procedures has unique advantages in establishing submucosal tunnels. It offers efficient safety measures, improves surgical visibility, reduces operative time, and lowers the occurrence rate of surgery-related complications. Hence, it can be considered the standard submucosal injection agent in STER procedures.

Acknowledgments

Fund Project: The Youth Cultivation Fund Project in The First Affiliated Hospital of Hainan Medical University in 2020 (Project Number: HYYFYYPY202019).

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