Cochrane
Library

Cochrane Database of Systematic Reviews

Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery (Review)

Gong J, He S, Cheng Y, Cheng N, Gong J, Zeng Z

Gong J, He S, Cheng Y, Cheng N, Gong J, Zeng Z.

Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery.

Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD009621.

DOI: 10.1002/14651858.CD009621.pub3.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	11
Figure 1.	12
Figure 2.	13
Figure 3.	14
ADDITIONAL SUMMARY OF FINDINGS	18
DISCUSSION	24
AUTHORS' CONCLUSIONS	25
ACKNOWLEDGEMENTS	25
REFERENCES	25
CHARACTERISTICS OF STUDIES	29
DATA AND ANALYSES	46
Analysis 1.1. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 1 Postoperative pancreatic fistula (ISGPF definition).	47
Analysis 1.2. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 2 Postoperative mortality.	48
Analysis 1.3. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 3 Overall postoperative morbidity.	49
Analysis 1.4. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 4 Reoperation rate.	50
Analysis 1.5. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 5 Length of hospital stay.	51
Analysis 2.1. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 1 Postoperative pancreatic fistula (ISGPF definition).	52
Analysis 2.2. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 2 Postoperative mortality.	53
Analysis 2.3. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 3 Overall postoperative morbidity.	54
Analysis 2.4. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 4 Reoperation rate.	55
Analysis 2.5. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 5 Length of hospital stay.	55
Analysis 3.1. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 1 Postoperative mortality.	56
Analysis 3.2. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 2 Overall postoperative morbidity.	57
Analysis 3.3. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 3 Reoperation rate.	58
Analysis 3.4. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 4 Length of hospital stay.	58
APPENDICES	59
WHAT'S NEW	65
CONTRIBUTIONS OF AUTHORS	65
DECLARATIONS OF INTEREST	65
SOURCES OF SUPPORT	65

DIFFERENCES BETWEEN PROTOCOL AND REVIEW	66
INDEX TERMS	66

Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Junhua Gong¹, Sirong He^{2a}, Yao Cheng³, Nansheng Cheng⁴, Jianping Gong³, Zhong Zeng¹

¹Organ Transplant Center, First Affiliated Hospital of Kunming Medical University, Kunming, China. ²Department of Immunology, College of Basic Medicine, Chongqing Medical University, Chongqing, China. ³Department of Hepatobiliary Surgery, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China. ⁴Department of Bile Duct Surgery, West China Hospital, Sichuan University, Chengdu, China

^aJoint first author

Contact address: Zhong Zeng, Organ Transplant Center, First Affiliated Hospital of Kunming Medical University, No. 295, Xi Chang Road, Kunming, Yunnan, 650032, China. zzeng2016@126.com, zzong@medmail.com.cn.

Editorial group: Cochrane Upper GI and Pancreatic Diseases Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2018.

Citation: Gong J, He S, Cheng Y, Cheng N, Gong J, Zeng Z. Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD009621. DOI: 10.1002/14651858.CD009621.pub3.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Postoperative pancreatic fistula is one of the most frequent and potentially life-threatening complications following pancreatic resections. Fibrin sealants are introduced to reduce postoperative pancreatic fistula by some surgeons. However, the use of fibrin sealants during pancreatic surgery is controversial. This is an update of a Cochrane Review last published in 2016.

Objectives

To assess the safety, effectiveness, and potential adverse effects of fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery.

Search methods

We searched trial registers and the following biomedical databases: the Cochrane Library (2018, Issue 4), MEDLINE (1946 to 12 April 2018), Embase (1980 to 12 April 2018), Science Citation Index Expanded (1900 to 12 April 2018), and Chinese Biomedical Literature Database (CBM) (1978 to 12 April 2018).

Selection criteria

We included all randomized controlled trials that compared fibrin sealant (fibrin glue or fibrin sealant patch) versus control (no fibrin sealant or placebo) in people undergoing pancreatic surgery.

Data collection and analysis

Two review authors independently identified the trials for inclusion, collected the data, and assessed the risk of bias. We performed the meta-analyses using Review Manager 5. We calculated the risk ratio (RR) for dichotomous outcomes (or a Peto odds ratio (OR) for very rare outcomes), and the mean difference (MD) for continuous outcomes, with 95% confidence intervals (CIs).

Main results

We included 11 studies involving 1462 participants in the review.

Application of fibrin sealants to pancreatic stump closure reinforcement after distal pancreatectomy

We included seven studies involving 860 participants: 428 were randomized to the fibrin sealant group and 432 to the control group after distal pancreatectomy. Fibrin sealants may lead to little or no difference in postoperative pancreatic fistula (fibrin sealant 19.3%; control 20.1%; RR 0.96, 95% CI 0.68 to 1.35; 755 participants; four studies; low-quality evidence). Fibrin sealants may also lead to little or no difference in postoperative mortality (0.3% versus 0.5%; Peto OR 0.52, 95% CI 0.05 to 5.03; 804 participants; six studies; low-quality evidence), or overall postoperative morbidity (28.5% versus 23.2%; RR 1.23, 95% CI 0.97 to 1.58; 646 participants; three studies; low-quality evidence). We are uncertain whether fibrin sealants reduce reoperation rate (2.0% versus 3.8%; RR 0.51, 95% CI 0.15 to 1.71; 376 participants; two studies; very low-quality evidence). There is probably little or no difference in length of hospital stay between the groups (12.1 days versus 11.4 days; MD 0.32 days, 95% CI -1.06 to 1.70; 755 participants; four studies; moderate-quality evidence). The studies did not report serious adverse events, quality of life, or cost effectiveness.

Application of fibrin sealants to pancreatic anastomosis reinforcement after pancreaticoduodenectomy

We included three studies involving 251 participants: 115 were randomized to the fibrin sealant group and 136 to the control group after pancreaticoduodenectomy. We are uncertain whether fibrin sealants reduce postoperative pancreatic fistula (1.6% versus 6.2%; RR 0.25, 95% CI 0.01 to 5.06; 57 participants; one study; very low-quality evidence). Fibrin sealants may lead to little or no difference in postoperative mortality (0.1% versus 0.7%; Peto OR 0.15, 95% CI 0.00 to 7.76; 251 participants; three studies; low-quality evidence) or length of hospital stay (12.8 days versus 14.8 days; MD -1.58 days, 95% CI -3.96 to 0.81; 181 participants; two studies; low-quality evidence). We are uncertain whether fibrin sealants reduce overall postoperative morbidity (33.7% versus 34.7%; RR 0.97, 95% CI 0.65 to 1.45; 181 participants; two studies; very low-quality evidence), or reoperation rate (7.6% versus 9.2%; RR 0.83, 95% CI 0.33 to 2.11; 181 participants; two studies, very low-quality evidence). The studies did not report serious adverse events, quality of life, or cost effectiveness.

Application of fibrin sealants to pancreatic duct occlusion after pancreaticoduodenectomy

We included two studies involving 351 participants: 188 were randomized to the fibrin sealant group and 163 to the control group after pancreaticoduodenectomy. Fibrin sealants may lead to little or no difference in postoperative mortality (8.4% versus 6.1%; Peto OR 1.41, 95% CI 0.63 to 3.13; 351 participants; two studies; low-quality evidence) or length of hospital stay (17.0 days versus 16.5 days; MD 0.58 days, 95% CI -5.74 to 6.89; 351 participants; two studies; low-quality evidence). We are uncertain whether fibrin sealants reduce overall postoperative morbidity (32.0% versus 27.6%; RR 1.16, 95% CI 0.67 to 2.02; 351 participants; two studies; very low-quality evidence), or reoperation rate (13.6% versus 16.0%; RR 0.85, 95% CI 0.52 to 1.41; 351 participants; two studies; very low-quality evidence). Serious adverse events were reported in one study: more participants developed diabetes mellitus when fibrin sealants were applied to pancreatic duct occlusion, both at three months' follow-up (33.7% fibrin sealant group versus 10.8% control group; 29 participants versus 9 participants) and 12 months' follow-up (33.7% fibrin sealant group versus 14.5% control group; 29 participants versus 12 participants). The studies did not report postoperative pancreatic fistula, quality of life, or cost effectiveness.

Authors' conclusions

Based on the current available evidence, fibrin sealants may have little or no effect on postoperative pancreatic fistula in people undergoing distal pancreatectomy. The effects of fibrin sealants on the prevention of postoperative pancreatic fistula are uncertain in people undergoing pancreaticoduodenectomy.

PLAIN LANGUAGE SUMMARY

Surgical tissue adhesives for the preventing pancreatic fistula following pancreatic surgery

Review question

Is surgical tissue adhesive able to reduce postoperative pancreatic fistula after pancreatic surgery?

Background

Postoperative pancreatic fistula is a complication that may follow major surgery for cancer or inflammation of the pancreas, a digestive gland situated at the back of the upper abdomen. The surgery involves disconnecting the pancreas from the nearby gut, and then

reconnecting this to allow pancreatic juice containing digestive enzymes to enter the digestive system after surgical removal of the head of the pancreas. The pancreatic stump is often left to heal itself after surgical removal of the tail of the pancreas. A fistula occurs when the reconnection or stump does not heal properly, creating a leak of pancreatic juice from the pancreas to the abdominal tissues. This delays recovery from surgery and often requires further treatment to ensure complete healing. The role of fibrin sealants (surgical tissue adhesives) to reduce postoperative pancreatic fistula after pancreatic surgery is controversial.

Study characteristics

We searched for all relevant, well-conducted studies up to April 2018. We included eleven studies which were divided into three comparisons. First, seven of the eleven studies randomized 860 participants undergoing surgical removal of the tail of the pancreas to either fibrin sealant use (428 participants) or no fibrin sealant use (432 participants) for pancreatic stump closure reinforcement. Second, three studies randomized 251 participants undergoing the 'Whipple' operation (surgical removal of the head of the pancreas) to fibrin sealant use (115 participants) or no fibrin sealant use (136 participants) for pancreatic stump reconstruction reinforcement. Third, two studies randomized 351 participants undergoing the 'Whipple' operation to fibrin sealant use (188 participants) and no fibrin sealant use (163 participants) for pancreatic duct blockage.

Key results

Application of fibrin sealants to pancreatic stump closure reinforcement after surgical removal of the tail of the pancreas

Fibrin sealants may have little to no difference in postoperative pancreatic fistula or postoperative death when fibrin sealants are used on stump closure reinforcement after surgical removal of the tail of the pancreas.

Application of fibrin sealants to pancreatic anastomosis reinforcement after 'Whipple' operation

We are uncertain whether fibrin sealants improve postoperative pancreatic fistula when used for pancreatic anastomosis reinforcement after the 'Whipple' operation. Fibrin sealants may have little to no difference on postoperative death.

Application of fibrin sealants to pancreatic duct occlusion after 'Whipple' operation

Postoperative pancreatic fistula was not reported in any of the studies. Fibrin sealants may have little to no difference in postoperative death when applied to a pancreatic duct occlusion after 'Whipple' operation.

Fibrin sealants may have little or no benefit on postoperative pancreatic fistula in people undergoing surgical removal of the tail of the pancreas. We cannot tell from our results whether fibrin sealants have an important effect on postoperative pancreatic fistula after the 'Whipple' operation because the sample size was small and the results were imprecise.

Quality of the evidence

Most of the included studies had some shortcomings in terms of how they were conducted or reported. Overall, the quality of the evidence varied from very low to moderate.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Application of fibrin sealants to pancreatic stump closure reinforcement for the prevention of postoperative pancreatic fistula following distal pancreatectomy							
Patient or population: people undergoing distal pancreatectomy Setting: hospital Intervention: fibrin sealant Comparison: no fibrin sealant							
Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no fibrin sealants	Risk with fibrin sealants					
Postoperative pancreatic fistula (ISGPF definition) Follow up: 30 days	Study population			RR 0.96 (0.68 to 1.35)	755 (4 studies)	⊕⊕○○ low ^{1,2,3}	
	201 per 1000	193 per 1000 (136 to 271)					
	Moderate						
	203 per 1000	195 per 1000 (138 to 274)					
Postoperative mortality	Study population			Peto OR 0.52 (0.05 to 5.03)	804 (6 studies)	⊕⊕○○ low ^{2,4}	
	5 per 1000	3 per 1000 (0 to 25)					
	Moderate						
	0 per 1000	0 per 1000 (0 to 0)					
Overall postoperative morbidity Follow up: 30 days	Study population			RR 1.23 (0.97 to 1.58)	646 (3 studies)	⊕⊕○○ low ^{1,2,3}	

	232 per 1000	285 per 1000 (225 to 367)			
	Moderate				
	239 per 1000	294 per 1000 (232 to 378)			
Reoperation rate Follow up: 30 days	Study population		RR 0.51 (0.15 to 1.71)	376 (2 studies)	⊕○○○ very low ^{1,2,4}
	38 per 1000	20 per 1000 (6 to 65)			
	Moderate				
	27 per 1000	14 per 1000 (4 to 46)			
Serious adverse events	This outcome was not reported in any of the included studies				
Quality of life	This outcome was not reported in any of the included studies				
Cost effectiveness	This outcome was not reported in any of the included studies				
Length of hospital stay (days)	The mean length of hos- pital stay was 11.4 days	The mean length of hos- pital stay was 0.32 days higher (1.06 lower to 1.70 higher)	MD 0.32 (-1.06 to 1.70)	755 (4 studies)	⊕⊕⊕○ moderate ^{1,2}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; MD: Mean difference; ISGPF: International Study Group on Pancreatic Fistula

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level for serious risk of bias.

² Publication bias could not be assessed because of there being few studies.

³ Downgraded one level for serious imprecision (the confidence interval of risk ratio overlapped 0.75 and 1.25).

⁴ Downgraded two levels for very serious imprecision (very few events, confidence intervals of risk ratios overlapped 0.75 and 1.25).

BACKGROUND

See 'Glossary' for an explanation of terms ([Appendix 1](#)).

Description of the condition

Pancreatic cancer ranks 13th in terms of most common cancers and 8th as a cause of cancer death from a global viewpoint ([Anderson 2006](#); [Dragovich 2015](#); [Lowenfels 2006](#)). Regional differences exist in the incidence of pancreatic cancer ([Anderson 2006](#); [Dragovich 2015](#); [Lowenfels 2006](#)), though the overall incidence is approximately four to ten cases per 100,000 persons per year ([Anderson 2006](#); [Dragovich 2015](#); [Lowenfels 2006](#)). Pancreatic cancer has become the third leading cause of death from cancer in the European Union countries ([Ferlay 2016](#)). The most common cause of pancreatic cancer is heavy tobacco usage ([Anderson 2006](#); [Dragovich 2015](#); [Lowenfels 2006](#)).

Although the exact incidence of chronic pancreatitis worldwide is unknown, the estimated incidence of chronic pancreatitis is six cases per 100,000 persons per year in European, and probably all Western, countries ([Spanier 2008](#)). The prevalence of chronic pancreatitis in the United Kingdom, France, Japan, and south India is three cases, 26 cases, four cases, and 114 to 200 cases per 100,000 persons, respectively ([Bornman 2001](#); [Braganza 2011](#); [Garg 2004](#); [Lévy 2006](#)). The most common cause of chronic pancreatitis is alcohol abuse ([Braganza 2011](#); [Spanier 2008](#)).

Pancreatic surgery is performed to treat pancreatic and extra-pancreatic diseases, including pancreatic cancers, chronic pancreatitis, as well as biliary, ampullary, and duodenal malignancy ([Cheng 2014](#); [Cheng 2016a](#); [Cheng 2016b](#); [Connor 2005](#); [Diener 2014](#); [Gurusamy 2013](#); [Lillemoe 2004](#)). Although the mortality of pancreatic surgery has been reduced to less than 5% currently, the overall morbidity is still high, ranging from 30% to 60% ([Bassi 2005](#); [Connor 2005](#); [Gurusamy 2013](#)). Postoperative pancreatic fistula (POPF) is one of the most frequent and potentially life-threatening complications ([Cheng 2016a](#); [Dong 2016](#); [Gurusamy 2013](#)). It is defined by the International Study Group on Pancreatic Fistula (ISGPF) as "Grade B POPF requires a change in the postoperative management; drains are either left in place >3 weeks or repositioned through endoscopic or percutaneous procedures. Grade C POPF requires reoperation or leads to single or multiple organ failure and/or mortality attributable to the POPF" ([Bassi 2017](#)). Its reported incidence varies between 2% and 24% in different studies ([Bassi 2005](#); [Connor 2005](#); [McMillan 2016](#)).

Generally, POPF originates from the pancreatic stump following pancreatic resection, as well as from the pancreatic-enteric anastomosis following pancreaticoduodenectomy ([Bassi 2005](#); [Hackert 2011](#)). The natural history of POPF is variable in different people ([Case 1960](#)). Many factors have been considered to influence the development of POPF (e.g. age, obesity, cardiovascular diseases, diabetes mellitus, pancreatic texture, pancreatic duct size) ([Ramacciato 2011](#)). It seems that older (i.e. more than 60 years

of age), overweight people with cardiovascular diseases, diabetes mellitus, soft pancreatic texture, a small pancreatic duct diameter (i.e. less than 3 mm) are more likely to suffer POPF ([Ramacciato 2011](#); [Riall 2008](#)).

Description of the intervention

Various methods have been suggested for the prevention of POPF, such as modification of anastomotic techniques, application of pancreatic duct stents, and administration of somatostatin or its analogues ([Gurusamy 2013](#); [Schulick 2009](#); [Cheng 2017](#); [Dong 2016](#)), but one of the most common and convenient interventions during an operation has been the application of fibrin sealants ([Fingerhut 2009](#); [Kuroki 2005](#); [Ohwada 1998](#)). Fibrin sealants are administered to seal the pancreatic stump, pancreatic-enteric anastomosis, or main pancreatic duct during pancreatic surgery.

How the intervention might work

Fibrin sealant (also known as fibrin glue) is a kind of surgical tissue adhesive that is widely used worldwide in various surgical procedures for bleeding control, incision closure, etc. ([Chow 2010](#); [Spotnitz 2010](#)). It is a product derived from human or animal blood ([Carless 2003](#)). Fibrin sealants are commercial products containing two separate components: primarily fibrinogen and thrombin ([Carless 2003](#); [Moblely 2002](#); [NLM 1990](#)). Mixing of the two components by single- or dual-syringe systems in a liquid form promotes blood clotting and cross-linking of fibrin ([Moblely 2002](#); [NLM 1990](#)). This process mimics the final stages of blood coagulation and forms a stable fibrin clot that provides a sealing barrier ([Carless 2003](#); [Spotnitz 2010](#)). This kind of commercial product is termed fibrin glue.

Another common type is a fibrin sealant patch which consists of felt coated with a mixture of freeze-dried fibrinogen and thrombin, and which can be applied directly to the tissue surface without additional manipulations ([Chirletti 2009](#); [Ochiai 2010](#); [Rickenbacher 2009](#)). Approximately 10 ml fibrin glue or several fibrin sealant patches are applied to stump closure reinforcement, pancreatic anastomosis reinforcement, or main pancreatic duct occlusion ([Fingerhut 2009](#); [Schulick 2009](#)). Theoretically, they have the potential to reduce the incidence of POPF by mechanically sealing ([Fingerhut 2009](#); [Schulick 2009](#)). As POPF often develops into various further abdominal complications (e.g. intra-abdominal abscess, subsequent serious infection, bleeding) and significantly contributes to mortality and morbidity ([Kuroki 2005](#); [Schulick 2009](#)), a reduction in the incidence of POPF might reduce mortality, morbidity, and length of hospital stay ([Fingerhut 2009](#); [Gurusamy 2013](#); [Schulick 2009](#)).

Why it is important to do this review

The use of fibrin sealants during pancreatic surgery is controversial. Fibrin sealants may potentially reduce the incidence of POPE, but it is also possible that they may have no benefits and may be associated with some adverse effects (Carless 2003; Fingerhut 2009; Siedentop 2001). Fibrin sealants are products derived from human or animal blood. Thus, they have the risk of allergy and transmission of some diseases (Carless 2003; Siedentop 2001). In addition, a recent experimental study performed in rats indicated that the fibrin sealants resulted in pancreatic toxicity (harmfulness). Theoretically, they may also be harmful to humans (Lämsä 2008). This is an update of a previous Cochrane Review assessing the role of fibrin sealants for the prevention of POPF following pancreatic surgery. We conducted this systematic review to explore uncertainty arising from conflicting results in a number of studies in this area.

OBJECTIVES

To assess the safety, effectiveness, and potential adverse effects of fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials, regardless of sample size, publication status, language, or publication date, that compared fibrin sealant with control for the prevention of postoperative pancreatic fistula (POPF) in people undergoing pancreatic resections. We excluded quasi-randomized trials, in which the allocation was performed on the basis of a pseudo-random sequence (e.g. odd/even hospital number or date of birth, alternation), and non-randomized studies because of the potential for bias (Reeves 2011).

Types of participants

We included people, regardless of age, sex, or race, who underwent elective pancreatic resections (open or laparoscopic) for any pancreatic or extra-pancreatic disease.

We excluded people who underwent total pancreatectomy as this eliminates any source for a POPF.

Types of interventions

Intervention: fibrin sealant, regardless of glue or patch, which was applied to stump closure reinforcement, pancreatic anastomosis reinforcement, or main pancreatic duct occlusion.

Comparison: placebo or no fibrin sealant treatment.

Types of outcome measures

Primary outcomes

1. Postoperative pancreatic fistula (30 days; defined by the International Study Group on Pancreatic Fistula; Bassi 2017).
2. Postoperative mortality (30 days).

Secondary outcomes

1. Overall postoperative morbidity (30 days; classified by the Clavien-Dindo classification of surgical complications; Clavien 2009).
 - i) Pancreas-associated morbidity (e.g. postoperative pancreatic fistula, delayed gastric emptying, postoperative pancreatitis).
 - ii) Other general postoperative morbidity (e.g. wound infection, pulmonary complications, renal failure).
2. Reoperation rate (30 days).
3. Number of people with any serious adverse events attributed to fibrin sealants.
 - i) Hepatitis transmission.
 - ii) HIV transmission.
 - iii) Allergy.
 - iv) Others.
4. Quality of life.
5. Cost effectiveness.
6. Length of hospital stay.

Search methods for identification of studies

We designed the search strategies with the help of a Cochrane Up-per Gastrointestinal and Pancreatic Diseases (UGPD) Information Specialist before searching. We placed no restrictions on the language of publication when searching the electronic databases or reviewing reference lists in identified studies.

Electronic searches

For the initial version of this review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 7), MEDLINE (1946 to 26 August 2015), Embase (1980 to 26 August 2015), Science Citation Index Expanded (1900 to 26 August 2015), and Chinese Biomedical Literature Database (CBM) (1978 to 26 August 2015) (New Reference). For this updated review, we searched the following electronic databases from 2015 to

12 April 2018, with no restrictions on language or date of publication:

1. CENTRAL ([Appendix 2](#));
2. MEDLINE (Ovid) ([Appendix 3](#));
3. Embase (Ovid) ([Appendix 4](#));
4. Science Citation Index Expanded (Web of Science) ([Appendix 5](#)); and
5. Chinese Biomedical Literature Database (CBM) ([Appendix 6](#)).

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We contacted authors of identified studies and asked them to identify other published and unpublished studies.

We searched PubMed for errata or retractions from eligible studies and reported the date this was done within the review (www.ncbi.nlm.nih.gov/pubmed). We also searched the meeting abstracts via the HPB journal (onlinelibrary.wiley.com/journal/10.1111/ISSN1477-2574; accessed 12 April 2018) and Conference Proceedings Citation Index to explore further relevant clinical studies.

Clinical study registers/study result registers

We searched the following databases to identify ongoing studies (accessed 12 April 2018).

1. World Health Organization International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/)
2. ClinicalTrials.gov (www.clinicaltrials.gov/)
3. Current Controlled Trials (www.controlled-trials.com/)
4. European (EU) Clinical Trials Register (www.clinicaltrialsregister.eu/)
5. Chinese Clinical Trial Registry (www.chictr.org.cn/enindex.aspx)

Data collection and analysis

We conducted this systematic review according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)); and the Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) Group Module ([Forman 2011](#)).

Selection of studies

Two review authors (Junhua Gong, YC) independently screened the titles and abstracts of all the studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications and two review authors (Junhua Gong, YC) independently screened the full text and identified studies for inclusion, and identified and recorded reasons for exclusion of the

ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third review author (ZZ). We identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a [Characteristics of excluded studies](#) table ([Moher 2009](#)).

Data extraction and management

We used a standard data collection form for study characteristics and outcome data, which had been piloted on at least one study in the review. Two review authors (NC, Jianping Gong) extracted the following study characteristics from included studies.

1. Methods: study design, total duration study and run in, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number (N), mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for study, notable conflicts of interest of study authors.

Two review authors (NC, Jianping Gong) independently extracted outcome data from included studies. We noted in the [Characteristics of included studies](#) table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third review author (ZZ). One review author (YC) copied across the data from the data collection form into Review Manager 5. We double checked that the data were entered correctly by comparing the study reports with how the data were presented in the systematic review. A second review author spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (Junhua Gong, YC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We resolved any disagreements by discussion or by involving a third review author (ZZ). We assessed the risk of bias for the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We graded each potential source of bias as high, low, or unclear risk, and provided a quote from the study report together with

a justification for our judgement in the 'Risk of bias' table. We summarized the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Cheng 2012), and reported any deviations from it in the [Differences between protocol and review](#) section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as risk ratio (RR) and continuous data as mean difference (MD) with 95% confidence intervals (CIs). In the case of rare events (e.g. mortality), we calculated the Peto odds ratio (Peto OR) (Deeks 2011). We ensured that higher scores for continuous outcomes had the same meaning for the particular outcome, explained the direction to the reader and reported where the directions were reversed if this was necessary.

We undertook meta-analyses only where this was meaningful, that is, if the treatments, participants, and underlying clinical question were similar enough for pooling to make sense.

A common way that trialists indicated when they had skewed data was by reporting medians and interquartile ranges. When we encountered this, we noted that the data were skewed and considered the implication of this.

Where multiple study arms were reported in a single study, we included only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were entered into the same meta-analysis, we halved the control group to avoid double counting.

Unit of analysis issues

The unit of analysis was the individual participant. We did not find any cross-over or cluster-randomized trials.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics, and obtained missing numerical outcome data where possible (e.g. when a study was identified as abstract only). However, there was no reply in most of the cases. Thus, we used only the available data in the analyses.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the studies in each analysis (Higgins 2003). When we identified substantial heterogeneity (greater than 50%), we explored it by prespecified subgroup analysis, and we interpreted summary effect measures with caution.

Assessment of reporting biases

We did not perform funnel plots to assess reporting biases because the number of studies included under each comparison was less than 10 (Sterne 2011).

Data synthesis

We performed the meta-analyses using Review Manager 5 software (RevMan 2014). For all analyses, we employed the random-effects model for conservative estimation, except for the Peto odds ratio (OR) which only has a fixed method.

'Summary of findings' table

We created 'Summary of findings' tables using the following outcomes: postoperative pancreatic fistula, postoperative mortality, overall postoperative morbidity, reoperation rate, serious adverse events, quality of life, cost effectiveness and length of hospital stay. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and used GRADEpro software (GRADEpro 2015). We justified all decisions to downgrade or upgrade the quality of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary. We considered whether there was any additional outcome information that we were unable to incorporate into meta-analyses and noted this in the comments, and stated if it supported or contradicted the information from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

We intended to perform the following subgroup analyses.

1. Randomized controlled trials with low risk of bias versus randomized controlled trials with high risk of bias
2. The type of fibrin sealants (glue and patch)
3. Different etiologies (pancreatic cancer, chronic pancreatitis, and others)
4. High-risk people (e.g. fatty pancreas, soft pancreas, small pancreatic duct) versus low-risk people

In previous versions of this review, we performed a meta-analysis of fibrin sealants versus no fibrin sealants for overall pancreatic

surgery, with subgroups of sealing location and type of operation. We have restructured this version of the review and the changes are detailed in the [Differences between protocol and review](#) section.

Sensitivity analysis

We performed sensitivity analyses to determine whether the conclusions were robust according to the decisions made during the review process, as follows.

1. Changing between a fixed-effect model and a random-effects model
 2. Changing statistics between risk ratios (RR), risk differences (RD), and odds ratios (OR) for dichotomous outcomes
 3. Changing statistics between mean difference (MD) and standardized mean differences (SMD) for continuous outcomes
 4. Excluding randomized controlled trials with low quality
 5. Excluding studies published in languages other than English
- If the results did not change, they were considered to have low sensitivity. If the results changed, they were considered to have high sensitivity.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We avoided making recommendations for practice and our implications for research could give the reader a clear sense of where the focus of

any future research in the area should be and what the remaining uncertainties were.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

We identified a total of 69 records through the electronic searches of *The Cochrane Library* (N = 5), MEDLINE (Ovid) (N = 9), Embase (Ovid) (N = 16), Science Citation Index Expanded (Web of Science) (N = 24), and Chinese Biomedical Literature Database (CBM) (N = 15). We excluded 13 duplicates and 51 clearly irrelevant records through reading titles and abstracts. We retrieved the remaining five records for further assessment. We excluded a quasi-randomized study ([Rehman 2016](#)) and two non-randomized studies ([Mita 2015](#); [Silvestri 2015](#)). In total, two randomized controlled trials fulfilled the inclusion criteria for this update. The study flow diagram is shown in [Figure 1](#).

Figure 1. Study flow diagram.

Included studies

The first published version of this review from 2016 included nine studies published between 1994 and 2013 (Bassi 1999; Carter 2013; D'Andrea 1994; Lillemoe 2004; Martin 2013; Montorsi 2012; Suc 2003; Suzuki 1995; Tran 2002). We added two recent studies published after 2015 into this updated review (Park 2016; Sa Cunha 2015). Therefore, we included 11 studies and all of these provided data for the analyses. These studies were conducted in Italy (N = 3; Bassi 1999; D'Andrea 1994; Montorsi 2012), America (N = 2; Carter 2013; Lillemoe 2004), France (N = 2; Sa Cunha 2015; Suc 2003), Australia (N = 1; Martin 2013), Japan (N = 1; Suzuki 1995), South Korea (N = 1; Park 2016), and the Netherlands (N = 1; Tran 2002). A total of 1462 participants were randomized to either fibrin sealant (N = 731) or control (N = 731). The average age of participants varied between 50.0 years and 64.0 years. The mean proportion of females varied between 28.6% and 72.5%. The outcomes measured were postoperative pancreatic fistula (POPF), grade of pancreatic fistula, mortality, morbidity, reoperation rate, serious adverse events, and length of hospital stay. We split all of the studies into three comparisons according to different sealing locations and different operations: application of fibrin sealants to pancreatic stump reinforcement after distal pan-

createctomy (Bassi 1999; Carter 2013; D'Andrea 1994; Montorsi 2012; Park 2016; Sa Cunha 2015; Suzuki 1995), pancreatic anastomosis reinforcement after pancreaticoduodenectomy (D'Andrea 1994; Lillemoe 2004; Martin 2013), and main pancreatic duct occlusion after pancreaticoduodenectomy (Suc 2003; Tran 2002). Details of the included studies are shown in the [Characteristics of included studies](#) table.

Excluded studies

We excluded five studies (Ohwada 1998; Pavlik Marangos 2011; Rehman 2016; Silvestri 2015; Tashiro 1987). Details are listed in the [Characteristics of excluded studies](#) table. None of these studies were randomized controlled trials.

Risk of bias in included studies

The risk of bias of the included studies is shown in [Figure 2](#) and [Figure 3](#). Following the evaluation of these seven domains, an included trial was judged to be at a low risk of bias if the risk of bias was evaluated as 'low risk' in all of the domains. If the risk of bias of any domain was judged as 'unclear risk' or 'high risk', the trial was listed as 'high risk of bias'. We considered all 11 studies to be at high risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bassi 1999	?	?	?	?	+	+	+
Carter 2013	+	+	-	?	-	-	+
D'Andrea 1994	?	?	?	?	+	+	+
Lillemoe 2004	+	?	?	+	+	+	+
Martin 2013	+	?	?	?	+	+	+
Montorsi 2012	?	?	?	?	+	+	-
Park 2016	+	+	-	+	-	+	+
Sa Cunha 2015	+	+	+	+	-	+	+
Suc 2003	+	+	-	+	+	+	-
Suzuki 1995	+	?	?	?	+	-	+
Tran 2002	?	?	?	?	+	+	+

Allocation

We judged six studies to have low risk of bias for random sequence generation (Carter 2013; Lillemoe 2004; Martin 2013; Park 2016; Suc 2003; Suzuki 1995). We judged four studies to have low risk of bias for allocation concealment (Carter 2013; Park 2016; Sa Cunha 2015; Suc 2003).

Blinding

We deemed three studies to be at high risk of bias for blinding of participants and personnel (Carter 2013; Park 2016; Suc 2003). Blinding of outcome assessment was at low risk of bias in four studies (Lillemoe 2004; Park 2016; Sa Cunha 2015; Suc 2003).

Incomplete outcome data

There were no post-randomization dropouts in seven studies (Bassi 1999; D'Andrea 1994; Lillemoe 2004; Martin 2013; Suc 2003; Suzuki 1995; Tran 2002). Although there were some dropouts in one study, it performed the data analysis on an intention-to-treat basis (Montorsi 2012). We considered these eight studies to be free from risk of bias due to incomplete outcome data (Bassi 1999; D'Andrea 1994; Lillemoe 2004; Martin 2013; Montorsi 2012; Suc 2003; Suzuki 1995; Tran 2002).

Selective reporting

The study protocol was available for three studies (Montorsi 2012; Park 2016; Sa Cunha 2015). All of the studies' pre-specified outcomes were reported. Thus, we considered these three studies to be free of selective reporting. Six studies reported all of the primary outcomes of this review (Bassi 1999; D'Andrea 1994; Lillemoe 2004; Martin 2013; Suc 2003; Tran 2002). There was some selective outcome reporting in the secondary outcomes, but the review authors considered the six studies to be free of selective reporting for the primary outcomes.

Other potential sources of bias

We judged two studies to be at high risk of bias due to baseline imbalance (Montorsi 2012; Suc 2003).

Effects of interventions

See: [Summary of findings for the main comparison](#)
Application of fibrin sealants to pancreatic stump closure reinforcement for the prevention of postoperative pancreatic fistula following distal pancreatectomy; [Summary of findings 2](#) Application of fibrin sealants to pancreatic anastomosis reinforcement for the prevention of postoperative pancreatic

fistula following pancreaticoduodenectomy; [Summary of findings 3](#) Application of fibrin sealants to pancreatic duct occlusion for the prevention of postoperative pancreatic fistula following pancreaticoduodenectomy

Application of fibrin sealants to pancreatic stump closure reinforcement after distal pancreatectomy

Seven studies (860 participants) compared fibrin sealant use with no fibrin sealant use for pancreatic stump closure reinforcement after distal pancreatectomy (Bassi 1999; Carter 2013; D'Andrea 1994; Montorsi 2012; Park 2016; Sa Cunha 2015; Suzuki 1995). Four hundred and twenty-eight participants were randomized to the fibrin sealant group and 432 participants to the control group. See: [Summary of findings for the main comparison](#).

Postoperative pancreatic fistula (30 days)

Postoperative pancreatic fistula (POPF) at 30 days, as defined by the International Study Group on Pancreatic Fistula (ISGPF) (Bassi 2017). The POPF rate was 19.3% in the fibrin sealant group and 20.1% in the control group. The estimated risk ratio (RR) for clinically significant pancreatic fistula was 0.96 (95% confidence interval (CI) 0.68 to 1.35, 4 studies, 755 participants) ([Analysis 1.1](#)). We downgraded our assessment of the quality of evidence from high to low due to high risk of bias, serious imprecision, and concerns of publication bias.

Postoperative mortality (30 days)

Postoperative mortality was 0.3% in the fibrin sealant group and 0.5% in the control group. The estimated Peto odds ratio (OR) for postoperative mortality was 0.52 (95% CI 0.05 to 5.03, 6 studies, 804 participants) ([Analysis 1.2](#)). We downgraded our assessment of the quality of evidence from high to low due to very serious imprecision and concerns of publication bias.

Overall postoperative morbidity (30 days)

Overall postoperative morbidity at 30 days, as defined by the Clavien-Dindo classification of surgical complications (Clavien 2009). The overall postoperative morbidity was 28.5% in the fibrin sealant group and 23.2% in the control group. The estimated RR for overall postoperative morbidity was 1.23 (95% CI 0.97 to 1.58, 3 studies, 646 participants) ([Analysis 1.3](#)). We downgraded our assessment of the quality of evidence from high to low due to high risk of bias, serious imprecision, and concerns of publication bias.

Reoperation rate (30 days)

The reoperation rate was 2.0% in the fibrin sealant group and 3.8% in the control group. The estimated RR for reoperation rate was 0.51 (95% CI 0.15 to 1.71, 2 studies, 376 participants) ([Analysis 1.4](#)). We downgraded our assessment of the quality of evidence from high to very low due to high risk of bias, very serious imprecision, and concerns of publication bias.

Serious adverse events

None of the studies reported any serious adverse events related to fibrin sealants.

Quality of life

None of the studies reported this outcome.

Cost effectiveness

None of the studies reported this outcome.

Length of hospital stay

The mean length of hospital stay was 12.1 days in the fibrin sealant group and 11.4 days in the control group. The estimated mean difference (MD) for length of hospital stay was 0.32 days (95% CI -1.06 to 1.70, 4 studies, 755 participants, [Analysis 1.5](#)). We downgraded our assessment of the quality of evidence from high to very low due to high risk of bias, very serious imprecision, and concerns of publication bias.

Application of fibrin sealants to pancreatic anastomosis reinforcement after pancreaticoduodenectomy

Three studies (251 participants) compared fibrin sealant use with no fibrin sealant use for pancreatic anastomosis reinforcement after pancreaticoduodenectomy ([D'Andrea 1994](#); [Lillemoe 2004](#); [Martin 2013](#)). One hundred and fifteen participants were randomized to the fibrin sealant group and 136 participants to the control group. See: [Summary of findings 2](#).

Postoperative pancreatic fistula (30 days)

Postoperative pancreatic fistula (POPF) at 30 days, as defined by the International Study Group on Pancreatic Fistula (IS-GPF) ([Bassi 2017](#)). The POPF rate was 1.6% in the fibrin sealant group and 6.2% in the control group. The estimated RR for clinically significant pancreatic fistula was 0.25 (95% CI 0.01 to 5.06, 1 study, 57 participants, [Analysis 2.1](#)). We downgraded our assessment of the quality of evidence from high to very low due to high risk of bias, very serious imprecision, and concerns of publication bias.

Postoperative mortality (30 days)

Postoperative mortality was 0.1% in the fibrin sealant group versus 0.7% in the control group. The estimated Peto OR for postoperative mortality was 0.15 (95% CI 0.00 to 7.76, 3 studies, 251 participants, [Analysis 2.2](#)). We downgraded our assessment of the quality of evidence from high to low due to very serious imprecision and concerns of publication bias.

Overall postoperative morbidity (30 days)

Overall postoperative morbidity at 30 days, as defined by the Clavien- Dindo classification of surgical complications ([Clavien 2009](#)). Overall postoperative morbidity was 33.7% in the fibrin sealant group and 34.7% in the control group. The estimated RR for overall postoperative morbidity was 0.97 (95% CI 0.65 to 1.45, 2 studies, 181 participants, [Analysis 2.3](#)). We downgraded our assessment of the quality of evidence from high to very low due to high risk of bias, very serious imprecision, and concerns of publication bias.

Reoperation rate (30 days)

The reoperation rate was 7.6% in the fibrin sealant group and 9.2% in the control group. The estimated RR for reoperation rate was 0.83 (95% CI 0.33 to 2.11, 2 studies, 181 participants, [Analysis 2.4](#)). We downgraded our assessment of the quality of evidence from high to very low due to high risk of bias, very serious imprecision, and concerns of publication bias.

Serious adverse events

None of the studies reported any serious adverse events related to fibrin sealants.

Quality of life

None of the studies reported this outcome.

Cost effectiveness

None of the studies reported this outcome.

Length of hospital stay

The mean length of hospital stay was 12.8 days in the fibrin sealant group and 14.8 days in the control group. The estimated MD for length of hospital stay was -1.58 days (95% CI -3.96 to 0.81, 2 studies, 181 participants, [Analysis 2.5](#)). We downgraded our assessment of the quality of evidence from high to low due to high risk of bias, serious imprecision, and concerns of publication bias.

Application of fibrin sealants to pancreatic duct occlusion after pancreaticoduodenectomy

Two studies (351 participants) compared fibrin sealant use with no fibrin sealant use for pancreatic duct occlusion after pancreaticoduodenectomy (Suc 2003; Tran 2002). One hundred and eighty-eight participants were randomized to the fibrin sealant group and 163 participants to the control group. See: [Summary of findings 3](#).

Postoperative pancreatic fistula (30 days)

Postoperative pancreatic fistula (POPF) at 30 days, as defined by the International Study Group on Pancreatic Fistula (ISGPF) (Bassi 2017). Neither study reported on POPE.

Postoperative mortality (30 days)

The postoperative mortality was 8.4% in the fibrin sealant group and 6.1% in the control group. The estimated Peto OR for postoperative mortality was 1.41 (95% CI 0.63 to 3.13, 2 studies, 351 participants) (Analysis 3.1). We downgraded our assessment of the quality of evidence from high to low due to very serious imprecision and concerns of publication bias.

Overall postoperative morbidity (30 days)

Overall postoperative morbidity at 30 days, as defined by the Clavien-Dindo classification of surgical complications (Clavien 2009). Overall postoperative morbidity was 32.0% in the fibrin sealant group and 27.6% in the control group. The estimated RR for overall postoperative morbidity was 1.16 (95% CI 0.67 to 2.02, 2 studies, 351 participants, Analysis 3.2). We downgraded our assessment of the quality of evidence from high to very low due to high risk of bias, very serious imprecision, concerns of publication bias, and inconsistency in the direction and magnitude of effects across the studies ($I^2 = 65\%$).

Reoperation rate (30 days)

The reoperation rate was 13.6% in the fibrin sealant group and 16.0% in the control group. The estimated RR for reoperation rate was 0.85 (95% CI 0.52 to 1.41, 2 studies, 351 participants, Analysis 3.3). We downgraded our assessment of the quality of evidence from high to very low due to high risk of bias, very serious imprecision, and concerns of publication bias.

Serious adverse events

One study found that more participants developed diabetes mellitus when fibrin sealants were applied to pancreatic duct occlusion, both at three months' follow-up (33.7% fibrin sealant group versus 10.8% control group; 29 participants versus 9 participants) and

12 months' follow-up (33.7% fibrin sealant group versus 14.5% control group; 29 participants versus 12 participants) (Tran 2002). The other study did not report any serious adverse events related to fibrin sealants.

Quality of life

None of the studies reported this outcome.

Cost effectiveness

None of the studies reported this outcome.

Length of hospital stay

The mean length of hospital stay was 17.0 days in the fibrin sealant group and 16.5 days in the control group. The estimated MD for length of hospital stay was 0.58 days (95% CI -5.74 to 6.89; participants = 351; studies = 2) (Analysis 3.4). We downgraded our assessment of the quality of evidence from high to low due to high risk of bias, serious imprecision, and concerns of publication bias.

Subgroup analysis

We performed planned subgroup analyses based on the type of fibrin sealants (glue or patch) (Analysis 1.1; Analysis 1.2; Analysis 2.1; Analysis 2.2; Analysis 3.1). These subgroup analyses did not show any difference in the primary outcomes in the review.

We were unable to perform subgroup analysis based on the risk of bias in the studies as none of the studies was at low risk of bias. We were unable to perform planned subgroup analyses of different etiologies (pancreatic cancer, chronic pancreatitis, and others) and different risk of POPF (e.g. fatty pancreas, soft pancreas, small pancreatic duct), as the outcome data for the different subgroups were not available from the studies.

Sensitivity analysis

We performed the following planned sensitivity analyses.

1. Changing between a fixed-effect model and a random-effects model.
 2. Changing statistics between risk ratio (RR), risk differences (RDs), and odds ratios (ORs) for dichotomous outcomes.
 3. Changing statistics between mean difference (MD) and standardized mean differences (SMDs) for continuous outcomes.
- We observed no change in results by changing between a fixed-effect model and a random-effects model, calculating RDs and ORs for dichotomous outcomes, or calculating SMDs for continuous outcomes. We did not perform the other planned sensitivity analyses because none of the studies were at low risk of bias or were published in the non-English language literature.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Application of fibrin sealants to pancreatic anastomosis reinforcement for the prevention of postoperative pancreatic fistula following pancreaticoduodenectomy							
Patient or population: people undergoing pancreaticoduodenectomy Setting: hospital Intervention: fibrin sealant Comparison: no fibrin sealant							
Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no fibrin sealants	Risk with fibrin sealants					
Postoperative pancreatic fistula (ISGPF definition) Follow up: 30 days	Study population			RR 0.25 (0.01 to 5.06)	57 (1 study)	⊕○○○ very low ^{1,2,3}	
	62 per 1000	16 per 1000 (1 to 316)					
	Moderate						
	63 per 1000	16 per 1000 (1 to 319)					
Postoperative mortality Follow up: 30 days	Study population			Peto OR 0.15 (0 to 7.76)	251 (3 studies)	⊕⊕○○ low ^{2,3}	
	7 per 1000	1 per 1000 (0 to 54)					
	Moderate						
	0 per 1000	0 per 1000 (0 to 0)					
Overall postoperative morbidity Follow up: 30 days	Study population			RR 0.97 (0.65 to 1.45)	181 (2 studies)	⊕○○○ very low ^{1,2,3}	

⊕○○○
very low^{1,2,3}

⊕⊕○○
low^{2,3}

⊕○○○
very low^{1,2,3}

	347 per 1000	337 per 1000 (226 to 503)			
	Moderate				
	370 per 1000	359 per 1000 (240 to 537)			
Reoperation rate Follow up: 30 days	Study population		RR 0.83 (0.33 to 2.11)	181 (2 studies)	⊕○○○ very low ^{1,2,3}
	92 per 1000	76 per 1000 (30 to 194)			
	Moderate				
	133 per 1000	110 per 1000 (44 to 281)			
Serious adverse events	This outcome was not reported in any of the included studies				
Quality of life	This outcome was not reported in any of the included studies				
Cost effectiveness	This outcome was not reported in any of the included studies				
Length of hospital stay (days)	The mean length of hospital stay was 14.8 days	The mean length of hospital stay was 1.58 days lower (3.96 lower to 0.81 higher)	MD -1.58 (-3.96 to 0.81)	181 (2 studies)	⊕⊕○○ low ^{1,3,4}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference; **ISGPF:** International Study Group on Pancreatic Fistula

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level for serious risk of bias.

² Downgraded two levels for very serious imprecision (small sample size, confidence intervals of risk ratios overlapped 0.75 and 1.25).

³ Publication bias could not be assessed because of there being few studies.

⁴ Downgraded one level for serious imprecision (total population size was less than 400).

Application of fibrin sealants to pancreatic duct occlusion for the prevention of postoperative pancreatic fistula following pancreaticoduodenectomy							
Patient or population: people undergoing pancreaticoduodenectomy Setting: hospital Intervention: fibrin sealant Comparison: no fibrin sealant							
Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no sealants	fibrin sealants	Risk with fibrin sealants				
Postoperative pancreatic fistula (ISGPF definition)	This outcome was not reported in any of the included studies						
Postoperative mortality Follow up: 30 days	Study population			Peto OR 1.41 (0.63 to 3.13)	351 (2 studies)	⊕⊕○○ low ^{1,2}	
	61 per 1000		84 per 1000 (40 to 170)				
	Moderate						
	61 per 1000		84 per 1000 (40 to 170)				
Overall postoperative morbidity Follow up: 30 days	Study population			RR 1.16 (0.67 to 2.02)	351 (2 studies)	⊕○○○ very low ^{1,2,3,4}	
	276 per 1000		320 per 1000 (185 to 558)				
	Moderate						
	277 per 1000		321 per 1000 (185 to 559)				

Reoperation rate Follow up: 30 days	Study population		RR 0.85 (0.52 to 1.41)	351 (2 studies)	⊕○○○ very low ^{1,2,3}
	160 per 1000	136 per 1000 (83 to 225)			
	Moderate				
	160 per 1000	136 per 1000 (83 to 226)			
Serious adverse events (Diabetes mellitus) Follow-up: 3 to 12 months	3 months follow up		-	169 (1 study)	⊕⊕○○ low ^{1,3,5}
	108 per 1000	337 per 1000			
	12 months follow up				
	145 per 1000	337 per 1000			
Quality of life	This outcome was not reported in any of the included studies				
Cost effectiveness	This outcome was not reported in any of the included studies				
Length of hospital stay (days)	The mean length of hospital stay was 16.5 days	The mean length of hospital stay was 0.58 days higher (5.74 lower to 6.89 higher)	MD 0.58 (-5.74 to 6.89)	351 (2 studies)	⊕⊕○○ low ^{1,3,5}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference; **ISGPF:** International Study Group on Pancreatic Fistula

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

-
- ¹ Downgraded two levels for very serious imprecision (small sample size, confidence intervals of risk ratios overlapped 0.75 and 1.25).
 - ² Publication bias could not be assessed because of there being few studies.
 - ³ Downgraded one level for serious risk of bias.
 - ⁴ Downgraded one level for serious heterogeneity
 - ⁵ Downgraded one level for serious imprecision (small sample size; total population size was less than 400).

DISCUSSION

Summary of main results

Evidence from seven studies in 860 people undergoing distal pancreatectomy contributed data to the primary outcomes of this review. The results showed that fibrin sealants may have little to no difference in the postoperative pancreatic fistula (POPF) rate or mortality, compared to control. The impact of fibrin sealants on POPF rate and mortality was less certain when fibrin sealants were applied to pancreatic anastomosis reinforcement or pancreatic duct occlusion after pancreaticoduodenectomy. One study showed more participants developing diabetes mellitus at three and 12 months' follow-up when fibrin sealants were applied to pancreatic duct occlusion after pancreaticoduodenectomy. None of the other studies reported any serious adverse events related to fibrin sealants.

The definition of POPF varied in different studies. The incidence of POPF ranged from 11% to 65%, according to the different definitions applied in each study (Bassi 1999; Carter 2013; D'Andrea 1994; Lillemoe 2004; Martin 2013; Montorsi 2012; Park 2016; Sa Cunha 2015; Suc 2003; Suzuki 1995; Tran 2002). The International Study Group on Pancreatic Fistula (ISGPF) proposed a definition of POPF by consensus in order to compare different surgical experiences in pancreatic surgery (Bassi 2005; Bassi 2017). POPF has been graded as B and C (Bassi 2005; Bassi 2017): grade B requires a change in the management of the patient or persistent drainage more than 3 weeks; and grade C requires reoperation or leads to organ failure or death (or both) attributable to the POPF. Both POPF grade B and C have significant clinical impact and may be associated with increased morbidity and mortality (Bassi 2005; Gurusamy 2013). In this review, the incidence of POPF (grade B or C) was similar in the fibrin sealant group and the control group in various pancreatic resections.

The safety of fibrin sealants for people undergoing pancreatic surgery is another major concern for patients, surgeons, and healthcare funders (Siedentop 2001). Only one study reported that fibrin sealants were associated with higher risk of endocrine pancreatic insufficiency (diabetes mellitus) when fibrin sealants were applied to pancreatic duct occlusion (Tran 2002). None of the other studies reported any serious adverse events (e.g. hepatitis transmission, HIV transmission, allergy) related to fibrin sealants. The safety of fibrin sealants for people undergoing pancreatic surgery needs further evaluation.

The cost of fibrin sealants varies, but is relatively high (Carter 2013; Lillemoe 2004; Siedentop 2001). For example, the commercial fibrin glue Tissucol costs approximately USD 100 per 1 ml (Lovisetto 2007). In other words, it costs approximately USD 500 per case using 5 ml Tissucol for pancreatic surgery. None of the studies reported the quality of life in participants, so that a formal cost-effectiveness analysis cannot be conducted. Further cost-

effectiveness evaluation of fibrin sealants in pancreatic surgery is necessary.

Overall completeness and applicability of evidence

This review included people undergoing distal pancreatectomy, pancreaticoduodenectomy, and other pancreatic procedures such as those for malignancy and chronic pancreatitis. Thus, the results of this review are applicable to people undergoing various pancreatic resections.

Quality of the evidence

None of the studies were at low risk of bias. The studies included in each comparison were too few to assess publication bias. There was no indirectness of evidence because the studies did not perform the indirect comparison of one type of fibrin sealant versus another. The confidence intervals of the majority of outcomes were wide, indicating that the estimates of effect obtained were imprecise. Overall, we considered the quality of the evidence to be very low to moderate (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Potential biases in the review process

We did not create funnel plots to assess the publication bias due to the small number of studies included in each analysis. In addition, the data for length of hospital stay were skewed. The lack of normality for this outcome measure might introduce bias in this review. We contacted study investigators or study sponsors in order to verify key study characteristics, and obtained missing numerical outcome data. However, there was incomplete correspondence with study investigators or sponsors.

Agreements and disagreements with other studies or reviews

Another systematic review, Fingerhut 2009, included six studies that we included (Bassi 1999; D'Andrea 1994; Lillemoe 2004; Suc 2003; Suzuki 1995; Tran 2002). Because of the heterogeneity and lack of high-level evidence, the review by Fingerhut and colleagues did not draw a definitive conclusion on the role of fibrin sealants for preventing POPF (Fingerhut 2009). Since then, many systematic reviews and meta-analyses on this topic have published (Hüttner 2016; Orci 2014; Smits 2015; Weniger 2016). All of these systematic reviews and meta-analyses found that fibrin sealant use was associated with similar POPF rate as no fibrin sealant use following pancreatic surgery. This review agrees with most of the findings of these four systematic reviews and meta-analyses (Hüttner 2016;

Orci 2014; Smits 2015; Weniger 2016). We included two recent studies in the update of our review (Park 2016; Sa Cunha 2015). We found that fibrin sealants may have little to no difference in the POPF rate for people undergoing distal pancreatectomy, and that the impact of fibrin sealants on POPF rate was uncertain for people undergoing pancreaticoduodenectomy.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current available evidence, fibrin sealants may have little or no effect on postoperative pancreatic fistula or mortality in people undergoing distal pancreatectomy. The effects of fibrin sealants on the prevention of postoperative pancreatic fistula are uncertain in people undergoing pancreaticoduodenectomy.

Implications for research

1. Future studies should assess the effect of fibrin sealants for people undergoing pancreaticoduodenectomy.
2. Future studies should report the rate and the grade of the postoperative pancreatic fistula according to the updated definition of the International Study Group on Pancreatic Fistula (Bassi 2005; Bassi 2017).

3. Future randomized studies should use adequate methods of randomization and allocation concealment. Future studies need to employ blinding of participants and outcome assessors.

4. The long-term occlusion of the pancreatic duct by any means may cause atrophy of the pancreatic parenchyma and chronic pancreatitis in the occluded segment; consequently, the risk of diabetes mellitus with this procedure must be considered (Spanier 2008; Tran 2002).

ACKNOWLEDGEMENTS

We acknowledge the contribution of authors of previous version of this review: Cheng Y, Ye M, Xiong X, Peng S, Wu HM, Cheng N, Gong J.

We acknowledge the help and support of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group. The authors would also like to thank the following editors and peer referees who provided comments to improve the review: Sarah Rhodes (Editor), and Paul Moayyedi (Editor), and to Jessica Sharp for copy-editing the review.

The methods section of this review is based on a standard template used by Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group.

REFERENCES

References to studies included in this review

Bassi 1999 {published data only}

Bassi C, Butturini G, Falconi M, Salvia RNS, Caldiron E, Talamini G, et al. Prospective randomised pilot study of management of the pancreatic stump following distal resection. *HPB: the official journal of the International Hepato Pancreato Biliary Association* 1999;**1**(4):203–7.

Carter 2013 {published data only}

Carter TI, Fong ZV, Hyslop T, Lavu H, Tan WP, Hardacre J, et al. A dual-institution randomized controlled trial of remnant closure after distal pancreatectomy: does the addition of a falciform patch and fibrin glue improve outcomes?. *Journal of Gastrointestinal Surgery* 2013;**17**(1): 102–9.

D'Andrea 1994 {published data only}

D'Andrea AA, Costantino V, Sperti C, Pedrazzoli S. Human fibrin sealant in pancreatic surgery: it is useful in preventing fistulas? A prospective randomized study. *Italian Journal of Gastroenterology* 1994;**26**(6):283–6.

Lillemoe 2004 {published data only}

Lillemoe KD, Cameron JL, Kim MP, Campbell KA, Sauter PK, Coleman JA, et al. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy?

Results of a prospective randomized trial. *Journal of Gastrointestinal Surgery* 2004;**8**(7):772–4.

Martin 2013 {published data only}

Martin I, Au K. Does fibrin glue sealant decrease the rate of anastomotic leak after a pancreaticoduodenectomy? Results of a prospective randomized trial. *HPB: the Official Journal of the International Hepato Pancreato Biliary Association* 2013;**15**(8):561–6.

Montorsi 2012 {published data only}

Montorsi M, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M, et al. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. *Annals of Surgery* 2012;**256**(5):853–60.

Park 2016 {published data only}

Park JS, Lee DH, Jang JY, Han Y, Yoon DS, Kim JK, et al. Use of TachoSil® patches to prevent pancreatic leaks after distal pancreatectomy: a prospective, multicenter, randomized controlled study. *Journal of Hepato-Biliary-Pancreatic Sciences* 2016;**23**(2):110–7.

Sa Cunha 2015 {published data only}

Sa Cunha A, Carrere N, Meunier B, Fabre JM, Sauvanet A, et al. Stump closure reinforcement with absorbable

fibrin collagen sealant sponge (TachoSil) does not prevent pancreatic fistula after distal pancreatectomy: the FIABLE multicenter controlled randomized study. *The American Journal of Surgery* 2015;**210**(4):739–48.

Suc 2003 {published data only}

Suc B, Msika S, Fingerhut A, Fournanier G, Hay JM, Holmières F, et al. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: prospective randomized trial. *Annals of Surgery* 2003;**237**(1):57–65.

Suzuki 1995 {published data only}

Suzuki Y, Kuroda Y, Morita A, Fujino Y, Tanioka Y, Kawamura T, et al. Fibrin glue sealing for the prevention of pancreatic fistulas following distal pancreatectomy. *Archives of Surgery* 1995;**130**(9):952–5.

Tran 2002 {published data only}

Tran K, Van Eijck C, Di Carlo V, Hop WC, Zerbi A, Balzano G, et al. Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. *Annals of Surgery* 2002;**236**(44):422–8.

References to studies excluded from this review

Mita 2015 {published data only}

Mita K, Ito H, Murabayashi R, Asakawa H, Nabetani M, Kamasako A, Koizumi K, et al. Use of a fibrinogen/thrombin-based collagen fleece (TachoComb, TachoSil) with a stapled closure to prevent pancreatic fistula formation following distal pancreatectomy. *Surgical Innovation* 2015; **22**(6):601–5.

Ohwada 1998 {published data only}

Ohwada S, Ogawa T, Tanahashi Y, Nakamura S, Takeyoshi I, Ohya T, et al. Fibrin glue sandwich prevents pancreatic fistula following distal pancreatectomy. *World Journal of Surgery* 1998;**22**(5):494–8.

Pavlik Marangos 2011 {published data only}

Pavlik Marangos I, Rösok BI, Kazaryan AM, Rosseland AR, Edwin B. Effect of TachoSil patch in prevention of postoperative pancreatic fistula. *Journal of Gastrointestinal Surgery* 2011;**15**(8):1625–9.

Rehman 2016 {published data only}

Rehman S, Jaques BC. Does a fibrin glue sealant decrease post-operative pancreatic fistulae after pancreaticoduodenectomy; a single centre comparative study in 100 consecutive patients undergoing Whipple's procedure by a single surgeon. HPB: the official journal of the International Hepato Pancreato Biliary Association. Manchester: Elsevier, 2016; Vol. 18:e836–e837.
* Rehman S, Jaques BC. Does fibrin glue sealant used during pancreaticoduodenectomy reduce post-operative complication? Audit of 100 consecutive patients undergoing Whipple's procedure by a single surgeon. *Journal of the Pancreas* 2016;**17**(2):189–95.

Silvestri 2015 {published data only}

Silvestri S, Franchello A, Gonella F, Deiro G, Campora D, Cassine D, et al. Role of TachoSil® in distal

pancreatectomy: a single center experience. *Minerva Chirurgica* 2015;**70**(3):175–80.

Tashiro 1987 {published data only}

Tashiro S, Murata E, Hiraoka T, Nakakuma K, Watanabe E, Miyauchi Y. New technique for pancreaticojejunostomy using a biological adhesive. *The British Journal of Surgery* 1987;**74**(5):392–4.

Additional references

Anderson 2006

Anderson KE, Mack TM, Silverman DT. Cancer of the pancreas. In: Schottenfeld D, Fraumeni JF Jr editor(s). *Cancer Epidemiology and Prevention*. 3rd Edition. New York: Oxford University Press, 2006:721–63.

Bassi 2005

Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;**138**(1):8–13.

Bassi 2017

Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery* 2017;**161**(3):584–91.

Bornman 2001

Bornman PC, Beekingham IJ. ABC of diseases of liver, pancreas, and biliary system: Chronic pancreatitis. *BMJ* 2001;**322**(7287):660–3.

Braganza 2011

Braganza JM, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. *Lancet* 2011;**377**(9772):1184–97.

Carless 2003

Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2003, Issue 1. DOI: 10.1002/14651858.CD004171

Case 1960

Case TC. Postoperative pancreatic fistula. *American Journal of Surgery* 1960;**99**(6):898–903.

Cheng 2014

Cheng Y, Jia Q, Xiong X, He D, Cheng NS. Hepatobiliary and pancreatic: traumatic neuroma of the ampulla of Vater. *Journal of Gastroenterology and Hepatology* 2014;**29**(7):1342.

Cheng 2016a

Cheng Y, Xia J, Lai M, Cheng N, He S. Prophylactic abdominal drainage for pancreatic surgery. *Cochrane Database of Systematic Reviews* 2016, Issue 10. DOI: 10.1002/14651858.CD010583.pub3

Cheng 2017

Cheng Y, Briarava M, Lai M, Wang X, Tu B, Cheng N, et al. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction for the prevention of postoperative pancreatic fistula following pancreaticoduodenectomy. *Cochrane*

Database of Systematic Reviews 2017, Issue 9. DOI: 10.1002/14651858.CD012257.pub2

Chirletti 2009

Chirletti P, Caronna R, Fanello G, Schiratti M, Stagnitti F, Peparini N, et al. Pancreaticojejunostomy with application of fibrinogen/thrombin-coated collagen patch (TachoSil) in Roux-en-Y reconstruction after pancreaticoduodenectomy. *Journal of Gastrointestinal Surgery* 2009;**13**(7):1399–400.

Chow 2010

Chow A, Marshall H, Zacharakis E, Paraskeva P, Purkayastha S. Use of tissue glue for surgical incision closure: a systematic review and meta-analysis of randomized controlled trials. *Journal of the American College of Surgeons* 2010;**211**(1):114–25.

Clavien 2009

Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Annals of Surgery* 2009;**250**(2):187–96.

Connor 2005

Connor S, Alexakis N, Garden OJ, Leandros E, Bramis J, Wigmore SJ. Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. *British Journal of Surgery* 2005;**92**(9):1059–67.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Diener 2014

Diener MK, Fitzmaurice C, Schwarzer G, Seiler CM, Hüttner FJ, Antes G, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database of Systematic Reviews* 2014, Issue 11. DOI: 10.1002/14651858.CD006053.pub5

Dong 2016

Dong Z, Xu J, Wang Z, Petrov MS. Stents for the prevention of pancreatic fistula following pancreaticoduodenectomy. *Cochrane Database of Systematic Reviews* 2016, Issue 5. DOI: 10.1002/14651858.CD008914.pub3

Dragovich 2015

Dragovich T, Erickson RA, Larson CR, Shabahang M. Pancreatic cancer. emedicine.medscape.com/article/280605-overview#showall (accessed 6 February 2017).

Ferlay 2016

Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. *Acta Oncologica* 2016;**55**(9-10):1158–60.

Fingerhut 2009

Fingerhut A, Veyrie N, Ata T, Alexakis N, Leandros E. Use of sealants in pancreatic surgery: critical appraisal of the literature. *Digestive Surgery* 2009;**26**(1):7–14.

Forman 2011

Forman D, Delaney B, Kuipers E, Malthaner R, Moayyedi P, Gardener E, et al. Cochrane Upper Gastrointestinal and Pancreatic Diseases Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2011, Issue 12. Art. No.: COLOCA.

Garg 2004

Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. *Journal of Gastroenterology and Hepatology* 2004;**19**(9):998–1004.

GRADEpro 2015 [Computer program]

Brozek J, Oxman A, Schunemann H. GRADEprofiler (GRADEpro). Canada: Evidence Prime, 2015.

Gurusamy 2013

Gurusamy KS, Koti R, Fusai G, Davidson BR. Somatostatin analogues for pancreatic surgery. *Cochrane Database of Systematic Reviews* 2013, Issue 4. DOI: 10.1002/14651858.CD008370.pub3

Hackert 2011

Hackert T, Werner J, Buchler MW. Postoperative pancreatic fistula. *The Surgeon* 2011; Vol. 9, issue 4:211–7.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011a

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hüttner 2016

Hüttner FJ, Mihaljevic AL, Hackert T, Ulrich A, Böhler MW, Diener MK. Effectiveness of Tachosil® in the prevention of postoperative pancreatic fistula after distal pancreatectomy: a systematic review and meta-analysis. *Langenbeck's Archives of Surgery* 2016;**401**(2):151–9.

Kuroki 2005

Kuroki T, Tajima Y, Kanematsu T. Surgical management for the prevention of pancreatic fistula following distal pancreatectomy. *Journal of Hepato-Biliary-Pancreatic Surgery* 2005;**12**(4):283–5.

Lovisetto 2007

Lovisetto F, Zonta S, Rota E, Mazzilli M, Bardone M, Bottero L, et al. Use of human fibrin glue (Tissucol) versus

- staples for mesh fixation in laparoscopic transabdominal preperitoneal hernioplasty: a prospective, randomized study. *Annals of Surgery* 2007;**245**(2):222–31.
- Lowenfels 2006**
Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. *Best Practice and Research. Clinical Gastroenterology* 2006;**20**(2):197–209.
- Lämsä 2008**
Lämsä T, Jin HT, Sand J, Nordback I. Tissue adhesives and the pancreas: biocompatibility and adhesive properties of 6 preparations. *Pancreas* 2008;**36**(3):261–6.
- Lévy 2006**
Lévy P, Barthet M, Mollard BR, Amouretti M, Marion-Audibert AM, Dyard F. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. *Gastroenterologie Clinique et Biologique* 2006;**30**(6-7): 838–44.
- McMillan 2016**
McMillan MT, Soi S, Asbun HJ, Ball CG, Bassi C, Beane JD, et al. Risk-adjusted outcomes of clinically relevant pancreatic fistula following pancreatoduodenectomy: a model for performance evaluation. *Annals of Surgery* 2016; **264**(2):344–52.
- Mobley 2002**
Mobley SR, Hilinski J, Toriumi DM. Surgical tissue adhesives. *Facial Plastic Surgery Clinics of North America* 2002;**10**(2):147–54.
- Moher 2009**
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLOS Medicine* 2009;**3**(3):12–130.
- NLM 1990**
National Library of Medicine. Medical subject heading: Fibrin tissue adhesive. ncbi.nlm.nih.gov/mesh/68015718. Washington: Department of Health, Education and Welfare, (accessed 6 February 2017).
- Ochiai 2010**
Ochiai T, Sonoyama T, Soga K, Inoue K, Ikoma H, Shiozaki A, et al. Application of polyethylene glycolic acid felt with fibrin sealant to prevent postoperative pancreatic fistula in pancreatic surgery. *Journal of Gastrointestinal Surgery* 2010; **14**(5):884–90.
- Orci 2014**
Orci LA, Oldani G, Berney T, Andres A, Mentha G, Morel P, et al. Systematic review and meta-analysis of fibrin sealants for patients undergoing pancreatic resection. *HPB: the official journal of the International Hepato Pancreato Biliary Association* 2014;**16**(1):3–11.
- Ramacciato 2011**
Ramacciato G, Mercantini P, Petrucciani N, Nigri GR, Kazemi A, Muroli M, et al. Risk factors of pancreatic fistula after pancreaticoduodenectomy: a collective review. *American Journal of Surgery* 2011;**77**(3):257–69.
- Reeves 2011**
Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- RevMan 2014 [Computer program]**
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Riall 2008**
Riall TS, Reddy DM, Nealon WH, Goodwin JS. The effect of age on short-term outcomes after pancreatic resection: a population-based study. *Annals of Surgery* 2008;**248**(3): 459–67.
- Rickenbacher 2009**
Rickenbacher A, Breitenstein S, Lesurtel M, Frilling A. Efficacy of TachoSil a fibrin-based haemostat in different fields of surgery—a systematic review. *Expert Opinion on Biological Therapy* 2009;**9**(7):897–907.
- Schulick 2009**
Schulick RD, Yoshimura K. Stents, glue, etc.: is anything proven to help prevent pancreatic leaks/fistulae?. *Journal of Gastrointestinal Surgery* 2009;**13**(7):1184–6.
- Siedentop 2001**
Siedentop KH, Park JJ, Shah AN, Bhattacharyya TK, O’Grady KM. Safety and efficacy of currently available fibrin tissue adhesives. *American Journal of Otolaryngology* 2001;**22**(4):230–5.
- Smits 2015**
Smits FJ, van Santvoort HC, Besselink MG, Borel Rinkes IH, Molenaar IQ. Systematic review on the use of matrix-bound sealants in pancreatic resection. *HPB: the official journal of the International Hepato Pancreato Biliary Association* 2015;**17**(11):1033–9.
- Spanier 2008**
Spanier BW, Dijkgraaf MG, Bruno MJ. Epidemiology, aetiology and outcome of acute and chronic pancreatitis: an update. *Best Practice and Research. Clinical Gastroenterology* 2008;**22**(1):45–63.
- Spotnitz 2010**
Spotnitz WD. Fibrin sealant: past, present, and future: a brief review. *World Journal of Surgery* 2010;**34**(4):632–4.
- Sterne 2011**
Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Weniger 2016**
Weniger M, D’Haese JG, Crispin A, Angele MK, Werner J, et al. Autologous but not fibrin sealant patches for stump

coverage reduce clinically relevant pancreatic fistula in distal pancreatectomy: a systematic review and meta-analysis. *World Journal of Surgery* 2016;**40**(11):2771–81.

References to other published versions of this review

Cheng 2012

Cheng Y, Xiong X, Peng S, Wu HM, Cheng N. Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery. *Cochrane Database*

of Systematic Reviews 2012, Issue 2. DOI: 10.1002/14651858.CD009621

Cheng 2016b

Cheng Y, Ye M, Xiong X, Peng S, Wu HM, Cheng N, et al. Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery. *Cochrane Database of Systematic Reviews* 2016, Issue 2. DOI: 10.1002/14651858.CD009621.pub2

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bassi 1999

Methods	Randomized controlled trial	
Participants	Country: Italy Number randomized: 69 Post-randomization dropout: 0 (0%) Mean age: not mentioned Females: 50 (72.5%) Malignancy: 69 (100%) Chronic pancreatitis: 0 (0%) Pancreaticoduodenectomy: 0 (0%) Distal pancreatectomy: 69 (100%) Other pancreatic surgery: 0 (0%) Inclusion criteria 1. People suffering pancreatic tumors of the body or tail 2. People with high risk of postoperative pancreatic fistula (soft pancreas)	
Interventions	Fibrin glue (Tissucol) was applied to reinforce pancreatic stump closure Participants (N = 69) were randomly assigned to five groups Group 1: manual suture (N = 15) Group 2: fibrin glue and manual suture (N = 11) Group 3: polypropylene mesh and manual suture (N = 15). This group was not included in the review Group 4: pancreaticojejunostomy (N = 14). This group was not included in the review Group 5: stapler (N = 14). This group was not included in the review	
Outcomes	The outcomes reported were postoperative pancreatic fistula, mortality, operative time, and general morbidity	
Notes	Definition of pancreatic fistula: the loss of at least 10ml/day of drainage fluid with an amylase content of at least 1000 IU/L beyond day 7	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided

Bassi 1999 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomization drop-outs
Selective reporting (reporting bias)	Low risk	Comment: all the primary outcomes were reported. There was some selective outcome reporting in the secondary outcomes, but the review authors consider this trial to be free of selective reporting for the primary outcomes
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Carter 2013

Methods	Randomized controlled trial
Participants	<p>Country: America Number randomized: 109 Post-randomization dropout: 8 (7.3%) Mean age: 62.2 years Females: 60 (59.4%) Malignancy: 77 (76.2%) Other pancreatic diseases: 24 (23.8%) Pancreaticoduodenectomy: (0%) Distal pancreatectomy: 109 (100%) Other pancreatic surgery: 0 (0%) Inclusion criteria: people undergoing distal pancreatectomy Exclusion criteria</p> <ol style="list-style-type: none"> 1. Total or completion pancreatectomy (no pancreas remnant) 2. Central pancreatectomy 3. A surgically absent falciform ligament 4. Pregnancy
Interventions	<p>Fibrin glue (Vigagel) and falciform ligament patch were applied to pancreatic stump closure reinforcement Participants were randomly assigned to two groups Group 1: fibrin glue and falciform ligament patch (N = 54) Group 2: stapling or suturing without using fibrin glue (N = 55)</p>
Outcomes	The outcomes reported were postoperative pancreatic fistula, grade of pancreatic fistula, mortality, hospital readmission, length of hospital stay, and radiological drainage requiring insertion of drain

Notes	Definition of pancreatic fistula: an abnormal communication between the pancreatic ductal system and another epithelial surface containing pancreatic fluid (defined by the International Study Group on Pancreatic Fistula)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was conducted utilizing random permuted blocks within each stratum"
Allocation concealment (selection bias)	Low risk	Quote: "...opaque envelope containing the patient's assignment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Surgeons and staff were blinded from the randomization process until intraoperative stratification"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Due to insufficient numbers, the hard gland stratum of the trial was excluded from analysis, leaving only patients in the soft stratum to be fully analyzed"
Selective reporting (reporting bias)	High risk	The study protocol is available and one of the study's pre-specified outcomes (morbidity) that is of interest in the review was not reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

D'Andrea 1994

Methods	Randomized controlled trial
Participants	Country: Italy Number randomized: 97 Post-randomization dropout: 0 (0%) Mean age: 50.0 years Females: 34 (35.1%) Malignancy: 51 (52.6%) Pancreatic inflammatory diseases: 46 (46.4%) Pancreaticoduodenectomy: 30 (31%) Pancreaticojejunostomy: 40 (41%) Distal pancreatectomy: 23 (24%) Other pancreatic surgery: 4 (4%)

	Inclusion criteria: people undergoing pancreatic surgery	
Interventions	Fibrin glue (Fibrinogen-Green Cross) was applied to reinforce pancreatic anastomosis or pancreatic stump closure Participants were randomly assigned to two groups. Group 1: fibrin glue (N = 43) 1. Pancreatic anastomosis reinforcement: 32 2. Pancreatic stump closure reinforcement: 10 3. Others: 1 Group 2: no fibrin glue (N = 54)	
Outcomes	The outcomes reported were postoperative pancreatic fistula, mortality, and serious adverse events	
Notes	Definition of pancreatic fistula: No information provided	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomization drop-outs
Selective reporting (reporting bias)	Low risk	Comment: all the primary outcomes were reported. There was some selective outcome reporting in the secondary outcomes, but the review authors consider this trial to be free of selective reporting for the primary outcomes
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Methods	Randomized controlled trial
Participants	Country: America Number randomized: 124 Post-randomization dropout: 0 (0%) Mean age: 64.0 years Females: 47 (37.9%) Malignancy: 81 (65.3%) Chronic pancreatitis: 2 (1.6%) Pancreaticoduodenectomy: 124 (100%) Distal pancreatectomy: 0 (0%) Other pancreatic surgery: 0 (0%) Inclusion criteria: people with high risk of postoperative pancreatic fistula (soft pancreas with normal pancreatic duct)
Interventions	Fibrin glue (Hemaseel APR) was applied to reinforce pancreatic anastomosis. Participants were randomly assigned to two groups. Group 1: fibrin glue (N = 58) Group 2: no fibrin glue (N = 66)
Outcomes	The outcomes reported were postoperative pancreatic fistula, mortality, morbidity, reoperation rate, serious adverse events, costs, length of hospital stay, operative time, blood loss, and blood transfusion
Notes	Definition of pancreatic fistula: a drain output of greater than 50 ml fluid on or after postoperative day 10 with an amylase content greater than 3 times the serum amylase or pancreatic anastomotic disruption demonstrated radiographically

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the patients were randomized using a randomly generated number pattern"
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinical information regarding the postoperative course and complications were collected by study nurses without knowledge of the treatment arm"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomization dropouts

Lillemoe 2004 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: all the primary outcomes were reported. There was some selective outcome reporting in the secondary outcomes, but the review authors consider this trial to be free of selective reporting for the primary outcomes
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Martin 2013

Methods	Randomized controlled trial	
Participants	Country: Australia Number randomized: 57 Post-randomization dropout: 0 Mean age: 63.4 years Females: 28 (49.1%) Malignancy: 44 (77.2%) Chronic pancreatitis: 2 (3.5%) Pancreaticoduodenectomy: 57 (100%) Distal pancreatectomy: 0 (0%) Other pancreatic surgery: 0 (0%) Inclusion criteria: people undergoing a pancreaticoduodenectomy for any pancreatic or extra-pancreatic disease	
Interventions	Fibrin glue (Tisseel) was applied to reinforce all reconstructive anastomoses Participants were randomly assigned to two groups Group 1: fibrin glue (N = 25) Group 2: no fibrin glue (N = 32)	
Outcomes	The outcomes reported were postoperative pancreatic fistula, grade of pancreatic fistula, mortality, complications, reoperation, length of hospital stay, and drain lipase levels	
Notes	Definition of pancreatic fistula: an abnormal communication between the pancreatic ductal system and another epithelial surface containing pancreatic fluid (defined by the International Study Group on Pancreatic Fistula)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “randomization occurring during the operation using a coin toss”
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided

Martin 2013 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomization dropouts
Selective reporting (reporting bias)	Low risk	Comment: all the primary outcomes were reported. There was some selective outcome reporting in the secondary outcomes, but the review authors consider this trial to be free of selective reporting for the primary outcomes
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Montorsi 2012

Methods	Randomized controlled trial
Participants	<p>Country: Italy Number randomized: 275 Post-randomization dropout: 0 (0%) Mean age: 61.0 years Females: 172 (62.5%) Malignancy: not mentioned Chronic pancreatitis: not mentioned Pancreaticoduodenectomy: 0 (0%) Distal pancreatectomy: 275 (100%) Other pancreatic surgery: 0 (0%)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. People undergoing elective distal pancreatectomy 2. People aged 18 years or older <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. People undergoing emergency operations 2. People undergoing pancreatic resection other than distal pancreatectomy 3. People undergoing pancreatic resection as an enlargement of other oncological resections 4. People with chronic pancreatitis 5. People undergoing distal pancreatectomy with a visceral anastomosis 6. People using hemostatics or sealants other than TachoSil on the pancreatic remnant 7. People undergoing prophylaxis with somatostatin analogues

Interventions	Fibrin sealant patch (TachoSil) was applied to pancreatic stump closure reinforcement. Participants were randomly assigned to two groups. Group 1: fibrin sealant patch (N = 145) Group 2: no patch (N = 130)	
Outcomes	The outcomes reported were postoperative pancreatic fistula, grade of pancreatic fistula, mortality, morbidity, reoperation, length of hospital stay, operative time, intraoperative blood loss, amylase levels, daily drain output, days to drain removal, various postoperative complications, interventional radiology procedures, and adverse events	
Notes	Definition of pancreatic fistula: any measurable amount of drainage fluid, with amylase concentration greater than 3 times the upper limit of normal after postoperative day 3 (defined by the International Study Group on Pancreatic Fistula)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A major protocol violation occurred in 2 patients (0.7%), however, no patients were excluded from analysis"
Selective reporting (reporting bias)	Low risk	Comment: all the primary outcomes were reported. There was some selective outcome reporting in the secondary outcomes, but the review authors consider this trial to be free of selective reporting for the primary outcomes
Other bias	High risk	Quote: "There was no significant difference between the 2 groups in clinical and operative characteristics other than a higher proportion of men in the TachoSil group" Comment: baseline imbalance

Methods	Randomized controlled trial	
Participants	Country: South Korea Number randomized: 108 Post-randomization dropout: 7 (6.5%) Mean age: 56.2 years Females: 63 (62.4%) Malignancy: 71 (70.3%) Chronic pancreatitis: not mentioned Pancreaticoduodenectomy: 0 (0%) Distal pancreatectomy: 108 (100%) Other pancreatic surgery: 0 (0%) Inclusion criteria 1. People undergoing elective distal pancreatectomy 2. People aged 20 to 85 years Exclusion criteria 1. People with chronic pancreatitis-induced atrophic pancreas or calcification of the pancreatic parenchyma 2. People undergoing immunosuppressive therapy 3. People with history of chemoradiotherapy 4. People undergoing treatment with clinically relevant drugs, including somatostatin analogs	
Interventions	Fibrin sealant patch (TachoSil) was applied to pancreatic stump closure reinforcement. Participants were randomly assigned to two groups. Group 1: fibrin sealant patch (N = 50) Group 2: no patch (N = 58)	
Outcomes	The outcomes reported were postoperative pancreatic fistula, grade of pancreatic fistula, mortality, morbidity, reoperation, length of hospital stay, operative time, intraoperative blood loss, various postoperative complications, interventional radiology procedures, and adverse events	
Notes	Definition of pancreatic fistula: any measurable amount of drainage fluid, with amylase concentration greater than 3 times the upper limit of normal after postoperative day 3 (defined by the International Study Group on Pancreatic Fistula)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation sequence was computer generated"
Allocation concealment (selection bias)	Low risk	Quote: "After randomization, all clinical and pathologic data, including operation field photographs, were stored in a central database"

Park 2016 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind randomized controlled study" and "safety monitoring board blinded to the treatment group"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "safety monitoring board blinded to the treatment group" Comment: The outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Overall, 108 patients were enrolled and randomized Seven patients were subsequently excluded from the study Therefore, 101 patients were analyzed in this study'
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified outcomes were reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Sa Cunha 2015

Methods	Randomized controlled trial
Participants	<p>Country: France Number randomized: 297 Post-randomization dropout: 27 (9.1%) Mean age: 60.8 years Females: 166 (61.5%) Malignancy: 142 (52.6%) Chronic pancreatitis: 15 (5.6%) Pancreaticoduodenectomy: 0 (0%) Distal pancreatectomy: 270 (100%) Other pancreatic surgery: 0 (0%) Inclusion criteria 1. People undergoing elective distal pancreatectomy 2. People with life expectancy of at least 6 months Exclusion criteria 1. People with history of allergy to human thrombin and fibrinogen or collagen 2. People with preoperative signs of chronic pancreatitis 3. People with indications for simple enucleation or intraabdominal anastomosis, including pancreatoenterostomy</p>
Interventions	<p>Fibrin sealant patch (TachoSil) was applied to pancreatic stump closure reinforcement Participants were randomly assigned to two groups Group 1: fibrin sealant patch (N = 134) Group 2: no patch (N = 136)</p>

Outcomes	The outcomes reported were postoperative pancreatic fistula, grade of pancreatic fistula, mortality, morbidity, length of hospital stay, operative time, various postoperative complications, and adverse events	
Notes	Definition of pancreatic fistula: any measurable amount of drainage fluid, with amylase concentration greater than 3 times the upper limit of normal after postoperative day 3 (defined by the International Study Group on Pancreatic Fistula)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomized with random sequence generation, and the sequence was generated by computer"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centralized by a vocal server"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The evaluation of patient outcome for both the diagnosis of POPF and the causality of adverse events was double blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The evaluation of patient outcome for both the diagnosis of POPF and the causality of adverse events was double blinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Two hundred ninety-seven patients underwent randomization, 27 were ultimately found to not correctly fulfill the entry requirements, and were not included in final analysis"
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified outcomes were reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Suc 2003

Methods	Randomized controlled trial
Participants	Country: France Number randomized: 182 Post-randomization dropout: 0 (0%) Mean age: 56 years Females: 80 (44%) Malignancy: 118 (64.8%)

	<p>Chronic pancreatitis: 29 (15.9%)</p> <p>Pancreaticoduodenectomy: 141 (77.5%)</p> <p>Distal pancreatectomy: 41 (22.5%)</p> <p>Other pancreatic surgery: 0 (0%)</p> <p>Inclusion criteria: people undergoing pancreatic resection for either benign or malignant (pancreatic or extra-pancreatic (biliary, ampullary, or duodenal)) tumors or chronic pancreatitis</p> <p>Exclusion criteria</p> <ol style="list-style-type: none">1. People undergoing total pancreatectomy, tumorectomy or enucleation2. People undergoing internal drainage for pseudocyst3. People undergoing pancreaticoduodenectomy in whom the pancreatic stump was not anastomosed4. People undergoing side-to-side pancreaticojejunostomy without resection5. People undergoing pancreatic resection for acute pancreatitis or trauma	
Interventions	<p>Fibrin glue (Tissucol) was applied to pancreatic duct occlusion with pancreatodigestive anastomosis after pancreaticoduodenectomy</p> <p>Fibrin glue was applied to pancreatic duct occlusion after distal pancreatectomy with or without pancreatodigestive anastomosis</p> <p>Participants were randomly assigned to two groups.</p> <p>Group 1: occlusion by fibrin glue (N = 102)</p> <p>Group 2: no ductal occlusion (N = 80)</p>	
Outcomes	<p>The outcomes reported were postoperative pancreatic fistula, mortality, morbidity, re-operation rate, serious adverse events, and length of hospital stay</p>	
Notes	<p>Definition of pancreatic fistula: fluid obtained through drains or percutaneous aspiration with an amylase content greater than 4 times the serum amylase for 3 days, or anastomotic leaks demonstrated by fistulography, or by hydrosoluble contrast studies in the case of pancreatogastrostomy</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment with ductal occlusion or not, as generated by computerized random-number tables"
Allocation concealment (selection bias)	Low risk	Quote: "Treatment with ductal occlusion or not was allotted through a telephone call to the coordinating center"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients as well as the nursing staff were not aware of the treatment arm to which the patients were allotted, but the surgeon performing the operation, obviously, was (single-blind study without placebo)"

Suc 2003 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Postoperative complications, however, were assessed by a physician who was unaware of the allotted treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were no protocol violations, especially as concerned randomization. No patient was withdrawn from analysis after randomization, and there were no crossovers after allocation"
Selective reporting (reporting bias)	Low risk	Comment: all the primary outcomes were reported. There was some selective outcome reporting in the secondary outcomes, but the review authors consider this trial to be free of selective reporting for the primary outcomes
Other bias	High risk	Quote: "The two groups were similar in pre- and intraoperative characteristics except that there were significantly more patients in the ductal occlusion group who received octreotide (53% vs. 26%; $P < 0.001$), who had reinforcement of their anastomosis by fibrin glue (59% vs. 10%; $P < 0.001$), or who had fibrotic pancreatic stumps (46% vs. 30%; $P = 0.02$)"

Suzuki 1995

Methods	Randomized controlled trial
Participants	Country: Japan Number randomized: 56 Post-randomization dropout: 0 (0%) Mean age: 60 years Females: 16 (28.6%) Malignancy: not mentioned Chronic pancreatitis: not mentioned Pancreaticoduodenectomy: 0 (0%) Distal pancreatectomy: 56 (100%) Other pancreatic surgery: 0 (0%) Inclusion criteria: people undergoing distal pancreatectomy Exclusion criteria: people with esophagojejunostomy separation postoperatively
Interventions	Fibrin glue (Tisseel) was applied to reinforce pancreatic stump closure. Participants were randomly assigned to two groups. Group 1: fibrin glue (N = 26) Group 2: no fibrin glue (N = 30)
Outcomes	The outcomes reported were postoperative pancreatic fistula and serious adverse events

Suzuki 1995 (Continued)

Notes	Definition of pancreatic fistula: pancreatic fluid discharge more than 7 postoperative days with an amylase content greater than 3 times the serum amylase	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned by drawing of lots"
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomization drop-outs
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as mortality and morbidity were not reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Tran 2002

Methods	Randomized controlled trial
Participants	Country: Netherlands Number randomized: 169 Post-randomization dropout: 0 (0%) Mean age: 59 years Females: 64 (37.9%) Malignancy: 149 (88.2%) Chronic pancreatitis: 19 (11.2%) Pancreaticoduodenectomy: 169 (100%) Distal pancreatectomy: 0 (0%) Other pancreatic surgery: 0 (0%) Inclusion criteria: people undergoing a pancreaticoduodenectomy for suspected pancreatic cancer and periampullary cancer

Interventions	Fibrin glue (Tissucol) was applied to pancreatic duct occlusion without pancreatodigestive anastomosis Participants were randomly assigned to two groups. Group 1: occlusion by fibrin glue without pancreatodigestive anastomosis (N = 86) Group 2: pancreaticojejunostomy without ductal occlusion by fibrin glue (N = 83)
Outcomes	The outcomes reported were postoperative pancreatic fistula, mortality, morbidity, re-operation rate, length of hospital stay, operative time, blood loss, blood transfusion, body weight, defecation frequency, aspect of stool, pancreas enzyme substitution, and occurrence of diabetes mellitus
Notes	Definition of pancreatic fistula: a drain output of any measurable volume of fluid with an amylase and lipase content greater than 3 times the serum concentration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomization drop-outs
Selective reporting (reporting bias)	Low risk	Comment: all the primary outcomes were reported. There was some selective outcome reporting in the secondary outcomes, but the review authors consider this trial to be free of selective reporting for the primary outcomes
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Mita 2015	A non-randomized study
Ohwada 1998	A non-randomized study
Pavlik Marangos 2011	A non-randomized study
Rehman 2016	A quasi-randomized study
Silvestri 2015	A non-randomized study
Tashiro 1987	A non-randomized study

DATA AND ANALYSES

Comparison 1. Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative pancreatic fistula (ISGPF definition)	4	755	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.68, 1.35]
1.1 Fibrin glue	1	109	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.44, 2.37]
1.2 Fibrin sealant patch	3	646	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.45]
2 Postoperative mortality	6	804	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.05, 5.03]
2.1 Fibrin glue	3	158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Fibrin sealant patch	3	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.05, 5.03]
3 Overall postoperative morbidity	3	646	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.97, 1.58]
4 Reoperation rate	2	376	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.15, 1.71]
5 Length of hospital stay	4	755	Mean Difference (IV, Random, 95% CI)	0.32 [-1.06, 1.70]

Comparison 2. Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative pancreatic fistula (ISGPF definition)	1	57	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.01, 5.06]
1.1 Fibrin glue	1	57	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.01, 5.06]
1.2 Fibrin sealant patch	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Postoperative mortality	3	251	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.00, 7.76]
2.1 Fibrin glue	3	251	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.00, 7.76]
2.2 Fibrin sealant patch	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Overall postoperative morbidity	2	181	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.65, 1.45]
4 Reoperation rate	2	181	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.33, 2.11]
5 Length of hospital stay	2	181	Mean Difference (IV, Random, 95% CI)	-1.58 [-3.96, 0.81]

Comparison 3. Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative mortality	2	351	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [0.63, 3.13]
1.1 Fibrin glue	2	351	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [0.63, 3.13]
1.2 Fibrin sealant patch	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Overall postoperative morbidity	2	351	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.67, 2.02]
3 Reoperation rate	2	351	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.52, 1.41]
4 Length of hospital stay	2	351	Mean Difference (IV, Random, 95% CI)	0.58 [-5.74, 6.89]

Analysis 1.1. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 1 Postoperative pancreatic fistula (ISGPF definition).

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy)

Outcome: 1 Postoperative pancreatic fistula (ISGPF definition)

Analysis 1.2. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 2 Postoperative mortality.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy)

Outcome: 2 Postoperative mortality

Analysis 1.3. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 3 Overall postoperative morbidity.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy)

Outcome: 3 Overall postoperative morbidity

Analysis 1.4. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 4 Reoperation rate.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy)

Outcome: 4 Reoperation rate

Analysis 1.5. Comparison 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy), Outcome 5 Length of hospital stay.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 1 Fibrin sealants versus no fibrin sealant (pancreatic stump closure reinforcement after distal pancreatectomy)

Outcome: 5 Length of hospital stay

Analysis 2.1. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 1 Postoperative pancreatic fistula (ISGPF definition).

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy)

Outcome: 1 Postoperative pancreatic fistula (ISGPF definition)

Analysis 2.2. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 2 Postoperative mortality.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy)

Outcome: 2 Postoperative mortality

Analysis 2.3. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 3 Overall postoperative morbidity.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy)

Outcome: 3 Overall postoperative morbidity

Analysis 2.4. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 4 Reoperation rate.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy)

Outcome: 4 Reoperation rate

Analysis 2.5. Comparison 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy), Outcome 5 Length of hospital stay.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 2 Fibrin sealants versus no fibrin sealant (pancreatic anastomosis reinforcement after pancreaticoduodenectomy)

Outcome: 5 Length of hospital stay

Analysis 3.1. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 1 Postoperative mortality.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy)

Outcome: 1 Postoperative mortality

Analysis 3.2. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 2 Overall postoperative morbidity.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy)

Outcome: 2 Overall postoperative morbidity

Analysis 3.3. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 3 Reoperation rate.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy)

Outcome: 3 Reoperation rate

Analysis 3.4. Comparison 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy), Outcome 4 Length of hospital stay.

Review: Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery

Comparison: 3 Fibrin sealants versus no fibrin sealant (pancreatic duct occlusion after pancreaticoduodenectomy)

Outcome: 4 Length of hospital stay

APPENDICES

Appendix I. Glossary of terms

Abscess: a collection of pus which is surrounded by inflamed tissue.

Adverse events: side effects.

Ampullary: related to the union of the pancreatic duct and the common bile duct.

Analogues: similar drugs.

Anastomosis: connection between two organs (e.g. stomach and small intestine) created by surgery.

Biliary: related to the bile duct.

Cardiovascular: of or relating to the heart and the blood vessels.

Chronic pancreatitis: long-standing inflammation of the pancreas.

Diabetes mellitus: a condition characterized by an increase in blood sugar due to the inadequate production and utilization of insulin by the pancreas.

Duodenal: related to the first section of the small intestine.

Enteric: relating to the intestines.

Etiology: the cause or origin of a disease or disorder.

Extra-pancreatic: surrounding the pancreas.

Fibrinogen: a protein in blood that is converted into fibrin during blood clot formation.

Fibrin sealant: a kind of surgical tissue adhesive.

Gastric: relating to the stomach.

Hepatitis: inflammation of the liver.

HIV (Human immunodeficiency virus): a virus that decreases the body's natural ability to fight off disease and infection. The later stages are called AIDS acquired immunodeficiency syndrome.

Incidence: the rate at which something happens.

Laparoscopic: related to key-hole surgery.

Malignancy: cancer.

Morbidity: the proportion of people with any postoperative complications.

Mortality: the proportion of deaths after surgery.

Occlusion: blockage or closure.

Pancreas: the organ in the body that produces insulin and a liquid that helps your body to use the food that you eat.

Pancreatectomy: surgical removal of part or all of the pancreas.

Pancreatic: relating to the pancreas.

Pancreatitis: inflammation of the pancreas.

Pancreatic-enteric anastomosis: the surgical connection of pancreatic duct and intestine to form a continuous channel.

Pancreatic fistula: a complication whereby the pancreas is disconnected from the nearby gut, and then reconnected to allow pancreatic juice containing digestive enzymes to enter the digestive system.

Pancreaticoduodenectomy: a major surgical operation involving the pancreas, duodenum, and other organs.

Parenchyma: the tissue of an organ responsible for its function.

Postoperative: relating to the time after someone has had a medical operation.

Prevalence: the total number of people with an illness at a designated time.

Randomized controlled trials: an experiment in which participants are randomly allocated to two or more interventions, possibly including a control intervention or no intervention, and the results are compared.

Somatostatin: a hormone produced by the pancreas and brain that inhibits the secretion of abdominal organs (e.g. the pancreas).

Stents: artificial tubes.

Stump: cut surface.

Thrombin: a protein in blood that facilitates blood clotting by converting fibrinogen to fibrin.

Appendix 2. EBM Reviews (via OVIDSP)- Cochrane Central Register of Controlled Trials

1. Pancreas/
2. pancreas.tw.
3. Common Bile Duct/
4. common bile duct.tw.
5. "Ampulla of Vater"/
6. (Vater adj2 papilla).tw.
7. Ampulla of Vater.tw.
8. Duodenum/
9. duodenum.tw.
10. or/1-97
11. (carcin* or cancer\$ or neoplas* or tumour\$ or tumor\$ or cyst\$ or growth\$ or adenocarcin* or malig*).mp.
12. 10 and 11
13. Pancreatic Neoplasms/
14. Common Bile Duct Neoplasms/
15. Carcinoma, Pancreatic Ductal/
16. Duodenal Neoplasms/
17. Pancreatitis/
18. or/13-17
19. 12 or 18
20. Surgical Procedures, Operative/
21. General Surgery/
22. (surger* or operati* or operative therap\$ or resection*).tw.
23. or/20-22
24. 19 and 23
25. Pancreatectomy/
26. Pancreaticojejunostomy/
27. Pancreaticoduodenectomy/
28. pancreaticogastrostom*.tw.
29. duodenopancreatectom*.tw.
30. Pancreatic Fistula/
31. ((pancreatic or pancreas) adj fistula*).tw.
32. pancreatic leak*.tw.
33. or/24-32
34. Fibrin Tissue Adhesive/
35. (fibrin adj2 adhesive\$).tw.
36. fibrin glue.tw.
37. (biological and glue\$).tw.
38. (biological and sealant\$).tw.
39. fibrin seal*.tw.
40. (beriplast or biocol or bolheal or evicel or collaseal or crosseal or hemaseel or omrixil or quixil).tw.
41. (tachocomb or tachosil or tisseel or tisseel or tisseal or tissucol or transglutine or vivostat).tw.
42. or/34-41
43. 33 and 42

Appendix 3. MEDLINE (via OVIDSP) search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10
12. Pancreas/
13. pancreas.tw.
14. Common Bile Duct/
15. common bile duct.tw.
16. "Ampulla of Vater"/
17. Vater papilla.tw.
18. Duodenum/
19. duodenum.tw.
20. or/12-19
21. (carcin* or cancer\$ or neoplas* or tumour\$ or tumor\$ or cyst\$ or growth\$ or adenocarcin* or malig*).mp.
22. 20 and 21
23. Pancreatic Neoplasms/
24. Common Bile Duct Neoplasms/
25. Carcinoma, Pancreatic Ductal/
26. Duodenal Neoplasms/
27. Pancreatitis/
28. or/23-27
29. 22 or 28
30. Surgical Procedures, Operative/
31. General Surgery/
32. (surger* or operati* or operative therap\$ or resection*).tw.
33. or/30-32
34. 29 and 33
35. Pancreatectomy/
36. Pancreaticojejunostomy/
37. Pancreaticoduodenectomy/
38. pancreaticogastrostom*.tw.
39. duodenopancreatectom*.tw.
40. Pancreatic Fistula/
41. ((pancreatic or pancreas) adj fistula*).tw.
42. pancreatic leak*.tw.
43. or/34-42
44. Fibrin Tissue Adhesive/
45. (fibrin adj2 adhesive\$).tw.
46. fibrin glue.tw.
47. (biological and glue\$).tw.
48. (biological and sealant\$).tw.
49. fibrin seal*.tw.
50. (beriplast or biocol or bolheal or evicel or collaseal or crosseal or hemaseal or omrixil or quixil).tw.
51. (tachocomb or tachosil or tisseel or tisseel or tisseel or tissucol or transglutine or vivostat).tw.

52. or/44-51
53. 11 and 43 and 52

Appendix 4. Embase (via OVIDSP) search strategy

1. random:.tw. or placebo:.mp. or double-blind:.tw.
2. exp pancreas/
3. pancreas.tw.
4. common bile duct/
5. common bile duct.tw.
6. Vater papilla/
7. Vater papilla.tw.
8. duodenum/
9. duodenum.tw.
10. or/2-9
11. (carcin* or cancer\$ or neoplas* or tumour\$ or tumor\$ or cyst\$ or growth\$ or adenocarcin* or malig*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
12. 10 and 11
13. exp pancreas cancer/ or pancreas adenocarcinoma/ or pancreas carcinoma/
14. duodenum cancer/ or duodenum carcinoma/ or vater papilla carcinoma/
15. Vater papilla tumor/
16. bile duct carcinoma/ or bile duct cancer/
17. pancreatitis/
18. pancreatiti*.tw.
19. or/13-18
20. surgery/
21. (surger* or operati* or operative therap\$ or resection*).tw.
22. 20 or 21
23. (12 or 19) and 22
24. pancreas resection/
25. pancreaticojejunostomy/
26. pancreaticoduodenectomy/
27. pancreaticogastrostom*.tw.
28. duodenopancreatectom*.tw.
29. pancreas fistula/
30. ((pancreatic or pancreas) adj fistula).tw.
31. pancreatic leak\$.tw.
32. or/23-31
33. fibrin glue/
34. fibrin glue.tw.
35. fibrin sealant\$.tw.
36. (biological and glue\$).tw.
37. (biological and sealant\$).tw.
38. (beriplast or biocol or bolheal or evicel or collaseal or crosseal or hemaseel or omrixil or quixil).tw.
39. tachocomb/
40. fibrinogen plus thrombin/
41. (tachocomb or tachosil or tisseel or tisseel or tissucol or transglutine or vivostat).tw.
42. (fibrin adj2 adhesive\$).tw.
43. or/33-42
44. 1 and 32 and 43

Appendix 5. Science Citation Index Expanded search strategy

1. Topic=(randomized controlled trial OR controlled clinical trial OR RCT OR randomized OR placebo OR random* OR trial OR groups AND humans)
2. Topic=(Pancreatic Neoplasms OR Common Bile Duct Neoplasms OR Malignant Tumor of ampullary OR Benign Tumour of ampullary OR Duodenal Neoplasms OR Pancreatitis OR pancrea* cancer* OR pancrea* neoplasm* OR pancrea* carcinoma* OR pancrea* tumo* OR pancreatiti*)
3. Topic=(Operative Surgical Procedures OR Surgery OR operati* OR operative therap* OR surger* OR resection*)
4. (#2 AND #3)
5. Topic=(Pancreatectomy OR Pancreaticojejunostomy OR Pancreaticoduodenectomy OR pancreatectom* OR pancreaticojejunostom* OR pancreaticoduodenectom* OR pancreaticogastrostom* OR duodenopancreatectom* OR Pancreatic Fistula OR pancrea* fistula* OR pancrea* leak*)
6. (#4 OR #5)
7. Topic=(Fibrin tissue adhesive OR fibrin adhesive OR fibrin glu* OR fibrin seal* OR biological glu* OR biological seal* OR Berialplast OR Biocol OR Bolheal OR Collaseal OR Crosseal OR Hemaseal OR Omrixil OR Quixil OR Tachocomb OR Tachosil OR Tisseel OR Tissel OR Tissucol OR Transglutine OR Vivostat)
8. (#1 AND #6 AND #7)

Appendix 6. Chinese Biomedical Literature Database (CBM) search strategy

1. 主题词:随机对照试验/全部树/全部副主题词
2. 主题词:临床对照试验/全部树/全部副主题词
3. 主题词:临床试验/全部树/全部副主题词
4. 主题词:病例对照研究/全部树/全部副主题词
5. 主题词:随机分配/全部树/全部副主题词
6. 主题词:对比研究/全部树/全部副主题词
7. 主题词:前瞻性研究/全部树/全部副主题词
8. 主题词:安慰剂/全部树/全部副主题词
9. 全部字段:随机
10. 全部字段:单盲
11. 全部字段:双盲
12. 全部字段:盲法
13. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
14. 主题词:胰腺肿瘤/全部树/全部副主题词
15. 主题词:胰腺疾病/全部树/全部副主题词
16. 全部字段:胰腺占位
17. 全部字段:胰腺癌
18. 全部字段:胰头癌
19. 主题词:胆总管肿瘤/全部树/全部副主题词
20. 全部字段:胆总管下端占位
21. 全部字段:胆总管下端肿瘤
22. 全部字段:胆总管下端癌
23. 主题词:肝胰管壶腹/全部树/全部副主题词

24. 全部字段:壶腹部占位
25. 全部字段:壶腹部肿瘤
26. 全部字段:壶腹癌
27. 全部字段:vater壶腹癌
28. 主题词:十二指肠肿瘤/全部树/全部副主题词
29. 主题词:十二指肠疾病/全部树/全部副主题词
30. 全部字段:十二指肠占位
31. 全部字段:十二指肠乳头腺癌
32. 主题词:胰腺炎/全部树/全部副主题词
33. 主题词:胰腺炎,慢性/全部树/全部副主题词
34. (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)
35. 主题词:外科手术/全部树/全部副主题词
36. 主题词:吻合术, 外科/全部树/全部副主题词
37. 全部字段:手术治疗
38. 全部字段:手术
39. 全部字段:切除术
40. (#35 OR #36 OR #37 OR #38 OR #39)
41. (#34 AND #40)
42. 主题词:胰腺/全部树/SU
43. 主题词:胰腺切除术/全部树/全部副主题词
44. 主题词:胰十二指肠切除术/全部树/全部副主题词
45. 全部字段:胰体尾切除术
46. 全部字段:胰腺部分切除
47. 全部字段:胰十二指肠吻合术
48. 全部字段:胰头十二指肠吻合术
49. 全部字段:Whipple术式
50. 全部字段:Child术式
51. 主题词:胰腺瘘/全部树/全部副主题词
52. 全部字段:胰瘘
53. 全部字段:胰肠吻合口瘘
54. (#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53)
55. 主题词:纤维蛋白组织黏着剂/全部树/全部副主题词
56. 全部字段:生物蛋白胶
57. 全部字段:纤维蛋白胶
58. 全部字段:纤维蛋白封闭剂
59. 全部字段:纤维蛋白粘合剂
60. 全部字段:组织胶

61. 全部字段:组织粘合剂
62. (#55 OR #56 OR #57 OR# 58 OR #59 OR #60 OR #61)
63. (#13 AND #54 AND #62)

WHAT'S NEW

Last assessed as up-to-date: 12 April 2018.

Date	Event	Description
12 April 2018	New search has been performed	Searches rerun, two additional trials identified.
12 April 2018	New citation required but conclusions have not changed	Two trials incorporated; results remain unchanged.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: YC.

Designing the review: Junhua Gong.

Co-ordinating the review: SH.

Designing search strategies: YC.

Study selection: Junhua Gong, YC

Data extraction: NC, Jianping Gong.

Writing the review: Junhua Gong, SH.

Providing general advice on the review: ZZ.

Securing funding for the review: Jianping Gong.

Performing previous work that was the foundation of the current study: YC.

DECLARATIONS OF INTEREST

Junhua Gong: none known.

SH: none known.

YC: none known.

NC: none known.

Jianping Gong: none known.

ZZ: none known.

SOURCES OF SUPPORT

Internal sources

- Kunming Medical University, China.
Provided funding for the review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For rare events, the Peto method has been observed to be less biased and more powerful than other methods. Thus we calculated the Peto odds ratio instead of risk ratio for rare events (mortality).

Differences between 2016 review and 2018 update

In the 2016 review, we included nine randomised controlled trials but the patient cohort was very heterogenous, including those undergoing a pancreaticoduodenectomy (Whipple's procedure) and those undergoing a distal pancreatectomy. Therefore some participants had an anastomosis and some had a transection with closure of the stump of pancreas. There were also other obvious variables such as different sealing methods and different types of fibrin sealants, which were so dissimilar that they should not be combined in the same meta-analysis. In the 2018 update, we did not perform a meta-analysis of fibrin sealants versus no fibrin sealants for overall pancreatic surgery. Instead, we split all of the studies into three subgroups according to different operations and different sealing methods and performed subgroup analysis of different types of fibrin sealants.

INDEX TERMS

Medical Subject Headings (MeSH)

Fibrin Tissue Adhesive [adverse effects; *therapeutic use]; Length of Stay; Pancreas [*surgery]; Pancreatic Fistula [*prevention & control]; Postoperative Complications [*prevention & control]; Randomized Controlled Trials as Topic; Reoperation [statistics & numerical data]; Tissue Adhesives [*therapeutic use]

MeSH check words

Humans