An update on topical haemostatic agents in liver surgery: systematic review and meta analysis

Raffaele Brustia, Benjamin Granger, Olivier Scatton

AN UP-TO-DATE ON TOPICAL HAEMOSTATIC AGENTS IN LIVER SURGERY: SYSTEMATIC REVIEW AND META-ANALYSIS

Raffaele BRUSTIA, MD*§; Benjamin GRANGER, MD**φ**§; Olivier SCATTON, MD, PhD*§.

* Department of Hepatobiliary and Liver Transplantation Surgery, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, France.

φ Department of Bio Statistics, Public Health and Medical Information, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, France.

§ Université Pierre et Marie Curie, Paris, France

Corresponding author: Olivier SCATTON

Department of HPB surgery and liver transplantation

Hôpital Pitié-Salpêtrière

47-83 Boulevard de l' Hôpital

Paris 75013

Tel: + 33 (1) 42.17.56.52

Fax: + 33 (1) 42.17.56.17

E-mail: olivier.scatton@aphp.fr

SYSTEMATIC REVIEW AND META-ANALYSIS

Key words: Topical Haemostatic Agents, Liver surgery, blood loss, bile leak.

Word count 2521

The Authors declare no conflict of interest

ABSTRACT

Background Mortality and morbidity in Hepatic surgery are affected by blood loss and transfusion. Topical haemostatic agents (THA) are composed by a Matrix and/or Fibrin sealants, and their association known as “carrier-bound fibrin sealant” (CBFS): despite widely used for secondary haemostasis, the level of evidence remains low.

Objectives To realize a meta-analysis on the results of CBFS on haemostasis and postoperative complications.

Search methods searches in PubMed, PubMed Central, Cochrane and Google Scholar using keywords: “topical_haemostasis” OR “haemostatic_agents” OR “sealant_patch” OR “fibrin_sealant” OR “collagen_sealant” AND “liver_surgery” OR “hepatic_surgery” OR “liver_transplantation”.

Selection criteria Randomized clinical trials, large retrospective cohort studies, case control studies evaluating THA on open/laparoscopic liver surgery and transplantation.

Main results From 1993 to 2016 were found 22 studies for qualitative synthesis and 13 for quantitative meta-analysis. The time to haemostasis was lower in the CBFS group (MD -2.33 minutes; p=0.00001). The risk of receiving blood transfusion, developing collections and bile leak was not influenced by the use of CBFS (OR 0.75; p=0.25), (OR 0.72; p=0.52), (OR 0.74; p=0.30) respectively.

Authors' conclusions The use of CBFS in liver surgery significantly reduce the time to haemostasis, but does not decrease transfusion, postoperative collection and bile leak.

INTRODUCTION

Technical refinements led to improve the safety of hepatic surgery. Recent series of major hepatectomy report postoperative mortality rates varying between 0.7% and 2.6% (1-3), while morbidity ranges from 1% and 56.4% (4,5). Moreover, more and more patients are affected by pathological underlying liver disease, such as chemotherapy associated steato-hepatitis (CASH), sinusoidal obstruction syndrome (SOS) or fibrosis, and undergo liver resection with potential higher risk of complications (6-8), especially bleeding. In fact, blood loss remains the recurrent Achille's heel of liver surgery: intra and post-operative bleeding and transfusion requirement significantly increase the rate of mortality, major morbidity and is responsible for a longer hospital stay (9–12). Moreover, recent experimental studies showed how prophylactic use of blood products in cirrhotic liver might paradoxically contribute to bleeding, rather than preventing it (13). Several improvements have been proposed to reduce bleeding and include low Central Venous Pressure during transection (14), inflow and outflow occlusion (15,16) and sharp anatomic dissection (17). Despite the use of meticulous surgical techniques and advanced equipment, blood oozing from the transected row liver surface may occur, especially when the liver resection leaves an empty, deep cavity. The use of topical haemostatic agents (THA) in order to obtain a secondary haemostasis may find its place in this context. THA, synthetic or biologic, are thought to reduce the time to haemostasis (TTH), and to minimize peri-operative transfusion rates (18).

Classes and mechanism of action

The ideal THA should have the capacity to seal or occlude small vessels and potentially bile ducts, and has to be safe and friendly to use (19).

Two classes of THA are currently available (Table 1):

1) A first group provides a matrix (M) for endogenous coagulation (collagen, cellulose or

gelatine) without active components.

2) A second group contains active components (fibrin sealants), mimicking endogenous coagulation (19). Fibrin sealants are component mixtures predominately comprised of fibrinogen (F) and activating agents, such as calcium chloride and thrombin (T): this necessitates intraoperative preparation and immediate application (18-20).

A few products combine both classes of THA in a ready-to-use device: a matrix (M) of human or animal collagen-based material, which can be coated with additional active components to improve the haemostatic effect. These components, added in varying concentrations, commonly include fibrinogen (F), coagulation factors such as thrombin (T) and anti-thrombolytic agents (18-20). These combined devices are also called “carrier-bound fibrin sealants”. Currently, the 4 commercialized devices are CoStasis™(MT), Evarrest™(FMT), TachoSil™(FMT) and Vitagel™(FMT). Instead of using a ready-to-use carrier-bound fibrin sealant, a self-made carrier-bound fibrin sealant can be obtained by combining a fibrin (F) and/or thrombin (T) sealant with a matrix (M) of choice (19).

Despite widespread THA use among liver surgeons - especially carrier-bound fibrin sealants - as well as a flourishing literature, the level of evidence remains low (18-21).

Objective

The aim of this systematic review is to offer an up-to-date point of view on the effectiveness of the two main classes of THA and/or their combination in liver surgery. Moreover, we decided to target a meta-analysis on the results of the following carrier-bound fibrin sealants, (ready-to-use or self-made) on blood loss and postoperative complications:

- Matrix and Fibrin based THA (FM)
- Matrix and Thrombin based THA (MT)
- Matrix and Thrombin plus Fibrin based THA (FMT)

Methodology

Study inclusion in this review was based on the patient, intervention, comparison, outcome, study design (PICOS) criteria and the PRISMA Statement (22).

Study population

The study included all adult patients undergoing major or minor, open or laparoscopic liver surgery (LS), as well as liver transplantation (LT) and split LT. Pediatric or experimental studies including animals were not considered for inclusion.

Types of intervention and comparison

All studies reporting LS or LT for benign or malignant disease, on normal or pathological liver parenchyma (CASH, SOS or cirrhosis) were considered for inclusion if the use of any THA for secondary haemostasis was described. For quantitative analysis were considered only studies combining a Matrix agent plus a Fibrin agent (FM), Thrombin agent (TM) or both (FMT).

Outcome measures

The primary outcome measures were TTH, red blood cells transfusions, collections requiring drainage or re-intervention and bile leak.

Types of studies

Inclusion criteria were: randomized clinical trials (RCT) evaluating the use of THA, retrospective comparative cohort studies, case control studies. Case series, case control and studies including less than 10 patients were excluded.

Search strategy

According to the PRISMA statement guidelines (21), digital searches were performed without chronological restriction, in PubMed, PubMed Central, Cochrane and Google Scholar among English full-text articles using a combination of the following key words: “topical

haemostasis" OR "haemostatic agents" OR "sealant patch" OR "fibrin sealant" OR "collagen sealant" AND "liver surgery" OR "hepatic surgery" OR "liver transplantation". We planned to do cross-references among the included studies, looking for related citations. The flow diagram of search strategy is presented in Figure 1.

A parallel research was held to list all topical haemostatic agents commonly used in surgery (Table 1).

Study selection and data extraction

Both authors were responsible for conducting the databases' search and retrieval of full text studies, their selection and to list excluded studies. The following data were extracted:

1. Year of publication
2. Type of study
3. Intervention (Topical Haemostatic Agent)
4. Surgical procedure
5. Sample size (Treatment vs Control)
6. Time to Haemostasis
7. Patients requiring red blood cell transfusion
8. Postoperative collections requiring drainage
9. Postoperative bile leak
10. Final findings

The following data were extracted for topical haemostatic agents:

1. Product name
2. Matrix/Fibrin/Thrombin based
3. Manufacturer
4. Device

5. Short description

Methodological quality assessment

For each study the Quality of Evidence was assessed on a four level scale ranging from Very Low Quality to High Quality, according to the GRADE system (23).

Risk of Bias

Methodological quality was defined as the confidence that the study design, conduct, analysis, and presentation limited biased comparisons of the intervention under consideration (24,25). Risk of bias in a trial can be assessed by using risk of bias domains, described as follows:

- Allocation sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinded outcome assessment
- Incomplete outcome data
- Other bias

Each domain was assessed for each study in one of three categories: 1) low risk of bias; 2) high risk of bias; 3) unclear risk of bias. We recorded this information for each included study in 'Risk of bias' tables in Review Manager 5.2 (RevMan 2014), and we have presented a summary 'Risk of bias' figure 2.

Measures of treatment effect

A meta-analysis was performed for the following outcomes:

- **TTH** for which we collected the mean and the standard deviation (SD) and we assessed the mean difference (MD) as effect.

- **Transfusion**, **post operative complication** as **collection** and **bile leak** for which we collected the number of patients affected by this outcome, and we assessed the odd ratio (OR) as effect.

Inverse variance method was used for pooling. A fixed-effect or random-effect model was used according to the between-study heterogeneity. Statistical heterogeneity was assessed using both the Cochran *Q* test and the I^2 statistic, which describes the percentage of total variation across studies caused by heterogeneity rather than chance. A value of $p < 0.05$ for the Cochran *Q* test or an I^2 statistic >50% (26) indicated the presence of significant heterogeneity across selected studies, which resulted in the use of the random-effect model based on the Der Simonian method for estimating the tau value. The small-study effect and publication bias were evaluated by visual inspection of funnel plots for all comparisons. All statistical analyses were performed using Review Manager 5.2 (RevMan 2014),

RESULTS

Study selection

The search of PubMed, PubMed Central, Cochrane and Google Scholar databases provided a total of 1336 citations. After adjusting for duplicates, 756 remained. Of them, 588 were excluded on a title basis, and 135 more were excluded after abstract reviewing because not consistent with the objectives of the review. The full text of the remaining 33 articles were assessed for eligibility and reviewed in detail: 11 papers were excluded because not pertinent with liver surgery. From 1993 to 2016 we found 22 full-text article studies (27-48), included in this systematic review for qualitative synthesis: among them, 13 combining FMT or MT or FM were included for quantitative meta-analysis (28,29,31,34-36,38-40,44,46-48) (Table2).

Risk of bias in included studies

Two great risk of bias were identified among the selected studies. The first concerns the blinding of participants. Apart one study from Briceno et al (29) in which a different "closure team" finished the intervention, using a THA when and were needed according to randomization protocol, and was not involved in the patient follow-up assessment, no further studies were blinded. The second important source of bias (Other bias) was the direct or indirect financial or organizational participation by the THA Product Manufacturers involved in the study (Figure 2).

Characteristics of included studies

Methods

The included studies were 16 RCT (27-29,31-37,41-47), 5 retrospective comparative cohort studies (38-40,46,48) and one case control (30). According to the GRADE system for quality

assessment of clinical studies, two studies were classified of High Quality, (32,33), 12 of Medium Quality (27,28,35,36-38,41,42,45-48) and 8 of Low Quality (29-31,34,39,40,43,44).

Participants

The included studies involved 1292 patients treated with THA vs a control cohort of 1176 patients. When considering the studies selected for meta-analysis, they involved 683 patients treated with THA vs a control cohort of 579 patients.

Intervention

Information on the intervention received was available for all the included studies: Matrix-based alone (M n=2) THA (30,43), Fibrin-based alone (F n=2) (27,42) or combined with thrombin (FT n=5) (32,33,37,41,45). Thirteen studies reported the association of both THA categories, and therefore included in the meta-analysis: matrix combined with a fibrin-based (FM n=1) (38) or thrombin-based THA (MT=1) (32) and homemade or ready-to-use carrier-bound fibrin sealants (FMT n=11) (28,29,33,35,38,39,40,44,46-48).

Effects of intervention on primary outcomes

Haemostasis

- Time to Haemostasis
    - Among the 13 studies included for the meta-analysis, five reported data on TTH (31,34,36,47) including 429 patients. The time to haemostasis was lower in the groups receiving combined THA, with three out of four studies using FMT (MD -2.33 minutes; 95% CI [-3.52, -1.15] random-effects analysis p=0.0001) (Analysis 1.1).
- Blood transfusion
    - Four studies reported data on patients requiring blood transfusion during or after surgery (29,44,47,48), including 354 patients. The risk of receiving blood

transfusion was not reduced by the use of THA (OR 0.75; 95% CI [0.46, 1.22] fixed-effects analysis; p=0.25) (Analysis 1.2).

Complications

- Collections requiring drainage or intervention
    - Three studies reported data on patients affected by collections requiring drainage or re-intervention (29,46,48), including 298 patients. The risk of developing postoperative collections was not influenced by the use of THA (OR 0.72; 95% CI [0.26, 2.01] fixed-effects analysis; p=0.52) (Analysis 2.1).
- Bile leak.
    - Nine studies reported data on the occurrence of postoperative bile leak (29,35,38-40,44,46-48), including 708 patients: the risk was not reduced by the use of THA (OR 0.74; 95% CI [0.42, 1.31] fixed-effects analysis; p=0.30) (Analysis 2.2).

Investigation of Heterogeneity

The possible explanation of heterogeneity observed relies on the fact that the THA are not always the same, the difference on the indication of application, the absence of blinding, the control group being highly heterogeneous (simple compression or other THA) and last but not least the presence of retrospective studies among the selected ones.

DISCUSSION

The universe of THA is composed by a heterogeneous constellation of matrix, fibrinogen or thrombin-based agents, used alone or associated in different combinations. There are two major weaknesses in the literature. First, as depicted in the risk bias table, companies producing the examined THA support the majority of studies that may induce a conflict of interest. Second, when comparing different RCT on THA, even in the selective field of liver surgery, interventions used and control groups are far to be homogeneous, leading to a higher heterogeneity of results and weaker conclusions. Both weaknesses have been observed in this study.

However, some key points can be stated.

First, THA, no matter of the product used, is highly appreciated by liver surgeons - as recently highlighted in a Dutch survey - in order to reduce intra-operative blood loss, TTH and potentially bile leakage (19). A fibrin sealant patch is often preferred since it seems the friendliest tool to use (49). Second, the best results – all outcomes confounded – seem to be obtained with the carrier-bound fibrin sealant, homemade or ready-to-use, that combines the effects of a matrix with active agents to trigger and accelerate coagulation.

THA and bleeding

Ten studies reported a significant reduction of TTH, transfusion rate, postoperative bleeding, complications and hospital stay in the intervention group (28,29,31,34-37,41,44,45,47): eight of them included the use of a carrier-bound fibrin sealant. Six studies (32,33,37,39,40,43) found no difference with the use of THA on TTH, postoperative bleeding or transfusion rate: only two of them used a carrier-bound fibrin sealant (40,43). A meta-analysis (21) focusing on six RCT (32,33,35,37,42,45) found no difference in operative blood loss, perioperative blood transfusion, postoperative haemorrhage, abdominal collections, hospital stay,

morbidity and mortality between the fibrin sealant group and control group. However, our meta-analysis herein, focusing on the combination of a matrix-based and a fibrin-based THA, revealed a significant lower TTH in the group receiving THA (Analysis 1.1). However, the patients requiring transfusion was not different between the two groups (Analysis 1.2). Overall, there is a trend of better haemostasis and reduced blood loss using THA especially when a carrier-bound fibrin sealant (ready-to-use or self-made) is used. More studies are needed to conclude on the advantages in the field of split liver transplantation.

THA and potential drawbacks

Overall, the use of the THA agents is safe. The study from Bochiccio et al (28) found no difference on the occurrence of anti-thrombin antibodies with the use of thrombin-fibrinogen based THA as compared to the use of gelatine matrix. Then, there is no risk of immunogenicity. Cauchy and coll. (30) reported that the use of an expanding foam matrix was significantly associated with perihepatic vascular thrombosis as compared to the control group, when vessels were exposed on the liver transected surface. A mechanical effect is suspected in this study. However, no cases of postoperative collection or infection directly related to the use of THA were reported in any of the included studies. In our analysis, the use of a carrier-bound fibrin sealant (ready-to-use or self-made) does not affect the presence or absence of postoperative collections requiring drainage or re-intervention (Analysis 2.1).

THA and bile leak

In a small number of studies, the incidence of bile leakage was reduced by using a self-made (38,40) or ready-to-use (46) carrier-bound fibrin sealant. Despite, larger RCT (32,33) found no difference on bile leakage when a THA was used. A meta-analysis (24) performed on 5 RCT (32,33,35,37,45) showed that there was no difference in the occurrence of

postoperative bile leak between the fibrin sealant and control group. Moreover, our meta-analysis confirmed the same results, even when a self-made or ready-to-use carrier-bound fibrin sealant was used (Analysis 2.2). Overall, the use of THA cannot be recommend to prevent bile leak.

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

According to the literature analysis, the use of carrier-bound fibrin sealant (ready-to-use or self-made combining a matrix-based and a fibrin-based THA) in liver surgery significantly reduce the time to haemostasis, but does not decrease red blood cell transfusion, postoperative collection and bile leak.

REFERENCES

(1) Dokmak S, Ftériche FS, Borscheid R, Cauchy F, Farges O, Belghiti J. Liver resections in the 21st century: we are far from zero mortality. HPB (Oxford). 2013;15:908-15.

(2) Virani S, Michaelson JS, Hutter MM, Lancaster RT, Warshaw AL, Henderson WG, et al. Morbidity and mortality after liver resection: results of the patient safety in surgery study. J Am Coll Surg. 2007;204:1284-92.

(3) Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Tahara M, Yamashita K, et al. Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. J Am Coll Surg.2010;211:443–449.

(4) Cauchy F, Aussilhou B, Dokmak S, Fuks D, Gaujoux S, Farges O, et al. Reappraisal of the risks and benefits of major liver resection in patients with initially unresectable colorectal liver metastases. Ann Surg. 2012;256:746-52

(5) Page AJ, Gani F, Crowley KT, Lee KH, Grant MC, Zavadsky TL, et al. Patient outcomes and provider perceptions following implementation of a standardized perioperative care pathway for open liver resection. Br J Surg. 2016. doi: 10.1002/bjs.10087.

(6) Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol. 2004;15:460–466.

(7) Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol.2006;24:2065–2072.

(8) Zaydfudim VM, Kerwin MJ, Turrentine FE, Bauer TW, Adams RB, Stukenborg GJ. The impact of chronic liver disease on the risk assessment of ACS NSQIP morbidity and mortality after hepatic resection. Surgery. 2015: S0039-6060(15)00967-8.

(9) Hallet J, Kulyk I, Cheng ES, Truong J, Hanna SS, Law CH, et al. The impact of red blood cell transfusions on perioperative outcomes in the contemporary era of liver resection. Surgery. 2016: S0039-6060(15)01053-3.

(10) Kooby DA, Stockman J, Ben-Porat L, et al.: Influence of transfusions on perioperative and long-term outcome in patient following hepatic resection for colorectal metastases. Ann Surg 2003;237:860–869

(11) Fan ST, Mau Lo C, Poon RT, et al.: Continuous improvement of survival outcomes of

resection of hepatocellular carcinoma: A 20-year experience. Ann Surg 2011;253:745–758

(12) Ibrahim S, Chen CL, Lin CC, et al.: Intraoperative blood loss is a risk factor for complications in donors after living donor hepatectomy. Liver Transpl 2006;12:950–957.

(13) Weeder PD, Porte RJ, Lisman T. Hemostasis in liver disease: implications of new concepts for perioperative management. Transfus Med Rev. 2014;28:107-13.

(14) Tympa A, Theodoraki K, Tsaroucha A, et al. Anesthetic considerations in hepatectomies under hepatic vascular control. HPB Surg 2012;2012:720754.

(15) Chouillard EK, Gumbos AA, Cherqui D. Vascular clamping in liver surgery: physiology, indications and techniques. Ann Surg Innov Res 2010; 4:1-12

(16) Smyrniotis V, Farantos C, Kostopanagiotou G, Arkadopoulos N. Vascular control during hepatectomy: review of methods and results. World J Surg 2005; 29:1384–1396

(17) Scatton O, Brustia R, Belli G, Pekolj J, Wakabayashi G, Gayet B. What kind of energy devices should be used for laparoscopic liver resection? Recommendations from a systematic review. J Hepatobiliary Pancreat Sci. 2015;22:327-34.

(18) Huntington JT, Royall NA, Schmidt CR. Minimizing blood loss during hepatectomy: a literature review. J Surg Oncol. 2014;109:81-8.

(19) Boonstra EA, Molenaar IQ, Porte RJ, de Boer MT. Topical haemostatic agents in liver surgery: do we need them? HPB (Oxford). 2009;11:306-10.

(20) Hanna EM, Martinie JB, Swan RZ, Iannitti DA. Fibrin sealants and topical agents in hepatobiliary and pancreatic surgery: a critical appraisal. Langenbecks Arch Surg. 2014;399:825-35

(21) Sanjay P, Watt DG, Wigmore SJ. Systematic review and meta-analysis of haemostatic and biliostatic efficacy of fibrin sealants in elective liver surgery. J Gastrointest Surg. 2013;17:829-36.

(22) Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:e1000100. doi: 10.1371/journal.pmed.1000100.

(23) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

(24) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12

(25) Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. Lancet 1998;352:609-13.

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

(27) Bektas H, Nadalin S, Szabo I, Ploder B, Sharkhawy M, Schmidt J. Hemostatic efficacy of latest-generation fibrin sealant after hepatic resection: a randomized controlled clinical study. Langenbecks Arch Surg. 2014;399:837-47.

(28) Bochicchio GV, Gupta N, Porte RJ, Renkens KL, Pattyn P, Topal B, et al. The FINISH-3 trial: a phase 3, international, randomized, single-blind, controlled trial of topical fibrocaps in intraoperative surgical hemostasis. J Am Coll Surg. 2015;220:70-81.

(29) Briceño J, Naranjo A, Ciria R, Díaz-Nieto R, Sánchez-Hidalgo JM, Luque A, et al.. A prospective study of the efficacy of clinical application of a new carrier-bound fibrin sealant after liver resection. Arch Surg. 2010;145:482-8.

(30) Cauchy F, Gaujoux S, Ronot M, Fuks D, Dokmak S, Sauvanet A, et al. Local venous thrombotic risk of an expanding haemostatic agent used during liver resection. World J Surg. 2014;38:2363-9.

(31) Chapman WC, Clavien PA, Fung J, Khanna A, Bonham A. Effective control of hepatic bleeding with a novel collagen-based composite combined with autologous plasma: results of a randomized controlled trial. Arch Surg 2000;135:1200–1204

(32) de Boer MT, Klaase JM, Verhoef C, van Dam RM, van Gulik TM, Molenaar IQ, et al. Fibrin sealant for prevention of resection surface-related complications after liver resection: a randomized controlled trial. Ann Surg 2012;256:229–234.

(33) Figueras J, Llado L, Miro M, Ramos E, Torras J, Fabregat J, et al.. Application of fibrin glue sealant after hepatectomy does not seem justified: results of a randomized study in 300 patients. Ann Surg. 2007;245:536-42.

(34) Fischer L, Seiler CM, Broelsch CE, de Hemptinne B, Klempnauer J, Mischinger HJ, et al. Hemostatic efficacy of TachoSil in liver resection compared with argon beam coagulator

treatment: an open, randomized, prospective, multicenter, parallel-group trial. Surgery. 2011;149:48-55.

(35) Frilling A, Stavrou GA, Mischinger HJ, de Hemptinne B, Rokkjaer M, Klempnauer J, Thorne A, Gloor B, Beckebaum S, Ghaffar MF, Broelsch CE. Effectiveness of a new carrier-bound fibrin sealant versus argon beamer as haemostatic agent during liver resection: a randomised prospective trial. Langenbecks Arch Surg 2005;390: 114–120.

(36) Genyk Y, Kato T, Pomposelli JJ, Wright JK Jr, Sher LS, Tetens V, Chapman WC. Fibrin Sealant Patch (TachoSil) vs Oxidized Regenerated Cellulose Patch (Surgicel Original) for the Secondary Treatment of Local Bleeding in Patients Undergoing Hepatic Resection: A Randomized Controlled Trial. J Am Coll Surg. 2015; 18. pii: S1072-7515(15)01777-9.

(37) Gugenheim J, Bredt LC, Iannelli A. A randomized controlled trial comparing fibrin glue and PlasmaJet on the raw surface of the liver after hepatic resection. Hepatogastroenterology. 2011;58:922-5.

(38) Hayashibe A, Sakamoto K, Shinbo M, Makimoto S, Nakamoto T New method for prevention of bile leakage after hepatic resection. J Surg Oncol 2006;94:57–60.

(39) Kobayashi S, Nagano H,Marubashi S,Wada H, Eguchi H, Tanemura M, Sekimoto M, Umeshita K, Doki Y, Mori M. Experience with the use of fibrin sealant plus polyglycolic acid felt at the cut surface of the liver in laparoscopic hepatectomy. Surg Endosc 2011;25: 3590–3596.

(40) Kobayashi S, Nagano H, Marubashi S,Wada H, Eguchi H, Takeda Y, Tanemura M, Doki Y, Mori M. Fibrin sealant with PGA felt for prevention of bile leakage after liver resection. Hepatogastroenterology 2012;59:2564–2568.

(41) Koea JB, Batiller J, Patel B, Shen J, Hammond J, Hart J, Fischer C, Garden OJ. A phase III, randomized, controlled, superiority trial evaluating the fibrin pad versus standard of care in controlling parenchymal bleeding during elective hepatic surgery. HPB (Oxford). 2013;15:61-70.

(42) LiuM, LuiWY. The use of fibrin adhesive for hemostasis after liver resection. Zhonghua Yi Xue Za Zhi (Taipei) 1993;51:19–22

(43) Moench C, Mihaljevic AL, Hermanutz V, Thasler WE, Suna K, Diener MK, Seehofer D, Mischinger HJ, Jansen-Winkeln B, Knaebel HP, Bechstein WO. Randomized controlled multicenter trial on the effectiveness of the collagen hemostat Sangustop® compared with a

carrier-bound fibrin sealant during liver resection (ESSCALIVER study, NCT00918619). Langenbecks Arch Surg. 2014;399:725-33.

(44) Ollinger R, Mihaljevic AL, Schuhmacher C, Bektas H, Vondran F, Kleine M, Sainz-Barriga M,Weiss S, Knebel P, Pratschke J, Troisi RI. A multicentre, randomized clinical trial comparing the Veriset haemostatic patch with fibrin sealant for the management of bleeding during hepatic surgery. HPB (Oxford) 2013;15:548–558.

(45) Schwartz M, Madariaga J, Hirose R, Shaver TR, Sher L, Chari R, Colonna JO 2nd, Heaton N, Mirza D, Adams R, Rees M, Lloyd D. Comparison of a new fibrin sealant with standard topical hemostatic agents. Arch Surg. 2004;139:1148-54.

(46) Toti L, Attia M, Manzia TM, Lenci I, Gunson B, Buckels JA, Mirza DF, Mayer AD, Bramhall SR, Wigmore SJ. Reduction in bile leaks following adult split liver transplant using a fibrin-collagen sponge: a pilot study. Dig Liver Dis 2010;42:205–209. doi:10.1016/j. dld.2009.06.010

(47) Verhoef C, Singla N, Moneta G, Muir W, Rijken A, Lockstadt H, de Wilt JH, O-Yurvati A, Zuckerman LA, Frohna P, Porte RJ. Fibrocaps for surgical hemostasis: two randomized, controlled phase II trials. J Surg Res. 2015;194:679-87.

(48) Zacharias T, Ferreira N. Carrier-bound fibrin sealant compared to oxidized cellulose application after liver resection. HPB (Oxford) 2012;14:839–847.

(49) Corral M, Ferko N, Hollmann S, Hogan A, Jamous N, Batiller J, Shen J. Clinician reported ease of use for a novel fibrin sealant patch for hemostasis: results from four randomized controlled trials. Curr Med Res Opin. 2016;32:367-75.

Fig.1 Flow Diagram

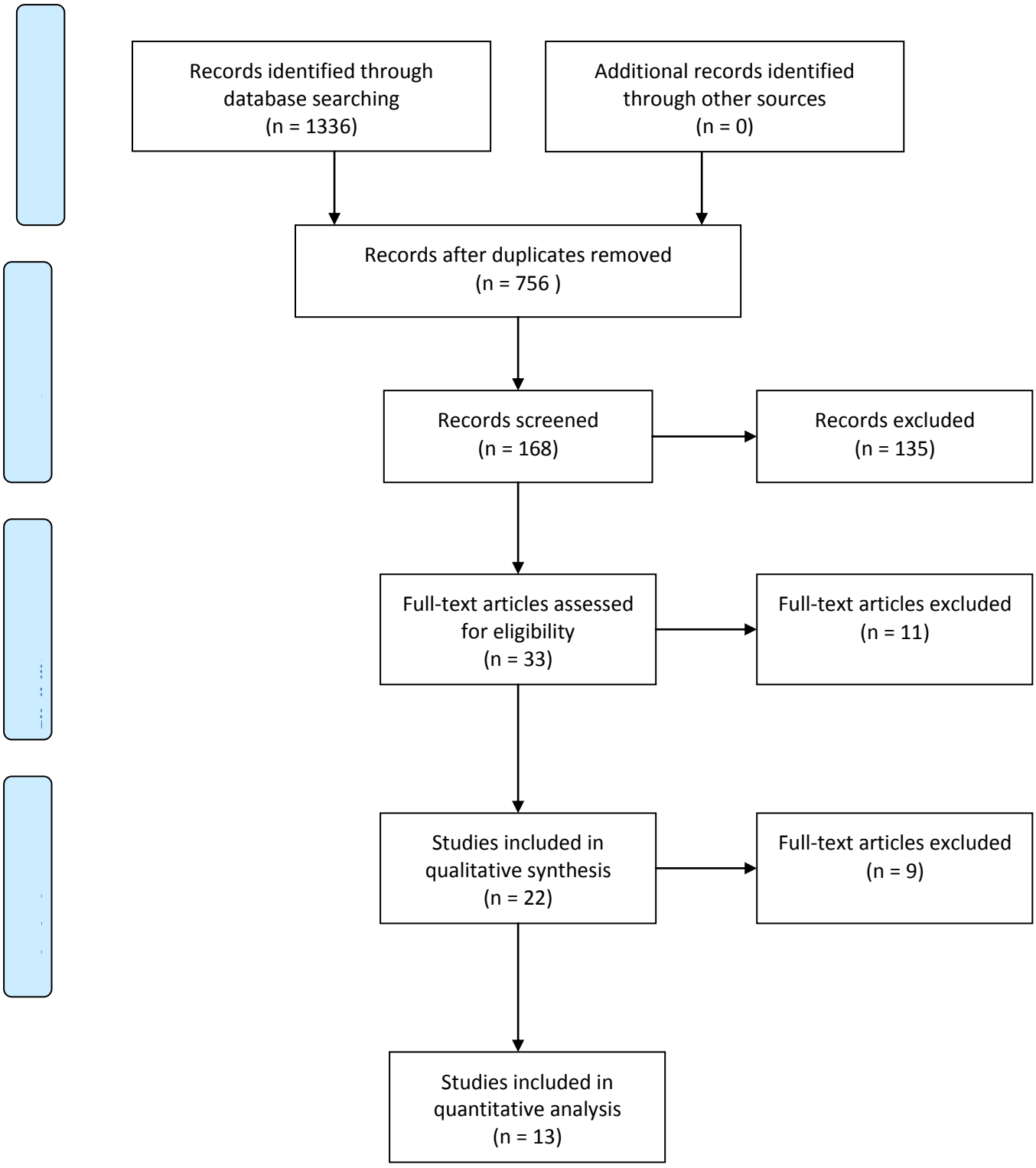


Figure. 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

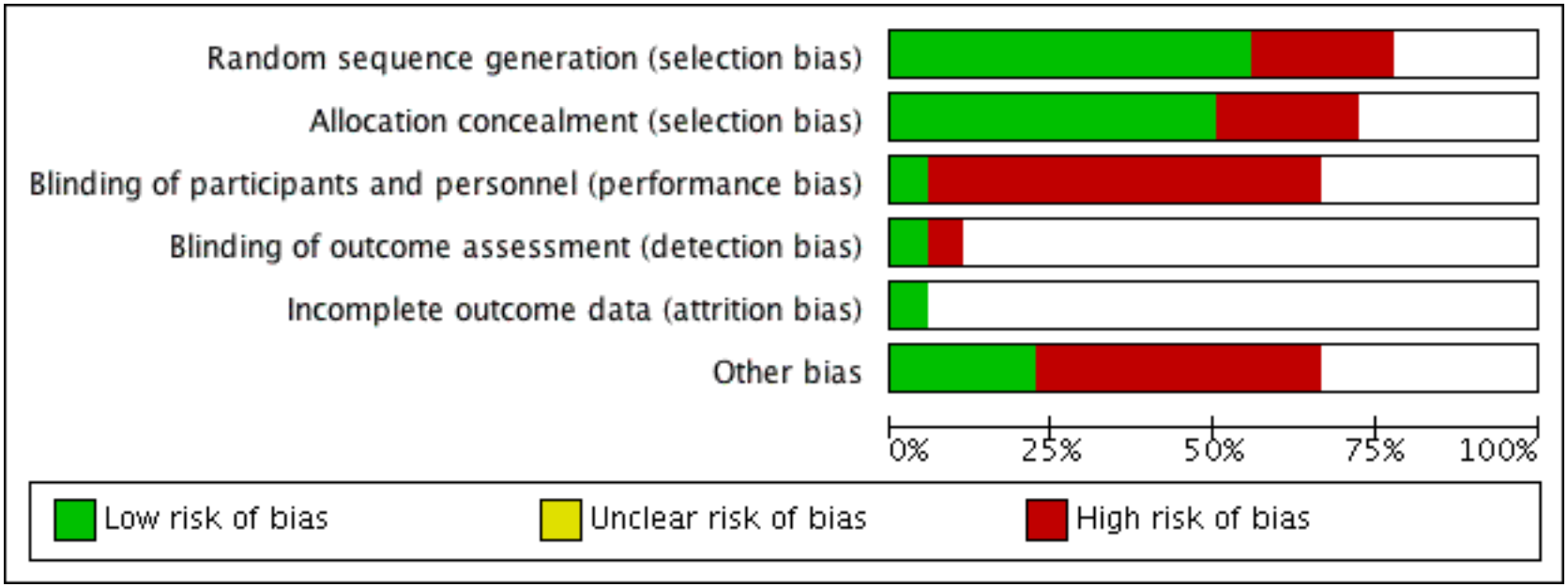


Table 1. Topical haemostatic agents commonly used in surgery

Table 2. Characteristics of included studies on Topical Haemostatic Agents in Liver Surgery or Liver Transplantation

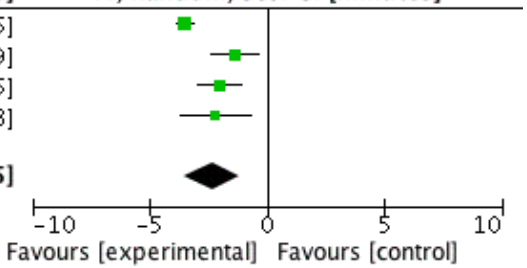
ANALYSIS

Analysis 1.1 Forest plot of comparison: 1 Haemostasis, outcome: 1.1 Time to Haemostasis [minutes].

Study or Subgroup	Experimental Mean [minutes]	Experimental SD [minutes]	Experimental Total	Control Mean [minutes]	Control SD [minutes]	Control Total	Weight	Mean Difference IV, Random, 95% CI [minutes]
Chapman 2000	2.5	0.3	38	6	0.9	29	29.6%	-3.50 [-3.84, -3.16]
Fischer 2011	3.6	0.9	54	5	3.6	52	24.8%	-1.40 [-2.41, -0.39]
Genyk 2016	3.5	1.3	101	5.5	4.6	99	25.4%	-2.00 [-2.94, -1.06]
Verhoef 2015	2.2	1.2	39	4.4	3.1	17	20.2%	-2.20 [-3.72, -0.68]
Total (95% CI)			**232**			**197**	**100.0%**	**-2.33 [-3.52, -1.15]**

Heterogeneity: $Tau^2 = 1.20$; $Chi^2 = 22.81$, df = 3 ($P < 0.0001$); $I^2 = 87\%$

Test for overall effect: Z = 3.87 (P = 0.0001)

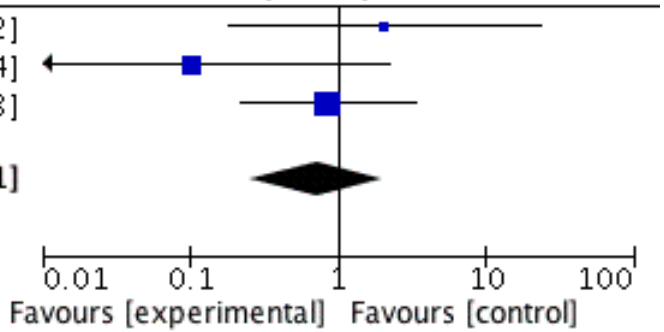


Analysis 1.2 Forest plot of comparison: 1 Haemostasis, outcome: 1.2 Transfusion.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Briceno 2010	2	57	1	58	11.1%	2.07 [0.18, 23.52]
Ollinger 2013	0	32	2	18	36.4%	0.10 [0.00, 2.24]
Zacharias 2012	4	64	5	69	52.5%	0.85 [0.22, 3.33]
Total (95% CI)		**153**		**145**	**100.0%**	**0.72 [0.26, 2.01]**
Total events	6		8			

Heterogeneity: $Chi^2 = 2.33$, df = 2 ($P = 0.31$); $I^2 = 14\%$

Test for overall effect: Z = 0.64 (P = 0.52)

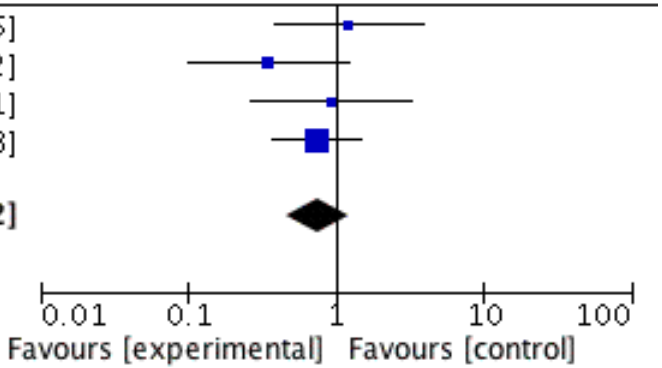


Analysis 2.1 Forest plot of comparison: 2 Postoperative Complications, outcome: 2.1 Collection.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Briceno 2010	7	57	6	58	14.1%	1.21 [0.38, 3.86]
Ollinger 2013	7	32	8	18	21.6%	0.35 [0.10, 1.22]
Verhoef 2015	11	39	5	17	13.5%	0.94 [0.27, 3.31]
Zacharias 2012	25	64	32	69	50.7%	0.74 [0.37, 1.48]
Total (95% CI)		**192**		**162**	**100.0%**	**0.75 [0.46, 1.22]**
Total events	50		51			

Heterogeneity: $Chi^2 = 2.22$, $df = 3$ ($P = 0.53$); $I^2 = 0\%$

Test for overall effect: $Z = 1.15$ ($P = 0.25$)



Analysis 2.2 Forest plot of comparison: 2 Postoperative Complications, outcome: 2.2 Bile leak.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Briceno 2010	4	57	6	58	20.1%	0.65 [0.17, 2.45]
Frilling 2005	4	59	2	62	6.6%	2.18 [0.38, 12.39]
Hayashibe 2006	0	51	3	37	14.5%	0.10 [0.00, 1.91]
Kobayashi 2011	0	18	0	22		Not estimable
Kobayashi 2012	0	34	4	39	15.0%	0.11 [0.01, 2.20]
Ollinger 2013	3	32	0	18	2.1%	4.39 [0.21, 89.92]
Toti 2010	1	16	7	16	23.8%	0.09 [0.01, 0.82]
Verhoef 2015	3	39	0	17	2.3%	3.36 [0.16, 68.60]
Zacharias 2012	7	64	5	69	15.6%	1.57 [0.47, 5.23]
Total (95% CI)		**370**		**338**	**100.0%**	**0.74 [0.42, 1.31]**
Total events	22		27			

Heterogeneity: $Chi^2 = 12.18$, df = 7 (P = 0.09); $I^2 = 43\%$

Test for overall effect: Z = 1.04 (P = 0.30)

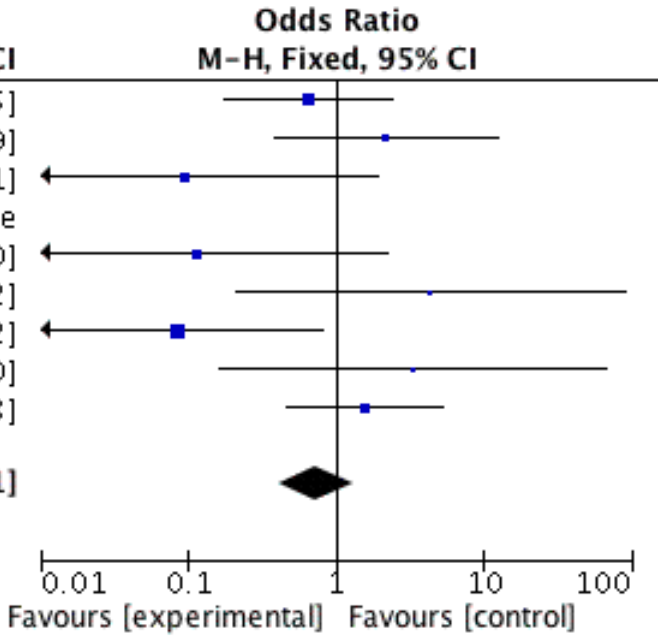


Table 1 Topical Haemostatic Agents commonly used in surgery : products, structure, device, description and indications

Product (Matrix Based)	Structure	Manufacturer	Device	Description	Indication
Arista™	M	Medafor, Minneapolis, MN	Spray	Polysaccharide spheres from purified plant starch	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Avitene™ Ultrafoam sponge and flour	M	Bard, Murray Hill, NJ	Foam	Collagen based	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
BioFoam™	M	Cryolife, Kennesaw, GA	Foam	Protein hydrogel biomaterial composed of bovine serum albumine and glutaraldehyde	An adjunct to hemostasis on liver or spleen surface during resection on empty and deep parenchymal cavity.
Bioglue™	M	Cryolife, Kennesaw, GA	Glue	Bovine albumin and 10 % glutaraldeyde	An adjunct to hemostasis in digestive and vascular surgery
CollaStat™	M	Integra Life Science, Plainsboro, NJ	Sponge	Bovine collagen, absorbable sponge	An adjunct to hemostasis in surgery (dental) when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
CoSeal™	M	Baxter Healthcare Corporation, Westlake, CA	Glue	Two polyethylene glycols	An adjunct to hemostasis in vascular surgery
Duraseal™	M	Covidien, Waltham, MA	Glue, spray	Single polyethylene glycol	An adjunct to sutured dura repair in neurosurgery
Gelfoam™ sponge and powder	M	Pfizer/Pharmacia, Kalamazoo, MI	Patch, microfibrillar	Porcine gelatin sponge	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Helistat™, Helitene	M	Integra Life Science, Plainsboro, NJ	Sponge	Bovine collagen	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Hemopad Novacol™	M	Datascope Corp.,Montvale, NJ		Bovine collagen	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Hemostase MPH™	M	Cryolife, Kennesaw, GA	Glue, spray	Absorbablehe hemostatic powder	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Instat, Instat MCH™	M	Johnson & Johnson Company, Somerville, NJ	Patch	Purified and lyophilized bovine dermal collagen	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Omnex™	M	Ethicon, Inc, a Johnson & Johnson Company,Somerville, NJ	Glue	Two cyanoacrylate monomers	An adjunct to hemostasis in vascular surgery
Progel™	M	Davol, Warwick, RI	Glue	Human serum albumin and	Air leaks in pulmonary surgery

				polyethylene glycol	
Surgicel™, fibrilar, snow or Nu-Knit	M	Johnson & Johnson Company, Somerville, NJ	Patch	Oxidized cellulose	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Surgifoam™ sponge and powder	M	Johnson & Johnson Company, Somerville, NJ	Patch, flour	Porcine gelatin sponge	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Veriset™	M	Covidien Inc.,Mansfield, MA	Patch	Oxidized cellulose and polyethylene glycol	Aid in hemostasis in general suegery
Product (Fibrine and/or Thrombine Based)	**Structure**	**Manufacturer**	**Device**	**Description**	**Indication**
CryoSeal Fibrin Sealant System ™	F	Thermogenesis, Rancho, Cordova, CA	Glue, spray	Fibrin sealant—human pooled	An adjunct to hemostasis on liver surface during liver resection when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Tisseel™	F	Baxter Healthcare Corporation, Westlake, CA	Glue	Fibrin sealant—human pooled	An adjunct to hemostasis in surgery (cardiac, spleen or fully heparinized patients) when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Evithrom™	T	Johnson & Johnson Company, Somerville, NJ	Glue	Lyophilized human pooled thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical
FloSeal Hemostatic Matrix™	T	Baxter Healthcare Corporation, Westlake, CA	Glue, spray	Flowable bovine gelatin matrix and licensed human thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical
Recothrom™	T	Zymogenetics, Seattle,WA	Glue	Recombinant thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical
Surgiflo™	T	Johnson & Johnson Company, Somerville, NJ	Glue	Porcine gelatin with or without thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical
Thrombin-JMI™	T	King Pharmaceuticals, Bristol, TN	Glue	Bovine thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical
Evicel™	FT	Johnson & Johnson; OMRIX Biopharmaceutical Ltd., Kiryat-Ono, Israel	Glue	Fibrin sealant—human pooled	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

Fibrocaps™	FT	Raplixa; ProFibrix BV, Leiden, the Netherlands	Powder	Thrombin and fibrinogen powders that does not require recostitution	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical
Quixil/Crosseal™	FT	OMRIX Biopharmaceutical Ltd., Kiryat-Ono, Israel	Glue	Two vials containing human thrombin and human fibrinogen	For use in obtaining liver hemostasis and in orthopedic surgery
Tissucol™	FT	Baxter Healthcare Corporation, Westlake, CA	Glue	Human fibrinogen and human thrombin	Aid in hemostasis in general suegery
Product association (Carrier-bound fibrine sealants: Matrix plus Fibrine and/or Thrombine Based)	**Structure**	**Manufacturer**	**Device**	**Description**	**Indication**
CoStasis™	MT	Cohesion Technologies Inc., CA	Glue	Flowable bovine gelatin matrix and licensed bovine thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical
Evarrest™	FMT	Ethicon, Inc, a Johnson & Johnson Company,Somerville, NJ	Patch	Human fibrinogen and human thrombin sealant patch	For use with manual compression as an adjunct to hemostasis for soft tissue bleeding during open retroperitoneal, intra-abdominal, pelvic, and non-cardiac surgery
TachoSil™	FMT	Nycomed GmbH, Linz, Austria	Patch	Dry collagen sponge made from horse tendons, and on one side coated with human fibrinogen and thrombin	An adjunct to hemostasis in cardiovascular surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Vitagel™	FMT	Orthovita, Malvern, PA	Glue	Fibrin sealant—plasma, bovine collagen and bovine thrombin	An adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
M=Matrix, F=Fibrin, T=Thrombin,					

Table 2 Caractheristics of included studies on Topical Haemostatic Agents in Liver Surgery or Liver Transplantation

Author	Ref	Year	Study		GRADE	Composition	Control	Intervention	Procedure	Intervention (n)	Control (n)	Conclusions
Bektas	27	2014	prospective	RCT	MQ	F	SoC	Fibrin glue vs Manual compression	LS	35	35	Fibrin sealant safe and superior to manual compression
Bochicchio	28	2015	prospective	RCT	MQ	FMT	M	Fibrocaps with gelatine sponge vs gelatine sponge alone	LS	120	61	Time to hemostasis reduced in Fibrocaps + gelatine than gelatine alone.
Briceno	29	2010	prospective	RCT	LQ	FMT	SoC	Tachosil vs nothing	LS	57	58	Decreased rates of drain output and blood transfusion. Moderate to severe complications with the use of fibrin sealant.
Cauchy	30	2014	retrospective	CC	LQ	M	SoC	Biofoam (expanding haemostatic surgical matrix) vs nothing	LS	14	14	Major incidence of perihepatic vascular thrombosis with Biofoam
Chapman	31	2000	prospective	RCT	LQ	MT	M	Costasis vs Collagen sponge	LS	38	29	Significantly faster control of hemostasis with use of fibrin sealant liquid.
De Boer	32	2012	prospective	RCT	HQ	FT	SoC	Quixil vs control	LS	156	154	No difference
Figueras	33	2007	prospective	RCT	HQ	FT	SoC	Fibrin glue (Tissucol) vs control	LS	150	150	No difference in drainage volume, morbidity or biliary fistula
Fischer	34	2011	prospective	RCT	LQ	FMT	Other	Tachosil vs Argon beamer	LS	54	52	Reduced time to hemostasis with Tachosil
Frilling	35	2005	prospective	RCT	MQ	FMT	Other	Tachosil vs Argon beamer	LS	59	62	Tachosil superior in hemostasis
Genyk	36	2016	prospective	RCT	MQ	FMT	M	Tachosil vs Surgicel	LS	101	99	Tachosil well tolerated and superior in secondary hemostasis
Gugheneim	37	2011	prospective	RCT	MQ	FT	Other	Tissucol vs PlasmaJet	LS	29	29	No difference in bleeding but reduction of collections requirement drainage.
Hayashibe	38	2006	retrospective	cohort	MQ	FM	F	Fibrin glue with PEG versus fibrin glue	LS	51	37	Reduced bile leak in the group FG+PAF

Kobayashi	39	2011	retrospective	cohort	LQ	FMT	SoC	Fibrin glue with polyglycolic acid felt	Lap LS	18	22	No difference
Kobayashi	40	2012	retrospective	cohort	LQ	FMT	FM	Fibrin glue with polyglycolic acid felt vs Fibrin coated collagen fleece	LS	34	39	Reduced bile leak in the group FG+PAF
Koea	41	2012	prospective	RCT	MQ	FT	SoC	Evarrest Fibrin sealant vs standard of care	LS	39	45	Reduced time to hemostasis with fibrin sealant, no difference in postoperatvive collections
Liu	42	1993	prospective	RCT	MQ	F	SoC	Fibrin glue	LS	20	20	Reduced time to hemostasis with fibrin glue
Moench	43	2014	prospective	RCT	LQ	M	FMT	Collagen Hemostat (Sangustop) vs Tachosil	LS	61	65	No difference
Ollinger	44	2013	prospective	RCT	LQ	FMT	M	Tachosil vs Veriset	LS	32	18	Reduced time to hemostasis with Tachosil
Schwartz	45	2004	prospective	RCT	MQ	FT	SoC	Crosseal vs standard hemostasis	LS	58	63	Reduced time to hemostasis with Crosseal
Toti	46	2010	retrospective	cohort	MQ	FMT	F	Tachosil vs fibrin glue	SLT	16	16	Reduced bile leak in the group Tachosil
Verhoef	47	2015	prospective	RCT	MQ	FMT	M	Fibrocaps with gelatine sponge vs gelatine sponge alone	LS	86	39	Time to hemostasis reduced in Fibrocaps + gelatine than gelatine alone.
Zacharias	48	2012	retrospective	cohort	MQ	FMT	M	Tachosil vs Surgicel	LS	64	69	Less complication only in Major Hepatectomy subgroup wiht Tachosil

Ref= Reference, F=Fibrinogen, M=Matrix, T=Thrombin, SoC=Standard of care, RCT=Randomized Clinical Trial, CC=Case control, SLT=Split Liver Transplantation, LS=Liver Surgery, Lap LS=Laparoscopic Liver Surgery, HQ=High Quality, MQ= Medium Quality, LQ=Low Quality, VLQ=Very Low Quality