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Review

The role of tissue adhesives in esophageal surgery, a systematic review of literature



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HIGHLIGHTS

• Tissue adhesives contribute to wound healing by enabling polymerization and forming tight approximation of the anastomosis.

due to a high degree of bias and lack of homogeneity.

- Two categories of tissue adhesives are used in gastrointestinal surgery: fibrin sealants and cyanoacrylates.
- Included articles mainly documented positive results for the use of tissue adhesives as anastomotic sealants.
- The use of tissue adhesives seems to be a valid treatment option for esophageal fistulas.
- Success of treatment is highly dependent on local expertise.

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ABSTRACT

Background: Anastomotic leakage following esophageal surgery is a major contributor to mortality. According to the national database leakage occurs in 20% of esophagectomies carried out in the Netherlands. Therefore anastomotic leakage has been the topic of many studies. However, studies discussing application of tissue adhesives for either prevention or management of anastomotic leakage are limited. This article systematically reviewed all available literature on the potential use of tissue adhesives in esophageal surgery.

Methods: Medline, Embase and Cochrane were searched to identify studies that used tissue adhesives as anastomotic sealants to prevent esophageal anastomotic leakage or used tissue adhesives to treat esophageal anastomotic leakage. Two authors independently selected nineteen out of 3107 articles. Results: Eight articles, of which five were experimental and three clinical, discussed prevention of anastomotic leakage. Eleven articles, of which one was experimental and ten clinical, discussed treatment of anastomotic leakage. Most articles reported positive results, however overall quality was low

Conclusion: This study shows mainly positive results for the use of tissue adhesives for the esophageal anastomosis both in prevention of leakage as treating anastomotic leakage. However, the quality of current literature is poor.

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1. Introduction

Anastomotic leakage (AL) after esophageal resection and formation of a gastric conduit remains the primary source of

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morbidity and mortality for patients with treatable esophageal cancer. Tissue adhesives are used in gastrointestinal surgery to prevent or manage AL. Tissue adhesives contribute to wound healing both by enabling polymerization and forming tight approximation of the anastomosis. Two categories of tissue adhesives, based on their chemical make-up, are used in gastrointestinal surgery: fibrin sealants (FS) and cyanoacrylates (CA). Generally, FS consist of thrombin and fibrinogen. These compounds are extracted from pooled human or animal sources. Sealants are carefully screened and therefore have a small risk of infectious transmission.

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They are directly applied on the surgical field by aerosolized spraying, liquid gluing or by means of patches. Within two weeks, sealants are naturally broken down by fibrinolytics. In contrast to FS, CA is not bio absorbable. They are generally used for lacerations of the skin and provide a stronger adhesion compared with FS. However, internal use is associated with inflammation, tissue necrosis and infection [1]. Modern literature on tissue adhesives now exceeds thousands of articles and continues to expand. The aim of this systematic review was to evaluate the current literature on the use of tissue adhesives in esophageal anastomotic surgery both for prevention and treatment of AL.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [2].

2.1. Searching

A comprehensive search was performed in the bibliographic databases PubMed, Embase and the Cochrane Library (via Wiley) from inception to 16th September 2016, in collaboration with a medical librarian. The following terms were used (including synonyms and closely related words) as index terms or free-text words: 'esophagus' AND 'tissue adhesives' OR 'glue' OR 'seal'. The full search strategies for all the databases is displayed in the supplementary Information.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) articles had to be published in English, (2) full texts had to be available, (3) articles had to be published between January 1980 and 16th September 2016, (4) tissue adhesives had to be applied on the esophageal anastomosis to prevent AL or (5) studies had to investigate tissue adhesives to endoscopically manage esophageal AL, esophageal fistulas or other esophageal perforations. Review articles, conference abstracts and small case reports (number of patients <4) were excluded.

2.3. Screening

Title and abstracts of all citations identified by means of our search strategy were independently screened by two authors (V.P. and B.B.). The full-text articles of all remaining citations were obtained and screened for inclusion. Further relevant publications were collected from the reference lists of included articles.

2.4. Data extraction and statistical analysis

Relevant information was extracted from papers included in the review. For clinical studies, the level of evidence (Centre of Evidence Based Medicine, University of Oxford) was determined. A data collection was used to extract the following information: authors, year of publication, study design, participant details including surgical procedure or type of leakage, follow-up time, primary outcomes and study outcomes. Primary outcomes included: bursting pressure, collagen synthesis, occurrence of AL, and treatment success. This manuscript contains descriptive statistics, data is presented as percentages, no biostatistical tests were used.

3. Results

3.1. Overview

A total of 3107 articles were collected through a combined search in Pubmed, Embase and Cochrane databases. After duplicate removal, screening on title and abstract a total of 157 articles were included for full-text assessment. After full-text assessment a total of nineteen articles were included for qualitative synthesis. A flow chart of the article selection is presented in Fig. 1. Results are presented by indication (prevention or treatment) and type of research (experimental or clinical).

3.2. Prevention of AL

Many studies have been conducted involving the use of tissue adhesives on gastrointestinal anastomotic sealing. However, few studies have assessed the use of tissue adhesives on esophageal anastomosis. To date, eight articles have been published regarding the role of tissue adhesives on sealing esophageal anastomosis [3–10]. A summary of the relevant articles is presented in Table 1.

3.2.1. Experimental research

Primary endpoints of interest for this review were bursting pressure, collagen synthesis and occurrence of AL. Five experimental studies have been published regarding esophageal sealing. Yurtcu et al. [4] applied FS (Beriplast®) or CA (Glubran® 2) on the esophagogastric anastomosis in rabbits. A 1 cm esophageal segment was resected after which FS or CA was injected on the esophagogastric anastomosis. Both groups were compared to controls. Collagen synthesis was determined by measuring the hydroxyproline levels in the esophageal tissue. A significantly higher bursting pressure and decreased collagen synthesis were documented for the CA group compared to controls. However, these endpoints did not differ between the FS group and controls. Verhage et al. [3] investigated the use of fibrin coated collagen patches (Tachosil®) on esophagogastric anastomosis in rats. The intra-abdominal distal esophagus was mobilized and dissected. Animals were randomized into two groups and sacrificed on day 0, 3, 5 and 7. Bursting pressure was significantly increased due to sealing during the first postoperative days (day 0 and 3). However, collagen synthesis, determined by immunohistochemistry, was comparable between groups at all time points.

At the end of the 20th century, three high-risk animal studies were published. A Canadian research group investigated the use of FS (Tisseel®) in rabbits. A 1 cm esophageal segment was resected after which an esophageal anastomosis was created under tension, mimicking esophageal reconstruction in children with esophageal atresia. The FS group was compared to controls and primary outcome was occurrence of AL. Leakage was determined during autopsy or histological examination. No reduction of AL or other benefits of additional sealing with FS were observed in this study [5]. McCarthy et al. [6] created an insufficient esophagogastric anastomosis in dogs. The esophagus was resected 8 cm above the gastroesophageal junction. In the experimental group, FS (Tisseel®) was used to reinforce the anastomosis. At autopsy, leak test was performed. A leakage rate of 36.4% was observed in the experimental group compared to 92.2% in controls (p < 0.01). A study conducted by Thorson et al. [7] documented similar results. An esophageal anastomosis was created in dogs, after which the animals were given a normal diet to reduce high leakage rates. The incidence of AL was decreased by 30% as a result of additional sealing with FS.

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