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The Use of Autologous Fibrin Glue (AFG) in Bowel Anastomosis: A Systematic Review and Meta-Analysis

Reno Rudiman [1], Prapanca Nugraha [1*], Andhika Rahmawan [1], Ardine Yew Siswanto [1], Muhammad Faiz Ulurrosyad [1], Kiki Lukman [1]
Department of Surgery, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.

* Corresponding Author: **Prapanca Nugraha**

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Abstract
Introduction: Postoperative anastomosis leaks (AL) are still common and serious complications of lower colorectal surgery in that they are a major cause of mortality and morbidity from the procedure. Liquid-based fibrin sealants have also been studied to prevent intestinal leakage after anastomosis. The aim of this review is to learn about the use of autologous fibrin glue (AFG) in bowel anastomosis written in the form of a systematic review.
Methods: This research is qualitative research with a research methods systematic review. Researchers obtained sources taken from electronic search engines via PubMed, Google Scholar and ScienceDirect using the keywords “Fibrin glue or Fibrin Sealant for Bowel Anastomosis or Surgery " based on inclusion and exclusion criteria set by author. This research was conducted based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.
Result: In the meta-analysis examining the effects of fibrin glue on anastomosis complications, including leak, fistula, and bleeding, the findings suggest no significant impact of fibrin glue. The relative risk (RR) for anastomosis leak was 0.92 (95% CI: 0.67 - 1.25, p = 0.58), indicating no substantial difference between the fibrin glue group and controls. Similarly, the RR for fistula was 0.64 (95% CI: 0.35 - 1.17, p = 0.15), and for bleeding, it was 0.68 (95% CI: 0.12 - 3.83, p = 0.66), neither reaching statistical significance.
Conclusion: Although it is difficult to conclude from the currently available evidence provided in this analysis, the use of AFG in bowel anastomosis is promising to improve clinical outcomes, reduce mortality and postoperative complications. Nevertheless, further research in humans with larger sample sizes is necessary to determine the benefits and superiority of AFG, as well as to establish a clinical recommendation of its usage.

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Keywords: Anastomosis leakage, Autologous Fibrin Glue, Bowel Anastomosis

1. Introduction

Bowel resection surgery is the removal of part or all of the intestine, depending on the underlying cause of the disease that needs to be removed. General indications for resection of the colon are colorectal malignancies, and resection should be carried out based on oncological principles, namely the resection limit of 5 cm proximal and distal from the tumor for colon malignancy, circumferential resection limit for the rectum, sufficient distal limit of 2 cm, removal of blood vessels and lymphatic channels at major level allowing resection of locoregional lymph node mesentery for healing and staging, Formation of well-vascularized and tension-free anastomosis.

The bowel proximal and distal from the resection must be mobilized to allow tension-free anastomosis, and the anastomosis must have a good blood supply [1, 2]. Intestinal resection surgery complications are still common, one of which is postoperative anastomosis leaks (AL) [3, 4, 5]. Postoperative anastomosis leaks (AL) are still common and serious complications of lower colorectal surgery, in that they are a major cause of mortality and morbidity from the procedure. Anastomotic leaks have been extensively studied, but it is uncertain whether their incidence will decrease over time. The incidence of anastomotic leak varies depending on the location of the anastomosis, but studies have ranged from 3% to 29% for the colon and 8% to 41% for the rectum. Patients who experience AL have a significant increase in morbidity of up to 56% and have a functional outcome from the gastrointestinal tract. AL after colorectal resection contributes to a mortality rate of 6-22%. Morbidity and sequelae pose challenges to management for both patients and operators. Several techniques have been developed to reduce leaks after anastomosis. Physical reinforcement of the anastomosis with a filling material is a readily available method that is frequently used to prevent anastomotic leakage. In addition, interactions between the gut microbiome and anastomotic healing have been investigated as a means of manipulating the microbiota environment to reduce leakage rates. Although no single technology has succeeded in eliminating leaks yet, understanding these emerging fields will be important for all surgeons who will operate on the gastrointestinal tract. Liquid-based sealants have also been studied to prevent intestinal leakage after anastomosis [6, 7, 8, 9]. The use of fibrin sealants to reduce anastomotic leaks has been studied for more than 30 years. Fibrin is a biological polymeric protein that is the final complex chemical product after thrombin lyses plasma fibrinogen. The fibrin clot is resistant to tension and compression but is also porous to cytokines and some other proteins. In addition, these polymers also facilitate the passage of immune cells. Fibrin can be recovered from donated plasma and cannot trigger an immune response when purified. This product can trigger procoagulant cell healing and aggregation for the process of hemostasis. Fibrin was first approved in 1998 by the FDA as a hemostatic agent and is used in many surgical procedures. Fibrin sealant contains fibrin and thrombin, which are inserted into two syringes with ends that form a single unit. This formulation is designed to mimic the natural processes of hemostasis and wound healing and aid in surgical incision closure. In several European countries, biologic fibrin-based adhesives have been approved in clinical practice for many indications to achieve postoperative hemostasis and tissue recovery. Several studies have also been conducted regarding the relationship between the use of fibrin sealants to close the anastomosis in colorectal surgery. However, studies regarding the efficacy and postoperative complications of using fibrin sealants have yet to be widely studied. In addition, until now there is no one technique that is superior to other techniques in dealing with bowel leaks after anastomosis. The aim of this review is to learn about the use of autologous fibrin glue (AFG) in bowel anastomosis written in the form of a systematic review.

2. Methods

2.1 Database and Literature Search

We searched for articles in PubMed, EuropePMC, Google Scholar, Cochrane Library, and ClinicalTrials.gov using the following keywords: ["fibrin glue" AND "anastomosis"] from 2013 to 2023. Two authors (P.N. and A.R.) did the initial search and screening for eligible papers. Any discrepancies were resolved by discussion with the other authors.

2.2 Selection Criteria

The inclusion criteria were: 1) type of patients: patients undergoing bowel anastomosis surgery; 2) type of intervention: use of AFG in bowel anastomosis; 3) type of comparison: use of non-AFG in bowel anastomosis; 4) analyzed outcomes: post-operative complications; 5) types of studies: randomized and non-randomized prospective and retrospective studies. Studies that did not provide the aforementioned criteria were excluded. We also excluded review articles, editorials, case reports, and case series.

2.3 Data Extraction and Synthesis

After the studies were selected, two authors independently extracted the data on authors, year of publication, study design, country of origin, number of patients, age, sex, indication, initiation of diet, time of anastomosis, length of hospitalization, and postoperative complication. When data from any synthesis points were not found in the literature, the researcher's writing was not available (NA) for data collection.

2.4 Statistical Analysis

We compared the outcome between AFG and non-AFG groups using odds ratios (OR) and 95% confidence intervals (CI). Heterogeneity among studies was evaluated using the I^2 statistic and Cochrane Q-statistic test. An I^2 value higher than 40% indicated a significant presence of heterogeneity.

We assessed the risk of bias using the Newcastle Ottawa Scale (NOS) for cohort studies. We used a funnel plot analysis to assess publication bias. We used the Review Manager version 5.4 (The Cochrane Collaboration) (https://training.cochrane.org/online-learning/core-software/revman/revman-5-download) program for all statistical analysis. We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. This review has been registered at The International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024522394.

3. Results

3.1 Study Selection and Characteristics

The PRISMA diagram outlined the process of identifying studies through databases and registers. Initially, a total of 3793 records were identified from PubMed (n = 79), Google Scholar (n = 3250), Cochrane library (n = 9), Europe PMC (n = 405), and Clinicaltrials.gov (n = 5). Among these, 373 duplicate records were removed prior to screening. During the screening phase, a total of 3375 records were screened, resulting in the exclusion of 3325 records. Fifty reports were sought for retrieval, and all were successfully retrieved. These 50 reports were then assessed for eligibility, with 14 studies ultimately being included in the review. The reports excluded during eligibility assessment were those not in English (n = 3), meeting abstracts (n = 4), feasibility reports (n = 5), technical notes (n = 6), literature reviews (n = 3), expert opinions (n = 3), and those that did not report the key outcome (n = 12). The PRISMA Flow Diagram of this study can be seen in Figure 1

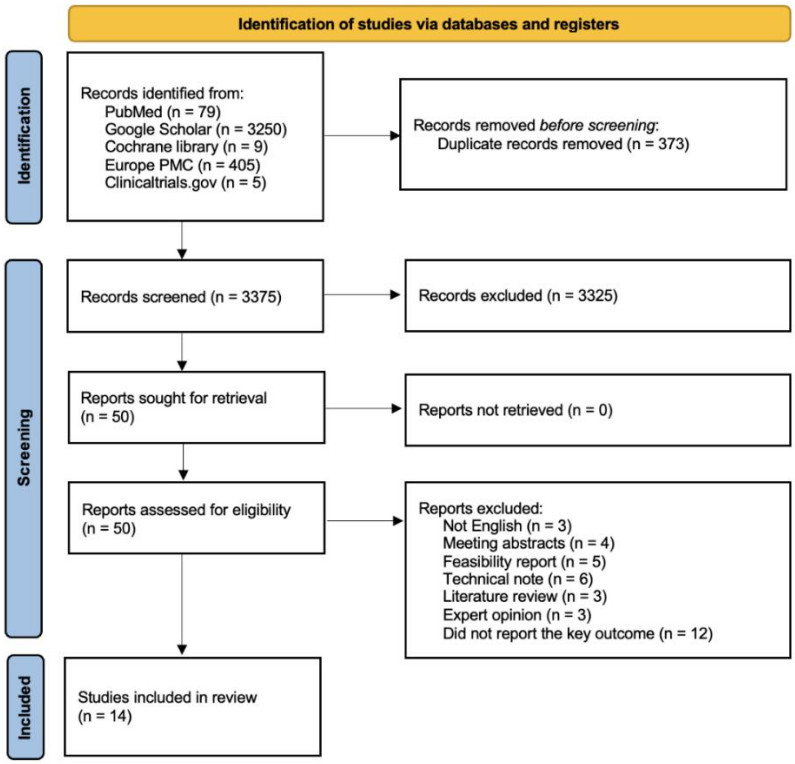

Fig 1: PRISMA flow Diagram

The characteristics of included studies (**table 1**) in a human population, totaling 1714 individuals, present a diverse array of findings. Across these studies, the representation of males fluctuates, with percentages ranging from as low as 17.8% to as high as 73%. The primary indication under investigation across these studies is malignancy, with rates varying between 37% and 75%. The initiation of diet post-surgery ranged from 3 ± 0.8 days to liquid diet initiation on the second postoperative day, depending on the specific study. Time of anastomosis ranged from 25 ± 3.5 minutes to 9 minutes, with some studies not specifying this parameter. Length of hospitalization varied widely, with averages ranging from 2.6 days to 22.1 days, and ranges extending from 5 to 81 days. The postoperative complications encompass leaks (8.6%), wound seroma (5.7%), bleeding (1.7%), anastomotic leak (0.5%), anastomotic stricture (11.3%), fistula (17.9%), biochemical leakage or fistula (59.9%), steatorrhea, diarrhea, and hypoalbuminemia. Specific findings include a leakage rate of 14.03%, with higher rates observed in the Tisseel group compared to the control group. Pancreatic fistula was noted in 25.8% of patients in the intervention group and 37.1% in the control group.

Table 1: Characteristics of Included Studies in Human Population

Author	Year	Study Design	N	Age	Male (%)	Indication	Initiation of Diet (days)	Time of Anastomosis (min)	Length of Hospitalization (days)	Postoperative complication
Seida & Gharib [13]	2015	Prospective	35	31-72	71.4	Malignancy (71.4%)	3 ± 0.8	25 ± 3.5	5 ± 1.7	Leaks (8.6%) and wound seroma (5.7%)
Kotzampassi & Eleftheriadis [14]	2015	Prospective	63	27-76	37	Malignancy	NA	9	8-32	NA
Ibele, *et al.* [15]	2014	Retrospective	425	NA	64	Malignancy	NA	NA	2.6	Bleeding (1.7%), anastomotic leak (0.5%), and anastomotic stricture (11.3%)
Inthasotti, *et al.* [16]	2018	Prospective	67	NA	44% in the N-butyl-2-cyanoacrylate glue group and 45.2% in the control group	Malignancy	NA	NA	7-60 days in the -butyl-2-cyanoacrylate glue group and 5-45 days in the control group	Fistula (17.9%)
Schindl, *et al.* [17]	2018	Prospective	142	≥18 years	47.9% in the patch group, 46.4% in the control group	NA	NA	NA	Mean duration of hospital stay was 22.1 days in the patch group and 18.2 days in the control group	Biochemical leakage or fistula (59.9%)
Alfieri, *et al.* [18]	2018	Prospective	32	≥18 years	56% in the pancreatico-jejunostomy	Malignancy	NA	NA	NA	Steatorrhea and diarrhea, hypoalbuminemia

					group, 75% in the pancreatic duct occlusion group					
Sdralis, *et al.* [19]	2019	Prospective	57	≥18 years	71.4% in the control group, 72.7% in the Tissel group	Malignancy	NA	NA	7-81 days	Leakage 14.03%. In the Tisseel group, 22.7% leaks, while 8.6% leaks in the control group.
Kwon, *et al.* [20]	2019	Prospective	126	19-80	67.7% in the intervention group, 59.7% in the control group	Malignancy	NA	NA	11.6 days in the intervention group and 12.1 days in the control group.	Pancreatic fistula in 25.8% of patients in the intervention group and 37.1% in the control group.
Plat, *et al.* [21]	2019	Prospective	15	43-76	73%	Malignancy	NA	NA	6-80 days	Leakage in 2 out of 15 cases (13.7%), and one patient suffered a grade III leak (6.7%). Pulmonary Complications: Pulmonary complications, unrelated to leakage of the anastomosis, occurred in 3 out of 15 patients (20%).
Younis, *et al.* [22]	2020	Retrospective	17	41 ± 11 years (range 23–57) in the postoperative leak group. 49 ± 14 years (range 24–65) in the postoperative stricture group	NA	Leaks and strictures	NA	NA	NA	Leakage in 44% and stricture in 12%.
Uccelli, *et al.* [23]	2020	Retrospective	450	18-65	32.4% totally. 41% in Group A (Fibrin Glue reinforcement), 30.6% in Group B (without Fibrin Glue Reinforcement), there were 114 males out of 372 patients.	Morbid obesity	Liquid diet on the second postoperative day if there were no signs of leakage	NA	3.5 ± 2.5 days (range 3.0–43.0 days).	Overall rate of reoperation due to leaks was 2.2%. Bleeding occurred in 2% of patients with no significant difference between Group A and Group B. No Grade IVb or Grade V complications reported.
Gaspar, *et al.* [24]	2021	Retrospective	62	NA	58.1% in the group without fibrin sealant (GWOS), 45.1% in the group with fibrin sealant (GWS)	Malignancy	NA	NA	Mean of 16.39 days in the GWOS group, 19.3 days in the GWS group	Pancreatic fistula in 29% in the GWOS group and 19% in the GWS group
Fukami, *et al.* [25]	2022	Prospective	133	NA	NA	Malignancy	NA	NA	18 (8–138) days in the without PGA group. 14 (8–104) days in the with PGA group.	CR-POPF in 49% patients in the without-PGA group and 6% in the with-PGA group (P < .001). All CR-POPF patients had grade B POPF. Zero mortality in both groups 90-day postoperative: Zero mortality in both groups
Dolan, *et al.* [26]	2023	Retrospective	90	NA	17.8% in the endoscopy group, 17.8% in the surgery group	Gastrogastric-fistula (GGF)	NA	NA	NA	Treatment-related adverse events in 8.9% endoscopy group and 35.6% in the surgery group, with 17.8% in the surgery group classified as serious. Specific complications in the SURG group included leak (4), abdominal hernia (3), abscess (3), severe abdominal pain (3), gastrointestinal bleeding (1), small bowel obstruction (1), and gastrojejunal anastomotic stricture (1). Among AEs in the SURG group, the open surgical technique

										was associated with three abdominal hernias, two leaks, one severe abdominal pain, and one small bowel obstruction. The remainder of AEs in the surgical group occurred using the laparoscopic technique.

In vivo studies characteristics are summarized in Table 2, in which several findings were obtained regarding the use of fibrin glue for bowel anastomosis. A study by Gerogiannis, *et al.* [16]. It was found that there was no statistical difference between the groups with and without fibrin glue regarding the amount of tissue adhesion, the presence of peritonitis, and bursting pressure, and the hydroxyproline levels in the FG group had high levels and the rate of angiogenesis in the FG group was 90%. A study by Christodoulidis, *et al.* [17]. obtained a mortality rate of 6.7%, leakage rate of 13.3%, no adhesion of 35.7%, adhesion I-II Zuhlke of 40%, adhesion III Zuhlke of 20%, and adhesion IV Zuhlke of 0%. A study by Kara & Ulualp [18] found that the average bursting pressure was 107.77 ± 23.21, the average hydroxyproline level was 13.61 ± 15.94, but there was no statistical difference between inflammatory cells, neutrophil levels, neovascularization, fibroblastic activity, and collagen fibers. A study by Zulfikar, *et al.* [19] found that the average hydroxyproline level was 2224.59 and the ANOVA test on hydroxyproline level samples showed that $p < 0.05$, which means that there was no statistically significant difference in hydroxyproline levels in the group with fibrin glue and not given fibrin glue. The study by Daglioglu, *et al.* [20]. found that there was no statistical difference in anastomotic bursting pressure and hydroxyproline levels in the group given platelet-rich plasma and fibrin glue as well as levels of pro-inflammatory cytokines (IL-6), anti-inflammatory cytokines (IL-10), and procalcitonin.

Table 2. Characteristics of Included Studies in Animal (*In vivo*)

Table 2: Characteristics of Included Studies in Animal (*In vivo*)

Author	Year	Study Design	Country	N	Findings
Gerogiannis, *et al.* [27]	2022	*In vivo*	United Kingdom	20	• No statistical difference between the group with and without FG regarding the numbers of tissue adhesions, presence of peritonitis and bursting pressure. • The levels of hydroxyproline in FG group were having higher level. • The levels of angiogenesis 90% in FG group
Christodoulidis, *et al.* [28]	2021	*In vivo*	Greece	15	• Mortality rate (6.7%) • Leakage (13.3%) • No adhesions (35.7%) • Adhesion I-II Zuhlke (40%) • Adhesion III Zuhlke (20%) • Adhesion IV Zuhlke (0%)
Kara & Ulualp [29]	2020	*In vivo*	Turkey	20	• Mean bursting pressure 107.77±23.21 • Mean hydroxyproline levels13.61±15.94 • The comparison of the inflammation cells, neutrophils levels, neovascularization, activity of fibriblastic, and collagen fibers was no significant difference
Zulfikar, *et al.* [30]	2021	*In vivo*	Indonesia	27	• Hydroxyproline levels 2224.59 • ANOVA test in hydroxyproline levels samples showed that P < 0.05 means that there is statistically significant difference in level of hydroxyproline in all group
Daglioglu, *et al.* [31]	2018	*In vivo*	Turkey	36	• No statistical differences of anastomotic bursting pressure and levels of hydroxyproline between platelet rich plasma and fibrin glue • No statistical difference between proinflammatory cytokine (IL-6), anti-inflammatory cytokine (IL-10) and procalcitonin levels
Daglioglu, *et al.* [32]	2018	*In vivo*	Turkey	36	• There were no significant differences in baseline weight values between the groups. • Mean body weights decreased in all groups during the study, but there were no statistical differences among them. • No local or systemic complications related to PRP and fibrin glue application were observed. • Anastomotic bursting pressure (ABP) and tissue hydroxyproline levels did not significantly differ between the PRP and fibrin glue groups. • Levels of proinflammatory cytokine (IL-6), anti-inflammatory cytokine (IL-10), and procalcitonin did not significantly differ between the groups. • Parameters related to wound healing, such as inflammatory infiltrations, capillary vascularization, and fibroblastic infiltration, showed no significant differences between the PRP and fibrin glue groups. • Collagen formation and inflammatory cell counts did not significantly differ between the groups. • Fibroblast density and neovascularization were similar between the PRP and fibrin glue groups.
Garcıa-Vasquez, *et al.* [33]	2018	*In vivo*	Spain	30	• Significant increases in HIF-1a and NF-jB-p65 expression were observed in uncovered anastomosis compared to normal tissue. • HIF-1a expression became cytoplasmic in all compartments with the Tachosil patch, with a significant reduction in nuclear expression. • There were no significant differences in NF-jB expression due to the patch. • Cytoplasmic expression of HIF-1a was associated with more intense inflammatory infiltrates. • NF-jB-p65 expression was significantly more intense in endothelial cells of the surgical bed.
Ozdenkaya, *et al.* [34]	2019	*In vivo*	Turkey	14	• Histopathologic examination showed significantly higher collagen deposition in the study group (FG applied) compared to the control group.

					• No significant differences were observed in inflammation, fibroblastic activity, neo-angiogenesis, or burst pressures between the study and control groups. • All surgical procedures were successful without complications, and there were no signs of leak in the resected specimens or intraabdominal findings. • Statistical analysis revealed a significantly higher mean score for collagen deposition in the study group compared to the control group. However, burst pressures did not significantly differ between the two groups.
Wenger, *et al.* [35]	2019	*In vivo*	Germany	40	• Length of resected colorectal tissue and location of anastomoses were similar in both groups. • In the control group, 20% (n=4) animals had anastomotic leakage (AL) confirmed via macroscopic examination, presented clinical signs. In the treatment group, there were no clinically apparent AL; 3 out of 20 animals had ulcerative lesions without clinical signs, sealed by sealant. • Treatment group had decreased rate of clinically apparent AL compared to control (4 vs 0) over a 21-day postoperative period. • Necrosis observed at the site of AL in control group; normal healing of anastomosis in treatment group. • In treatment group, animals identified with partial wall defects (ulcerations) at intersection point of staple lines. • Fistula observed in one animal in treatment group; healed ulcerative lesion and lesion on luminal side observed in other animals, sealed by sealant.
Hadavi, *et al.* [36]	2019	*In vivo*	Iran	36	• Significant differences were observed between the two groups, Control (C) and Study (S) in terms of the healing process ($p = 0.016$). • During the second exploration, leakage was observed in 83% of group S rats compared to 17% of group C rats. • Group S rats exhibited more small bowel peristaltic activity compared to group C rats. Group S showed more acute inflammatory cells, possibly due to continuous leakage leading to peritonitis and subsequent death. • Group C had more chronic inflammatory cells, fibroblast proliferation, and collagen formation, indicating progression to later healing stages. • Neoangiogenesis was more common in group S, while more collagen production occurred in group C. • Intravascular thrombosis, acute ileitis, gangrenous bowel, microscopic peritonitis, vasculitis, and hypersensitivity reaction were observed. TachoSil caused severe inflammatory reaction and adhesion in group S.
Kara, *et al.* [37]	2020	*In vivo*	Turkey	50	• Duraseal® demonstrated advantages such as easy preparation, good mechanical strength, and usability in moist conditions. • Fibrin glue (FG) showed positive effects on wound healing and hemostasis. • Duraseal® and FG significantly increased bursting pressures in both normal and ischemic colon anastomoses compared to control groups. • Mean bursting pressures were higher in Duraseal® groups but not significantly different from FG groups. • Hydroxyproline levels were significantly lower in Duraseal® groups compared to FG groups. • Comparison of inflammatory cells, neutrophils, neovascularization, fibroblastic activity, and collagen fibers showed no significant differences between groups. • Duraseal® and control groups had irregular collagen alignment despite similar collagen content. • Some rats died before postoperative day four, but autopsy showed no signs of macroscopic anastomotic leak or peritonitis. • No macroscopic leaks were observed in rats sacrificed at postoperative day four.
Stergios, *et al.* [38]	2020	*In vivo*	Greece	40	• Two rats developed significant hematochezia postoperatively, leading to re-operation. Both rats had partial bowel necrosis, with one rat recovering completely after re-operation, while the other succumbed to the procedure. • Tissue analysis revealed that the application of TISSEEL® led to improved tissue remodeling compared to the control group. • The Ehrlich-Hunt model showed significantly better results in the TISSEEL® group, with decreased inflammation and improved fibroblast and collagen formation. • Neovascularization was significantly increased in diabetic rats treated with TISSEEL® compared to those without treatment.
Christodoulidis, *et al.* [39]	2021	*In vivo*	Greece	30	• In the control group, an additional severe inflammatory reaction due to leakage was observed in two more animals. • In the group treated with Tachosil®, an intra-abdominal abscess due to leakage was detected in one rabbit. • There was no statistically significant difference in postoperative leakage between the two groups. • Adhesions were most commonly identified in the right upper quadrant of the abdomen. • Adhesions were present in 46.6% of animals in the control group and in 42.8% of animals in the Tachosil® group. • There was a statistically significant difference regarding the presence of adhesions between the two groups. • Histopathological evaluation showed inflammation, revascularization, and fibroblasts in the samples of both groups, with normal mucosal and serosal continuity in all surviving models.
Zulfikar, *et al.* [40]	2021	*In vivo*	NA	33	• The average age and body weight of rats in the three groups were comparable. • The hydroxyproline levels were significantly different among the three groups. • Group II (anastomosis with dry amniotic membrane) showed the highest hydroxyproline levels, indicating superior healing compared to the other groups. • There was no significant difference between Group I (control) and Group III (anastomosis with fibrin glue) in terms of hydroxyproline levels.

Fathurochman, *et al.* [41]	2021	*In vivo*	Indonesia	40	• Signs of inflammation and cloudy intraperitoneal fluid were observed post-peritonitis induction. • Microbiological examination revealed a mixture of aerobic and anaerobic bacteria, with Escherichia coli being dominant. • Mortality rates were observed in all groups, with deaths attributed to anastomotic leak. • The average age and body weight of the rats were similar across all treatment groups. • Hydroxyproline levels were significantly different among the treatment groups, with higher levels observed in groups where fibrin glue was used during anastomosis. • Post Hoc ANOVA tests revealed statistically significant differences in hydroxyproline levels between groups, indicating the effectiveness of fibrin glue in increasing tissue hydroxyproline levels, particularly in groups undergoing continuous knot sutures and simple knot sutures with the addition of fibrin glue.
Dorkhani, *et al.* [42]	2022	*In vivo* and *In vitro*	Iran	20	• *In vitro*: Scanning electron microscope (SEM) images revealed that the PVA film with oriented distribution of gelatin exhibited continuous and integrated phase separation, potentially leading to enhanced adhesion properties. PVA films with low molecular weight demonstrated higher swelling ratio and degradability compared to those with high molecular weight, indicating different mechanical properties. Cell viability on PVA films increased until day seven and decreased on day 14, suggesting degradation of low molecular weight PVA. Incorporation of gelatin increased surface roughness and porosity, with gelatin-modified films exhibiting higher total pore volume and surface area. PVA films with oriented gelatin distribution showed the highest mechanical properties and adhesion due to continuous morphology, potentially suitable for tissue repair engineering. • *In vivo*: Animals showed good clinical condition with no complications, and the PVA sealant degraded successfully after seven days. Immunohistochemistry staining revealed lower TNF-α expression and higher collagen deposition in the scaffold group compared to the control group on days 3 and 7 post-operation. The scaffold group demonstrated significantly lower TNF-α expression and NF-κB factor levels compared to the control group on days 3 and 7 post-operation. Expression of IL-10 and TGF-β as anti-inflammatory cytokines was significantly higher in the scaffold group on day 7 post-operation
Gerogiannis, *et al.* [43]	2022	*In vivo*	Greece	20	• The application of FG (fibrin glue) on the suture line during ileoileal anastomosis did not significantly affect the number of adhesions, presence of peritonitis, or bursting pressure regardless of the type of anastomosis. • There was a trend towards significance (p=0.064) in the hydroxyproline levels between the control group and the FG group, with the FG group showing higher levels. • Statistically significant differences were observed in angiogenesis levels between the control group and the FG group, with a higher proportion of animals in the FG group exhibiting higher levels of angiogenesis (90% vs. 50%, p=0.011). • Among animals that underwent complete anastomosis, there were no statistically significant differences between the control group and the FG group in terms of adhesions, bursting pressure, or hydroxyproline levels. However, significant differences were observed in angiogenesis levels, with a higher proportion of animals in the FG group showing higher levels of angiogenesis (80% vs. 20%, p=0.019). • For animals that had incomplete anastomosis, there were no statistically significant differences between the control group and the FG group in terms of adhesions, presence of peritonitis, bursting pressure, hydroxyproline levels, or neoangiogenesis. Additionally, there were no leaks observed in either group.
Yu, *et al.* [44]	2022	*In vivo* and *In vitro*	NA	NA	• *In vitro*: MSCs secretome boosted the viability of key cells involved in wound healing dose-dependently. • *In vivo*: Secretome/FG significantly improved the healing of surgical anastomosis in a rat model. The treatment with Secretome/FG resulted in increased body weight and fecal weight compared to other treatment groups. Anastomotic bursting pressure was increased significantly in the Secretome/FG group compared to the negative control and fibrin glue groups, indicating improved healing strength. Histological analysis showed increased thickness of granulation tissues and collagen deposition at the anastomotic site in the Secretome/FG group, indicating improved healing. Secretome/FG treatment led to enhanced cell proliferation, reduced cell apoptosis, and increased angiogenesis in anastomotic tissues. Secretome/FG treatment promoted M2 macrophage polarization and reduced inflammatory reaction in anastomotic tissues, creating a beneficial microenvironment for rapid healing.
Hasegawa, *et al.* [45]	2023	*In vivo*	Japan	NA	• Surgical procedures were uneventful, and the establishment of the bursting model was systematically reproduced in all anastomoses. • Anastomotic site reinforcement with the novel external coating device was successfully performed in all anastomoses. • In the control group, bursting pressure averaged 76.1 ± 5.7 mmHg with observed air leakage from the staple line in all anastomoses. • In the device group, bursting pressure averaged 126.8 ± 6.8 mmHg, significantly higher than the control group (p = 0.0006), with successful reinforcement in all anastomoses. However, in two out of three anastomoses, perforation was observed from the gastrointestinal tract on the mesenteric side instead of the staple line, resulting in mesenteric emphysema.

3.2 Meta-Analysis

In the meta-analysis examining the effects of fibrin glue on anastomosis complications, including leak, fistula, and bleeding, the findings suggest no significant impact of fibrin glue. The relative risk (RR) for anastomosis leak was 0.92 (95% CI: 0.67 - 1.25, p = 0.58), indicating no substantial difference between the fibrin glue group and controls. Similarly, the RR for fistula was 0.64 (95% CI: 0.35 - 1.17, p = 0.15), and for bleeding, it was 0.68 (95% CI: 0.12 - 3.83, p = 0.66), neither reaching statistical significance.

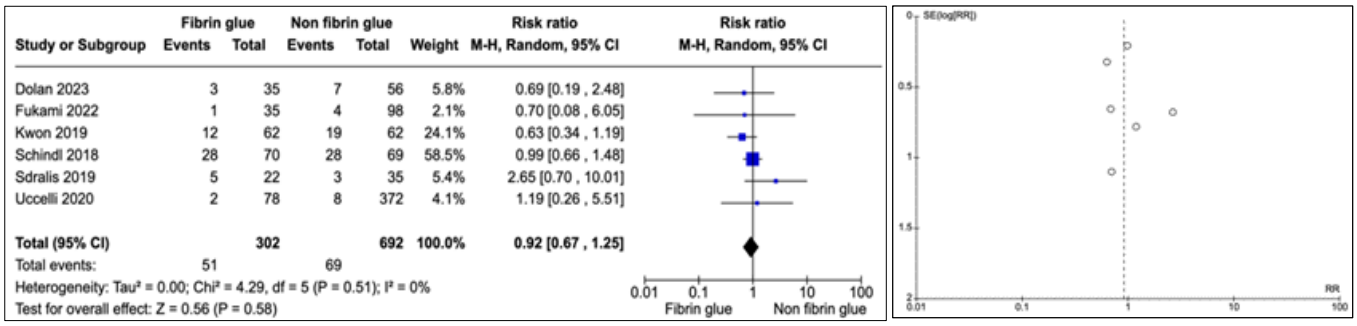

Fig 2: Forest plot for leakage between the fibrin flue and non-fibrin glue groups.

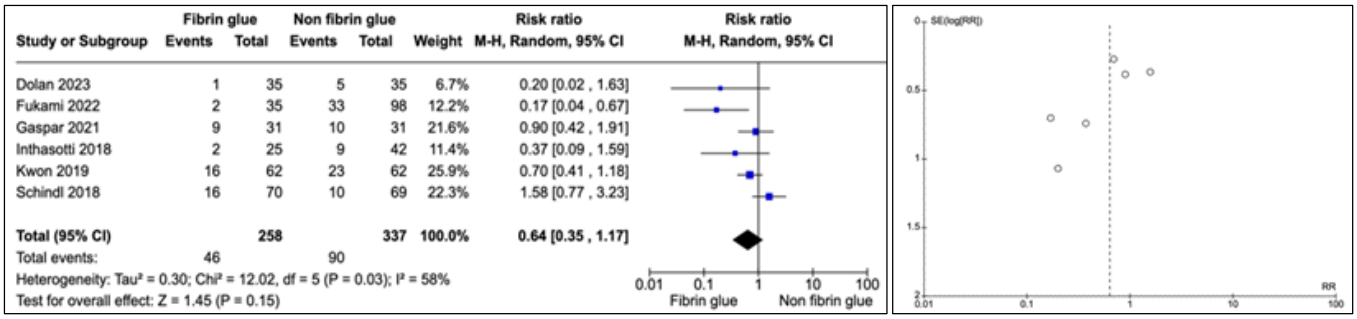

Fig 3: Forest plot for fistula between the fibrin flue and non-fibrin glue groups.

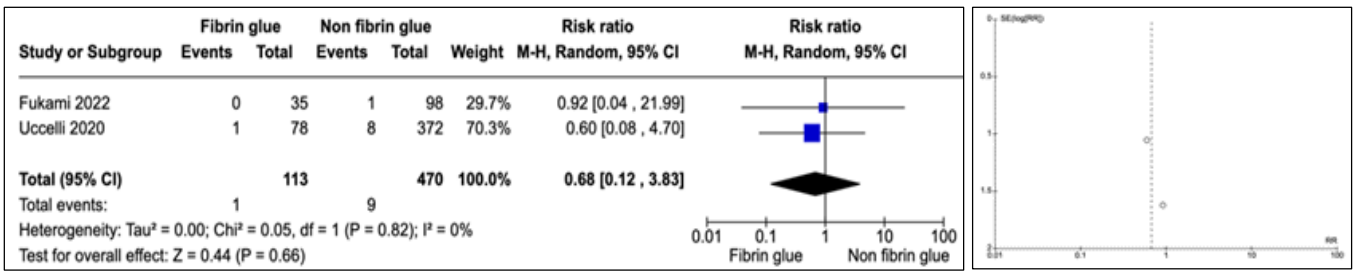

Fig 4: Forest plot for bleeding between the fibrin flue and non-fibrin glue groups.

3.3 Risk of Bias

Funnel-plot analysis showed a symmetrical funnel-plot. Each study's risk of bias was assessed using Newcastle Ottawa Scale (NOS). The majority of studies received a score of 7 or 8, indicating good quality. However, one study received a score of 6, indicating moderate quality. As shown in Table 3, both included studies are of good quality.

Table 3: Newcastle Ottawa Scale (NOS) quality assessment tool.

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Result
Seida & Gharib [13]	Prospective	****	*	***	8	Good
Kotzampassi & Eleftheriadis [14]	Prospective	****	*	***	8	Good
Ibele, *et al.* [15]	Retrospective	***	*	***	7	Good
Inthasotti, *et al.* [16]	Prospective	***	*	***	7	Good
Schindl, *et al.* [17]	Prospective	***	*	**	6	Moderate
Alfieri, *et al.* [18]	Prospective	****	*	***	8	Good
Sdralis, *et al.* [19]	Prospective	***	*	***	7	Good
Kwon, *et al.* [20]	Prospective	***	*	***	7	Good
Plat, *et al.* [21]	Prospective	****	*	***	8	Good
Younis, *et al.* [22]	Retrospective	****	*	***	8	Good
Uccelli, *et al.* [23]	Retrospective	****	*	***	8	Good
Gaspar, *et al.* [24]	Retrospective	***	*	***	7	Good
Fukami, *et al.* [25]	Prospective	****	*	***	8	Good
Dolan, *et al.* [26]	Retrospective	****	*	***	8	Good

[a](1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study

[b](1) comparability of cohorts on the basis of the design or analysis (maximum two stars)

[c](1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow-up of cohorts

4. Discussion

Fibrin glue (FG) is the name given to a product that causes the formation of a fibrin network where the product is applied. Fibrin glue functions as a local hemostasis with another name, fibrin sealant. FG technology is based on knowledge about blood coagulation or blood coagulation. The main components in FG are thrombin and fibrinogen. The mechanism of action of FG resembles the events that occur in the final stages of the process of blood coagulation or blood clotting. Other components are fibronectin, plasminogen, factor XIII, and calcium chloride. Some FG contain aprotinin, others do not [46, 47].

Fibronectin functions to help the adhesion of fibroblasts to fibrin tissue. Plasminogen is converted into plasmin which functions to prevent premature degradation of the fibrin network, factor XIII will become active and stabilize the fibrin network. Aprotinin inhibits fibrinolysis. Calcium chloride is a source of calcium ions which functions as a cofactor in the formation of fibrin tissue. Various added components play a role in the process of re-epithelialization and neovascularization. Currently, all components contained in FG come from blood donors (humans), except for aprotinin. Aprotinin comes from cows. Tranexamic acid functions as an anti-fibrinolytic agent widely used to replace aprotinin. The application of FG has been widely used in various procedures such as dental and maxillofacial surgery, orthopedic surgery and circumcision, and even bariatric surgery which functions as local hemostasis. FG can reduce bleeding during and after the procedure, especially seeping bleeding [46, 47].

The procedure for making fibrin glue with the examination material is 5 cc of blood with citrate anticoagulant and 3 cc of blood with heparin anticoagulant. The reagents used were aquadest, 1% acetic acid, physiological NaCl, Na_2CO_3 0.1 M, and $CaCl_2$ 0.1 M. The tools and materials needed are a 1 cc mini tube, 10 cc plastic/conical centrifuge tube, centrifuge, pH meter/universal pH indicator, water bath, 1 cc syringe, 3 cc syringe, yellow tips, blue tips, and parafilm. The procedure is (1) 3 cc of venous blood is put in a heparin tube, (2) Centrifuge at 3000 rpm for 10 minutes, (3) Separate plasma using an automatic pipette and put it in a mini tube, (4) Store plasma at a minimum temperature of -40C 1 hour. Method of making thrombin (1) Put venous blood into 3 citrate tubes of 2 cc each or 1 5 cc citrate tube, (2) Centrifuge at 3000 rpm for 10 minutes, (3) Separate plasma and put it in 2 plastic centrifuge tube, (4) Plasma is diluted using aquabidestilata to a volume of 10 cc, (5) Titrate using 1% acetic acid (drop by drop) until it reaches a pH of 5.3 (titration can use a 1 ml syringe), (6) Homogenize the solution plasma and leave for 1 hour until precipitate forms, (7) Centrifuge again at 3000 rpm for 5 minutes, (8) Precipitate and supernatant are formed; the supernatant is discarded, (9) Dissolve the precipitate again by adding physiological NaCl to the 1 cc line, (10) After mixing then vortex until homogeneous, (11) Combine the two solutions, (12) Titrate the solution with Na_2CO_3 0.1 M to pH 7 (drop by drop, can use a 1 cc syringe), (13) The tube containing the solution is incubated in a water bath at 37^0C for 2 minutes, (14) 50 µL CaCl was added$_2$ 0.1 M, the stopwatch is run, (15) Discard the lumps that form within 45-120 seconds (2 minutes), (16) The remaining clear solution is put in a minitube, (17) Then stored at 40C for at least 1 hour. How to make the reagent, namely (1) 1% acetic acid: 50 µL concentrated acetic acid diluted with 4950 µL distilled water (must be made fresh), (2) Na_2CO_3 0.1 M: Weighed Na_2CO_3 1.06gram diluted with 100 ml distilled water (stable for one year), (3) $CaCl_2$ 0.1 M: Weigh 1.47gram $CaCl_2$ dissolved in 100 ml distilled water (stable for one year) [48].

Side effects of using FG because it is produced from blood, carries a risk of disease transmission through transfusion. Other side effects that have been reported include the occurrence of anaphylactic reactions or the formation of factor V inhibitors. These side effects are generally reported in FGs using bovine thrombin or bovine aprotinin. In FG packaging, thrombin, and fibrinogen are stored in separate vials. Also included are two syringes. One syringe is to be filled with thrombin and the other syringe is filled with fibrinogen. The two syringes are then pressed together. a network of fibrin forms where the FG is applied. How to give FG can be injected or sprayed depending on needs [21, 47]. In this review, the authors reviewed data from 8 articles with a total sample size in human studies of 599 while the number of samples in *in vivo* studies was 118 with a publication period of 2019 to 2023 to obtain the use of AFG in bowel anastomosis. The result of our analysis showed that fibrin glue appears to reduce bowel anastomosis complications compared to non-fibrin glue. However, the evidence is not statistically significant (OR 0.41 [95% CI 0.14–1.14]; p 0.89; I2 0%). The result of this analysis mainly came from the study by Ibele *et al.*, which had the highest number of participants [13].

Complications reported by Seida *et al.* reported complications of postoperative leaks (8.6%) and wound seroma (5.7%) [13], while Ibele *et al.* included postoperative bleeding requiring blood transfusion (1.7%), anastomotic leak (0.5%), and anastomotic stricture (11.3%) [15]. The majority of previous studies have shown very good results on diet initiation, anastomotic time, length of stay, and postoperative complications. However, studies related to the use of AFG in bowel anastomosis are still not widely carried out. The current published literature does not conclusively demonstrate the superiority of AFG to non-AFG.

Phase II clinical trial study by Lin, *et al.* [49]. related to the use of FG for esophageal anastomosis, the results obtained were anastomotic stricture incidence of 1.8% and major postoperative complications of 17.5%, the median time required for initiation of feeding was 8 days, no side effects or death were found within 90 days. A report by Zhang, *et al.* [50]. demonstrated that the over-the-scope-clip (OTSC) approach combined with FG is a novel therapy for colonic anastomotic fistula. Although until now it is known that AL is still the most common complication of colorectal surgery, in the report by Silva, *et al.* Management of anastomotic leak after colorectal surgery with Vacuum-assisted therapy with FG also shows very significant results in the process of recovering anastomotic function. In addition, the use of FG in treating GI fistulas using endoscopic procedures has also been widely reported. endoscopic plomage with PGA sheets and FG can be used as a GI fistula therapy in GI perforations with an endoscopic approach [51, 52, 53]. The effect of FG can also be seen in its ability to leak lymphatics after lymphadenectomy and gastrectomy in patients with gastric cancer which can reduce the incidence of postoperative lymphatic leak [54]. In addition to FG, the application of FG and collagen-based laminar can also reduce postoperative leakage and sequelae [55]. A novel combination therapy between mesenchymal stem cell secretome and FG can improve the restoration of intestinal anastomosis. Under *in vitro* conditions, this MSC secretome can significantly induce

cell proliferation in a dose-dependent manner and can result in controlled release of growth factors through the administration of FG. In this study, it was found that FG containing MSC secretions could increase anastomotic bursting pressure, increase granulation tissue formation and collagen deposition, and significantly this would promote anastomotic healing. Mechanistically, FG can accelerate cell proliferation, angiogenesis, and macrophage proliferation at the surgical anastomosis site by releasing several cytokines in the secretome, and can also reduce the inflammatory response and cell apoptosis at the anastomosis site [56].

Several limitations of this study include the scarcity of human studies, limited data, and lack of standardization. The number of patients and results of the included studies cause limitation of the analysis. The lack of standardization should also be improved by designing more specific criteria and similar measured outcomes.

5. Conclusion

Although it is difficult to conclude from the currently available evidence provided in this analysis, the use of autologous fibrin glue (AFG) in bowel anastomosis is promising to improve clinical outcomes (initiation of diet, duration of anastomosis, length of hospitalization), reduce mortality and postoperative complications. Nevertheless, further research in humans with larger sample sizes is necessary to determine the benefits and superiority of AFG, as well as to establish a clinical recommendation of its usage.

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