

REVIEW ARTICLE

Systematic review and meta-analysis of fibrin sealants for patients undergoing pancreatic resection

Lorenzo A. Orci, Graziano Oldani, Thierry Berney, Axel Andres, Gilles Mentha, Philippe Morel & Christian Toso

Division of Visceral and Transplantation Surgery, Department of Surgery, Geneva University Hospitals, Geneva, Switzerland

Abstract

Introduction: Post-operative pancreatic fistula (POPF) is a common complication after partial pancreatic resection, and is associated with increased rates of sepsis, mortality and costs. The role of fibrin sealants in decreasing the risk of POPF remains debatable. The aim of this study was to evaluate the literature regarding the effectiveness of fibrin sealants in pancreatic surgery.

Methods: A comprehensive database search was conducted. Only randomized controlled trials comparing fibrin sealants with standard care were included. A meta-analysis regarding POPF, intra-abdominal collections, post-operative haemorrhage, pancreatitis and wound infections was performed according to the recommendations of the Cochrane collaboration.

Results: Seven studies were included, accounting for 897 patients. Compared with controls, patients receiving fibrin sealants had a pooled odds ratio (OR) of developing a POPF of 0.83 [95% confidence interval (CI): 0.6–1.14], $P = 0.245$. There was a trend towards a reduction in post-operative haemorrhage (OR = 0.43 (95%CI: 0.18–1.0), $P = 0.05$) and intra-abdominal collections (OR = 0.52 (95%CI: 0.25–1.06), $P = 0.073$) in those patients receiving fibrin sealants. No difference was observed in terms of mortality, wound infections, re-interventions or hospital stay.

Conclusion: On the basis of these results, fibrin sealants cannot be recommended for routine clinical use in the setting of pancreatic resection.

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Correspondence

Lorenzo Annibale Orci, Division of Visceral and Transplantation Surgery, Department of Surgery, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1205 Geneva, Switzerland. Tel: +41 22372 3311. Fax: +41 22372 7707. E-mail: lorenzo.orci@hcuge.ch

Introduction

Pancreatic resection represents a major surgical procedure, and although peri-operative mortality has been reduced to below 5% in most centres, post-operative morbidity remains high, with 30–60% of patients experiencing complications.^{1,2} Post-operative pancreatic fistula (POPF) is a commonly feared complication for hepatopancreatico-biliary surgeons, owing to its association with increased mortality, sepsis, hospital stay and costs.³ The incidence of POPF after pancreatoduodenectomy (PD) varies in different series, lying between 5% and 35%.^{4,5} The POPF rate after left pancreatectomy (LP) ranges from 13% to 64%.⁶

Several strategies have been proposed in order to prevent POPF formation, including peri-operative administration of somatostatin analogues,^{4,5} pancreaticogastrostomy instead of pancreaticoje-

junostomy⁷ and hand-sutured versus stapler closure of the pancreatic remnant after LP.⁶ Fibrin sealants are a group of therapeutic agents with several indications, such as helping to achieve improved local haemostatic control, reinforcing suture lines and stimulating wound healing.⁸ Although there are several commercialized formulae, with variations in their precise composition, fibrin sealants all share the common feature of combining fibrinogen and thrombin, in order to mimic the final step of physiological haemostasis.⁸ The effectiveness of fibrin sealants has been evaluated in several surgical settings, including liver,^{9,10} hernia,¹¹ orthopaedic,¹² urological,¹³ cardiac¹⁴ and breast surgery,¹⁵ with conflicting results.

In the setting of pancreatic resection, there are a number of previous retrospective and non-randomized studies that have assessed the role of fibrin sealants in decreasing the POPF rate.^{16–19}

However, considering the high cost of fibrin sealants, there is a need for quality evidence regarding their use in daily clinical practice. To clarify this issue, it was decided to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the effect of fibrin sealants on the incidence of POPF and other complications for patients undergoing pancreatic surgery.

Methods

Search strategy and inclusion criteria

The present methodology is in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA).²⁰

MEDLINE, EMBASE, and the Cochrane Register of clinical trials (CENTER) were searched from 1966 onwards. The following search terms were combined in MEDLINE: ((fibrin seal[MeSH Terms]) OR (fibrin sealant[MeSH Terms]) OR (fibrin sealant system[MeSH Terms]) OR (adhesive, fibrin tissue[MeSH Terms]) OR (fibrin sealant, human[MeSH Terms]) OR (human fibrin sealant[MeSH Terms]) OR (fibrin glue[MeSH Terms]) OR (tissucol[MeSH Terms]) OR (tisseel[MeSH Terms]) OR (tachosil) OR (vitagel) OR (beriplast) OR (biocol) OR (biostat) OR (tachocomb) OR (quixil) OR (evicel) OR (fibrin glue sealing) OR (artiss) AND ((pancreaticoduodenectomy[MeSH Terms]) OR (pancreaticojejunostomy[MeSH Terms]) OR (pancreaticoduodenectomies[MeSH Terms]) OR (pancreaticojejunostomies[MeSH Terms]) OR (pancreatic duct[MeSH Terms]) OR (anastomotic leak[MeSH Terms]) OR (leak, anastomotic[MeSH Terms]) OR (leakage, anastomotic[MeSH Terms]) OR (pancreatic fistula[MeSH Terms]) OR (pancreatic fistulas[MeSH Terms]) OR (fistula) OR (fistulae) OR (postoperative complications[MeSH Terms]) OR (pancreatic remnant) OR (pancreatic stump) OR (pancreatic surgery) OR (pancreas surgery)). An equivalent query was formulated in EMBASE and CENTER.

Inclusion criteria were: RCTs comparing the application fibrin sealants with placebo (or no drug) for adult patients undergoing pancreatic resection. Patients treated with both PD and LP were included. There was no inclusion limit regarding the various commercially available fibrin sealant preparation, date of publication, language or publication status.

Data collection

Two authors extracted data, and disagreements were resolved by reaching a consensus with the remaining authors. Demographic and clinical variables of interest were as follows: age, gender, indication for pancreatic resection and type of surgical procedure. The fibrin sealant preparation price was systematically collected (as reported in the included studies or according to the manufacturer product information). The primary outcome was overall incidence of POPF. The severity of the POPF was graded according to the International Study Group on Pancreatic Fistula (ISGPF) definition.²¹ Secondary outcomes included the impact of the POPF on the post-operative course (according to the ISGPF grading

system), overall complications (including POPF), sepsis, delayed gastric emptying, post-operative haemorrhage (digestive or intra-abdominal), acute pancreatitis, intra-abdominal collections (infected or not) as diagnosed by a computed tomography scan, wound infection, necessary invasive procedures (reoperation or interventional radiology), 30-day mortality and mean length of hospital stay. The included studies were critically appraised evaluating the quality of reporting of important methodological components. The Jadad score,²² which ranks the quality of RCTs on a five-points scale according to randomization, blinding and attrition, was also used.

Statistical analysis

When the included trials were deemed comparable, their results were pooled in several meta-analyses. Binary outcomes were combined as pooled odds ratio (OR), and for continuous outcomes, the weighted mean difference (WMD) was calculated. Ninety-five per cent confidence intervals (95% CI) were reported. The number needed to treat (NNT) was calculated as the inverse of the difference between the control and intervention group event rate. In studies which reported the median only, the median was either pooled in the meta-analysis assuming normal distribution or converted to the mean according to previously detailed methodology.²³ Statistical heterogeneity was assessed using the Q-test with a significance level set at $P = 0.05$. To quantify heterogeneity, the I^2 measure was used. Data were pooled applying either the fixed (inverse variance) or random effect model.²⁴ In case of heterogeneity or marked clinical variability, it was planned to perform sensitivity analyses. Separate analyses of populations undergoing PD or LP were performed. Looking for a consistent POPF definition, a sensitivity analysis was undertaken retaining only those trials using the ISGPF definition.²¹ Lastly, because surgical technique and the skills of the surgeon are considered to have an impact on the risk of POPF,²⁵ separate analyses for different surgical techniques (pancreaticojejunostomy or pancreaticogastrostomy, hand-sewn or stapled closure of the pancreatic stump in LP) were carried out. A funnel plot was used to assess publication bias, as explained in the illustration. All statistical analyses were performed using Stata 12®, Stata Corp., College Station, Texas, USA. Statistical significance was set at the $P < 0.05$ level.

Results

Literature search and characteristics of the included studies

The literature search identified 1415 articles. Hand searching the reference list of retrieved articles and congress attendance allowed identification of seven additional trials. Two studies were identified before publication.^{26,27} A majority of articles were excluded because of irrelevant subject based on abstract reading. Twenty-nine studies were scrutinized. Twenty non-randomized controlled studies were further excluded, as well as two RCTs: one because the intervention groups were not suitable for inclusion (pancreaticojejunostomy versus no anastomosis and pancreatic duct occlu-

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