Fibrin Glue Does Not Improve Healing of Gastrointestinal Anastomoses: A Systematic Review

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Key Words
Anastomoses · Fibrin glue · Fibrin sealant · Healing · Sealing

Abstract
Background/Aim: Anastomotic leakage remains a frequent and serious complication in gastrointestinal surgery. In order to reduce its incidence, several clinical and experimental studies on anastomotic sealing have been performed. In a number of these studies, the sealing material has been fibrin glue (FG), and the results in individual studies have been varying. The positive effect of anastomotic sealing with FG might be due to the mechanical/physical properties, the increased healing of the anastomoses or both. The aim of this systematic review was to evaluate the existing evidence on the healing effects of FG on gastrointestinal anastomoses. Methods: PubMed, EMBASE and the Cochrane databases were searched for studies evaluating the healing process of gastrointestinal anastomoses after any kind of FG application. The search period was from 1953 to December 2013. Results: Twenty-eight studies were included in the qualitative synthesis. These studies were all experimental studies, since no human studies used histological or biochemical evaluation of healing. In 7 of the 28 studies, a positive effect of FG on healing was found, while 8 studies reported a negative effect and 11 studies found no effect. Furthermore, 2 studies reported unclear results. The difference in the study outcome was independent of the study design and the type of FG used. Conclusion: In the available studies, FG did not consistently have a positive influence on the healing of gastrointestinal anastomoses. It is consequently plausible that the positive effect of FG sealing of gastrointestinal anastomoses, if there is any, may be due to a mechanical sealing effect rather than due to improved healing per se.

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**Introduction**

Gastrointestinal anastomosis is a common surgical procedure both in cancer surgery and in the treatment of benign gastrointestinal diseases. Anastomotic leakage is a serious complication after gastrointestinal surgery resulting in a significant increase in the 30-day mortality and morbidity rates. The mortality rate of this complication may be as high as 13–27% [1–8]. The reported anastomotic leakage rates are 1–39%, but a comparative evaluation of the studies is difficult due to the lack of standardized definitions [9–11]. In addition to the immediate clinical consequences, anastomotic leakage is an independent predictor of reduced cancer-specific and general survival [11–14]. Leakage may present as generalized peritonitis requiring surgical intervention, as a more localized accumulation of pus (abscess) or as subclinical leakage that may only be recognized radiologically. Subclinical leakages are considered to be less dangerous and have less impact on the outcome [15–17].

Sealing of the anastomosis with a variety of materials has been investigated in both clinical and experimental studies as an attempt to reduce the frequency as well as the consequences of anastomotic leakage. Unfortunately, many of these attempts have failed to show convincing results [18–48]. Numerous studies have reported on the sealing of gastrointestinal anastomoses with fibrin glue (FG), also called fibrin sealant. FG is designed to mimic the final steps of the blood coagulation cascade, forming a stable physiological fibrin clot that assists hemostasis and wound healing. The fibrin clots formed from FG are similar to normal blood clots and are naturally degraded after a few weeks by the body’s enzymes. FG is available as a fluid [49, 50] or bound to a mesh [51]. In most studies on FG, the commercially produced FG was used, but in some studies FG was produced locally in the clinical setting from human or animal blood. Positive effects of FG on intestinal anastomoses have been found in both human and experimental studies [47, 48]. However, healing has not been the primary endpoint in these studies. Therefore, it is unclear if the positive effect has been due to increased mechanical strength, protection of the anastomosis by a sealing effect or better healing per se.

The aim of the present systematic review was to investigate if FG has a histological or biochemical effect on the healing of gastrointestinal anastomoses.

**Methods**

This systematic review was conducted and reported according to the PRISMA guidelines [52, 53].

**Search Strategy**

The search strategy aimed to identify all human and experimental studies investigating the application of any kind of FG to gastrointestinal anastomoses. A systematic literature search was performed in December 2013 on PubMed (1953–2013; restriction: English language) and EMBASE (1947–2013; unrelated terms; restriction: English language). The following search string was used: (((((((((((fibrin adhesive[MeSH Terms]) OR fibrin glue[MeSH Terms]) OR fibrin[MeSH Terms]) OR ((fibrin) AND glue)))) OR fibrin sealant) OR fibrin coating) OR Tisseel)) AND ("Anastomosis, Surgical"[Mesh]) OR anastomo*). Likewise, a search in the Cochrane database was performed using the following search string: (Fibrin glue OR Fibrin sealant) AND (Anastomoses OR Anastomosis). The reference list of identified studies was hand-searched for additional studies.

**Definition of FG**

FG is mainly derived from blood plasma and contains fibrinogen and thrombin. Further ingredients are anti-fibrinolytic agents (such as aprotinin) and calcium chloride. Some fibrin sealants also contain factor XIII. FG is available as a fluid or bound to a mesh. It can be either commercially produced [49–51] or produced locally in the clinical setting from human or animal blood.
Study Selection

A study had to fulfill the following 3 criteria in order to be included in the analysis: (1) it had to involve gastrointestinal anastomoses (esophagus, stomach, bile system, duodenum, pancreas, small intestine, colon or rectum), which may have been performed in any way, i.e. hand-sewn, stapled or glued (sutureless), and should have been conducted on live humans or animals; (2) it had to use any kind of application of FG on the anastomosis according to the description of FG above, and (3) it had to evaluate the healing of the anastomoses by either histological or biochemical methods.

A study was excluded if one of the following criteria was fulfilled: (1) no control group in the study design; (2) anastomoses in the control group were not similar to those in the FG group; (3) no well-described method for the evaluation of histological or biochemical healing, and (4) no full-text available.

The studies identified in the search were screened by title and abstract for eligibility. After this screening, the full-text of the remaining studies were read and assessed according to the above-mentioned criteria. Eligible studies were included in the qualitative synthesis. In order to avoid bias, the selection procedure was performed independently by two of the authors (T.N. and M.P.A.). In case of disagreement, the disputed studies were discussed among all authors, and a consensus was achieved.

Data Extraction

The following data were extracted from the included studies: author names and year of publication; type of study (human or experimental); animals used (experimental studies); localization of anastomoses; type of anastomoses; intervention; type of FG; use of randomization; type(s) of histological or biochemical evaluation of healing; effect of FG, and conclusion of the study.

Data were extracted directly from the included articles. In one case, additional information about the significance of the results was obtained from the authors [54]. The primary outcome of the present review was the healing effect of FG on anastomoses.

Results

In the qualitative synthesis, 28 studies were included (fig. 1). These studies were all experimental studies, since no human studies applied histological or biochemical evaluation of healing. Of these studies, 23 were performed in rats, 2 in rabbits, 2 in pigs and 1 in mice. Anastomoses were performed on the colon in 20 studies, on the small intestine in 6 and on the esophagus in 2 studies. Of the 28 studies, 17 were randomized. Various methods of histological or biochemical evaluation of healing were used (table 1).

The application of FG for sealing, coating, reinforcement or other application to the anastomoses were obligate for studies included in the qualitative synthesis. Different liquid or mesh-bound FG were used in the studies. Liquid FG (Tisseel™, Tissucol™, Guang Zhou Bioseal™, Beriplast™) were used in 23 studies, while mesh-bound FG (TachoSil™, TachoCom) were used in 5 studies.

Effect on Healing

In 7 of the 28 studies, a positive effect of FG on healing was found [55–61], while 8 studies reported a negative effect [62–69] and 11 studies found no effect [54, 70–79]. Furthermore, 2 studies reported unclear results [80, 81] (table 2).

Different types of anastomoses, animals and FG were used in the included studies (table 3). In the group of studies with positive results, 3 of 7 (43%) anastomoses were made on the small intestine, while this was only the case in 11 and 18% of the groups reporting negative results and no effect, respectively. No differences were found relating to the type of animal or the type of FG used.
Discussion

The results from the analyzed studies were conflicting. Of the 28 studies included, 7 studies revealed a positive effect of FG on histological or biochemical healing of gastrointestinal anastomoses, 8 studies found a negative effect and 13 studies found no effect or had unclear results.

Several different designs were used in the included studies, e.g. different experimental animals, anastomoses on different parts of the gastrointestinal canal, different kinds of FG and different observation periods. In addition, various methods for the evaluation of healing have been used. These differences might explain the conflicting results. When comparing the group of studies with a positive effect on healing with the group of studies with a negative effect, it seems that a larger proportion of positive results came from studies on the small intestine. In this group, 3 out of 7 studies were made on the small intestine in contrast to the group of studies with negative results, where only 1 out of 8 studies was made on both the ileum and colon, and the remaining 7 studies used the colon.

The mechanisms behind the healing properties of FG, or lack thereof, are unknown. In 1 study on colonic anastomoses in rats, compromised healing after FG sealing was demonstrated, and these findings were hypothesized to be due to an inflammatory reaction caused by the sealing [64]. In 2 other studies, it was found that FG sealing inhibited healing of normal
colon anastomoses in rats [65, 69]. The hypothesis there was an increased inflammatory activity, which caused an increased production of collagenase and thereby reduced collagen concentration. In another study by the same authors, antibiotics were added to the FG sealant, causing reduced inflammation and increased bursting pressure and collagen content [68]. In line with this, another study suggested that impaired healing after sealing was due to the intraluminal confinement of bacteria together with a reduced peritoneal contact of the anastomoses [72]. These findings suggest that impaired healing may be due to inflammation and/or foreign body reaction caused by the sealing, by bacteria from the colon or both. This is in accordance with studies suggesting that fibrin matrices impair the phagocytic killing of bacteria by neutrophils [82] and impede macrophage migration [83]. In studies focusing on wound healing in general, infection was found to have an undesirable influence on the healing process as well [84]. These hypotheses are in accordance with the fact that more studies investigating anastomoses in the small intestine found a positive effect on healing compared with studies investigating anastomoses in the colon, since the bacterial content may be larger in the colon than in the small intestine.

To date, several methods for evaluating the integrity of an anastomosis have been proposed and tested. Most of these methods have focused on the macroscopic results such as anastomotic leakage, anastomotic strength and bursting pressure, but not on the healing process per se. Among the 28 studies included in the present review, which all focused on both healing and mechanical properties, it appears that the results on these macroscopic/mechanical properties differed considerably from the healing results. A total of 14 studies found a positive effect on anastomotic leakage, anastomotic strength or bursting pressure [55–61, 63, 70, 75–78, 80], while only 2 studies found a negative effect on these end points [69, 71]. Of the 8 studies with no effect on healing, 6 studies revealed a positive effect on bursting pressure or anastomotic strength [70, 75–78, 80]. Similar findings were seen in the group of studies reporting a negative effect on healing, where 1 study found a positive effect on bursting pressure and anastomotic strength [63], 6 studies found no effect on these

### Table 1. Types of examinations

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Description</th>
<th>qPCR = Quantitative polymerase chain reaction; α-SMA = alpha smooth muscle actin; MMP = matrix metalloproteinase.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyproline level</td>
<td>Biochemical extract analysis</td>
<td>Indicator of collagen content [93–97]</td>
<td></td>
</tr>
<tr>
<td>Ehrlich-Hunt score or modified Ehrlich-Hunt score</td>
<td>Histological analysis</td>
<td>Histological score estimating inflammatory cells, fibroblasts, neovascularization and collagen content on a scale from 0 to 4 [98, 99]</td>
<td></td>
</tr>
<tr>
<td>Collagen ratio I/III</td>
<td>Histological or biochemical extract analysis (qPCR)</td>
<td>Increased content of collagen III indicates formation of granulation tissue/regeneration/tissue repair [100]</td>
<td></td>
</tr>
<tr>
<td>MMP 2.9 and/or 13 level</td>
<td>Histological or biochemical extract analysis (zymogram or qPCR)</td>
<td>Increased MMP level during tissue repair [94, 100–102]</td>
<td></td>
</tr>
<tr>
<td>Sirius red staining</td>
<td>Histological analysis</td>
<td>Histochemical collagen staining</td>
<td></td>
</tr>
<tr>
<td>α-SMA</td>
<td>Histological analysis</td>
<td>Specific detection of α-SMA occurring in granulation tissue</td>
<td></td>
</tr>
<tr>
<td>Estimation of neangiogenesis</td>
<td>Histological analysis</td>
<td>Estimation of neangiogenesis in a systematical and/or blinded way; reflects tissue repair</td>
<td></td>
</tr>
<tr>
<td>Estimation of fibroblast proliferation</td>
<td>Histological analysis</td>
<td>Estimation of fibroblast proliferation in a systematical and/or blinded way; reflects tissue repair</td>
<td></td>
</tr>
<tr>
<td>Histological evaluation</td>
<td>Histological analysis</td>
<td>Simple histological evaluation in a systematical and/or blinded way</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Animal Type</td>
<td>Type of Anastomoses</td>
<td>Observation Time, days</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Senol et al. [55]</td>
<td>Rats (n = 40)</td>
<td>Colon</td>
<td>10</td>
</tr>
<tr>
<td>Subhas et al. [56]</td>
<td>Rats (n = 70)</td>
<td>Colon</td>
<td>3, 5</td>
</tr>
<tr>
<td>Pantelis et al. [57]</td>
<td>Mice (n = 206)</td>
<td>Colon</td>
<td>2, 5, 14</td>
</tr>
<tr>
<td>Wang et al. [58]</td>
<td>Pigs (n = 63)</td>
<td>Small intestine</td>
<td>10</td>
</tr>
<tr>
<td>Yilmaz et al. [61]</td>
<td>Rats (n = 48)</td>
<td>Colon</td>
<td>4</td>
</tr>
<tr>
<td>Saclarides et al. [60]</td>
<td>Rats (n = 69)</td>
<td>Ileum</td>
<td>7</td>
</tr>
<tr>
<td>Li et al. [59]</td>
<td>Rats (n = 360)</td>
<td>Ileum</td>
<td>1, 3, 5</td>
</tr>
<tr>
<td>van der Vijver et al. [62]</td>
<td>Rats (n = 108)</td>
<td>Ileum and colon</td>
<td>3, 5, 7</td>
</tr>
<tr>
<td>Akgun et al. [63]</td>
<td>Rats (n = 38)</td>
<td>Colon</td>
<td>3</td>
</tr>
<tr>
<td>Ozel et al. [64]</td>
<td>Rats (n = 36)</td>
<td>Colon</td>
<td>3, 7</td>
</tr>
<tr>
<td>Van der Ham et al. [65]</td>
<td>Rats (n = 120)</td>
<td>Colon</td>
<td>2, 4, 7</td>
</tr>
<tr>
<td>Van der Ham et al. [66]</td>
<td>Rats (n = 120)</td>
<td>Colon</td>
<td>2, 4, 7</td>
</tr>
<tr>
<td>Van der Ham et al. [67]</td>
<td>Rats (n = 120)</td>
<td>Colon</td>
<td>2, 4, 7</td>
</tr>
<tr>
<td>Van der Ham et al. [68]</td>
<td>Rats (n = 90)</td>
<td>Colon</td>
<td>2, 4, 7</td>
</tr>
<tr>
<td>Van der Ham et al. [69]</td>
<td>Rats (n = 90)</td>
<td>Colon</td>
<td>2, 4, 7</td>
</tr>
</tbody>
</table>
mechanical end points [62, 64–68] and only 1 study found a negative effect on bursting pressure [69]. On the contrary, all of the 7 studies that reported a positive effect on healing also showed a positive effect on the mechanical end points [55–61].

These results are in line with those from other studies on sealing of gastrointestinal anastomoses with FG [47, 48] that were not included in the present review due to a lack or inadequate evaluation of healing. The results from these studies are inconsistent, but a number of
human and experimental studies have revealed positive effects on anastomotic leakage, bursting pressure or anastomotic strength. In a randomized study on esophageal anastomoses in infants born with esophageal atresia, a significantly reduced incidence of anastomotic leakage and stricture was found in the group sealed with FG [85]. Two human studies on FG sealing of anastomoses in patients with Roux-en-Y gastric bypass found a nonsignificantly decreased incidence of anastomotic leakage in the sealing group [86, 87]. Another human study on anastomotic leakage after laparoscopic resection of rectal cancer found a leakage rate of 5.8% in the FG-sealed group compared with 10.9% in the nonsealed group. However, this difference was not statistically significant [88]. Beside the studies included in this review, other experimental studies have examined the mechanical effect of sealing with FG. In a model of anastomotic leakage of stapled gastrojejunostomy made on swine, a significantly reduced anastomotic leakage and abscess rate was found in the group sealed with FG compared with controls [89], and a comparable study found similar results [90].

The current evidence, in combination with the results of the present review, indicates that the potential positive effect of sealing is most likely due to a physical/mechanical effect and not due to improved healing of the anastomosis. This is in line with other suggested hypotheses on the strength of sealed anastomoses. In a study on rat esophagus anastomoses, it was found that increased anastomotic strength was mainly due to a mechanical strengthening of the anastomoses by the sealant [80]. Four of the studies analyzed in this review emphasize that FG, besides its adhesive properties, is water-resistant and thus constitutes a physical barrier around the anastomosis [59, 70, 75, 76]. Another study found that sealing of colonic anastomoses in rats with FG had a negative effect on healing but a positive effect on bursting pressure and anastomotic strength, suggesting that this may be due to the closure of microperforations [63].

The present paper has certain limitations. No bias assessment of the individual studies was performed in this review. Suitable tools for bias evaluation of studies exist for human

### Table 3. Type of anastomoses, animals and FG associated with sealing effects

<table>
<thead>
<tr>
<th>Conclusion of study</th>
<th>Studies, n</th>
<th>Anastomotic sites</th>
<th>Animals</th>
<th>Types of FG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive effect [55–61]</td>
<td>7</td>
<td>Colon: 4 Small intestine: 3 Esophagus: 0</td>
<td>Mice: 1 Rat: 5 Rabbit: 0 Pig: 1</td>
<td>Mesh-bound: 1 Liquid: 6</td>
</tr>
<tr>
<td>Negative effect [62–69]</td>
<td>8</td>
<td>Colon*: 8 Small intestine*: 1 Esophagus: 0</td>
<td>Mice: 0 Rat: 8 Rabbit: 0 Pig: 0</td>
<td>Mesh-bound: 1 Liquid: 7</td>
</tr>
<tr>
<td>No effect [54, 70–79]</td>
<td>11</td>
<td>Colon: 9 Small intestine: 2 Esophagus: 0</td>
<td>Mice: 0 Rat: 9 Rabbit: 1 Pig: 1</td>
<td>Mesh-bound: 2 Liquid: 9</td>
</tr>
<tr>
<td>Unclear [80, 81]</td>
<td>2</td>
<td>Colon: 0 Small intestine: 0 Esophagus: 2</td>
<td>Mice: 0 Rat: 1 Rabbit: 1 Pig: 0</td>
<td>Mesh-bound: 1 Liquid: 1</td>
</tr>
</tbody>
</table>

* One study on both the colon and small intestine.
interventional and observational clinical studies [91]. However, there are no validated methods for experimental studies. An important limitation of this review may be the high degree of heterogeneity between the studies with regard to the evaluation of healing, study design and outcome measures. The microscopical healing was not the primary end point in any of the studies. Hence, this was sparsely and occasionally unsystematically described, and a meta-analysis was not possible. Such heterogeneity is known to limit the comparability of studies, which may be reflected in the conflicting results reported in the included studies [91].

Publication bias is present for all types of study designs, but it is almost four times more common in experimental studies than in randomized controlled trials [92]. Thus, the experimental design of the included studies may be subject to a high degree of publication bias, which may overestimate the effect of FG. Therefore, despite the high proportion of studies reporting negative results included in the present review, this proportion may even be higher in the absence of publication bias. However, as we did not perform a meta-analysis with funnel plots, the degree of publication bias remains unknown. In general, selection bias is less common in experimental interventional studies due to a high degree of similarity between the animals compared with patients in clinical trials. Moreover, 61% of the included studies were randomized, which further minimizes the risk of selection bias. Another limitation is that the studies did not compare similar kinds of sealing but only compared sealing with or without FG. Thus, it remains unclear if the effect on macroscopical healing, e.g. bursting pressure, was due to a formation of adhesions around the anastomoses as a result of the sealing, or due to FG per se. Finally, none of the studies was performed on humans, which must be considered a limitation for clinical applicability.

From the present review, we conclude that FG does not have a consistent positive influence on the healing of gastrointestinal anastomoses. If FG has such an effect, this effect might be impaired by an infected environment such as in the colon. It is consequently plausible that the positive effect of FG sealing of gastrointestinal anastomoses, if there is any, is due to a mechanical sealing influence and not due to improved healing per se. Thus, future research on sealing with FG could focus on the mechanical properties of the sealing.

**Disclosure Statement**

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