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Autologous activated fibrin sealant for the esophageal anastomosis: a feasibility study

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ABSTRACT

Background: Esophageal cancer is surgically treated by means of an esophagectomy. However, esophagectomies are associated with high morbidity rates with dehiscence of the anastomosis occurring in 19% of these procedures in the Netherlands. Application of a fibrin sealant may improve mechanical strength of the anastomosis. The aim of this study was to determine the technical feasibility of the application of an autologous fibrin sealant by aerosolized spraying on esophageal anastomoses.

Methods: This study was designed as a single-center feasibility study. Patients undergoing elective minimal invasive esophageal surgery with the creation of a thoracic or a cervical anastomosis were eligible. Fibrin sealant (Vivostat) was applied to the anastomosis intraoperatively. Feasibility was measured using a nine-item checklist, designed for intraoperative application.

Results: In total, fifteen patients, between the ages of 43-79 y, were included in this study. One procedure scored eight out of nine points on the feasibility checklist, so application was considered as unsuccessful. The other fourteen procedures obtained a 100% score and were documented as successful procedures. Together, this led to a success rate of 93%. Grade III anastomotic leakage occurred in one of the fifteen patients (6.7%).

Conclusions: This study showed that application of fibrin sealant on esophageal anastomoses is technically feasible and safe. Future studies may investigate the possible protective effects of fibrin sealant application on the development of anastomotic leakage. NCT03251040.

Introduction

Esophageal cancer is the seventh most commonly diagnosed type of cancer in males.[1] For most patients, the only curative treatment is surgery with adequate lymph node dissection after neoadjuvant chemotherapy. According to the Dutch Upper Gastro Intestinal Cancer Audit, these procedures are associated with a 30-d mortality rate of 4-5%. Furthermore, dehiscence of the anastomosis, defined as anastomotic leakage, occurs in 19% of these procedures in the Netherlands.[2] Owing to anastomotic leakage, 30-d mortality increases up to 35%.[3-5] Therefore, prevention of anastomotic leakage has been the focus of many studies. A recent development in the attempt to reduce leakage has been the introduction of tissue adhesives, which are generally used as surgical sealants to seal air and fluid leaks during surgical procedures. Current literature suggests fibrin sealant could increase the strength of the esophageal anastomosis and

Conflict of interest: None.

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promote anastomotic healing. Use of fibrin sealant appears to be safe *in vivo* and might lower the incidence of esophageal anastomotic leakage.[6-12] To date, only one trial has been conducted that evaluated the application of tissue adhesives in routine esophagectomies in adults.[13,14] The aim of the present study was to investigate the technical feasibility of the application of an autologous fibrin sealant by aerosolized spraying on the esophageal anastomosis.

Methods

Study design

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Approval of the study protocol was obtained by the local institutional ethical review board of the VU Medical Center. This study was designed as a single-center feasibility study. The recruitment period was from August 2015 to April 2016. All participants were required to give informed consent to participate in this study. The inclusion criteria were as follows: patients had to be scheduled for elective minimal invasive esophageal surgery with thoracic or cervical anastomosis (i.e. Ivor Lewis, Orringer or McKeown esophagectomy) in the VU Medical Center, had to be 18-90 y old, and had to have a physical status (American Society of Anesthesiologists) of 3 or lower. Patients with other malignancies or previous esophageal surgery were excluded.

Fibrin sealant

The Vivostat system is a medical device used for intraoperative preparation of autologous fibrin sealant. It consists of the following three components: an automated processor, an application unit, and a single-patient-use disposable preparation unit. For each patient individually, several steps were taken to create 5 ml of autologous fibrin sealant. First, 120 mL of the patient's blood was drawn by gravity drainage into the preparation unit and mixed with tranexamic acid to prevent coagulation. Second, the preparation unit was inserted in the processor for centrifugation. During the centrifugation phase, about 60 mL of platelet-poor plasma was isolated from the residual. Third, a catalyzer (batroxobin) was used to release fibrinopeptide A from fibrinogen without activating factor XIII. This resulted in the formation of a fibrin I polymer. Finally, further centrifugation was used to extract the concentrated fibrin I polymer, which was then dissolved in acetate buffer to yield a concentrated autologous plasma fraction. This process, resulting in 5 mL of purified fibrin I solution, was completed in approximately 25 min. The vial containing the purified fibrin I solution was inserted in the applicator unit. Immediately before application, the fibrin I solution was mixed with a pH-activation solution, resulting in a neutral pH. Upon tissue contact, the fibrin sealant polymerizes within 60 s.[15]

Procedures

Patients were admitted to the hospital 1 d before surgery and received standard preoperative treatment according to local protocol. Patients received an epidural catheter, a central venous catheter, and an arterial catheter. A 120 mL blood sample was drawn from the central venous catheter to produce approximately 5 mL of fibrin sealant. Following creation of the anastomosis, fibrin sealant was applied to either the thoracic (Figure) or the cervical anastomosis.

Location of the anastomosis

Esophagectomy was performed through a transthoracic or a transhiatal approach. A transhiatal approach is associated with a limited lymphadenectomy compared with a transthoracic approach, which is essential to obtain an adequate radical resection with negative margins. The approach was decided based on the presence of thoracic lymphadenopathy, cardiac or respiratory comorbidities, and the preference of the patient. Transthoracic esophagectomy according to Ivor Lewis[16] resulted in a thoracic end-to-side anastomosis, which was created by linear stapling and closure of the stapling defect with a 3-0 V-loc suture (Covidien). Transthoracic esophagectomy according to McKeown[17] resulted in a cervical anastomosis and was carried out in three stages. In the case of cardiac or respiratory compromised patients, a transhiatal approach according to Orringer[18] was performed. The anastomosis was created using 3-0 monofilament absorbable sutures in a two-layer running fashion. All esophagectomies were performed minimally invasive, and every esophagectomy was performed by the same two gastrointestinal surgeons. Postoperatively, all patients were treated according to local protocol, consisting of admittance to the intensive care unit for extubation and stabilization. Patients were transferred to a general department or medium-care the following day.

Technical application

During all procedures, fibrin sealant was applied to either the thoracic or the cervical anastomosis by one of the two attending upper gastrointestinal surgeons. To determine the feasibility of the intervention, a nine-item checklist was drafted (Table 1). First, the prerequisites were checked to guarantee a safe blood donation. Second, the surgeon created the gastro-esophageal anastomosis and ruled out any torsion or tension on the anastomosis. In the third phase, fibrin sealant was applied, starting at the dorsal side of the anastomosis. Before application, the anastomosis was lifted, and the dorsal side was dried using surgical gauze. Fibrin sealant was subsequently applied approximately 2 cm proximal and distal to the anastomosis. Progressive whitening of the fibrin layer was a marker for successful polymerization. Finally, after 60 s of drying, the esophagus was gently put back into the surgical field. Finally, fibrin sealant was applied to the ventral side of the anastomosis.

Feasibility

This study was designed to investigate the technical feasibility of the application of an autologous fibrin sealant on the esophageal anastomosis. Feasibility was measured using a checklist intraoperatively. Nine items (Table 1) were scored