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REVIEW ARTICLE

Topical haemostatic agents in liver surgery: do we need them?

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Abstract

Background: Worldwide, partial liver resections are increasingly being performed for primary or secondary hepatic malignancies. There are various techniques to reduce blood loss druing liver surgery. Several topical haemostatic agents have been developed to improve haemostasis of the resection surface and these agents are used more and more, even although the true effects remain unclear.

Methods: The present literature about the use of topical haemostatic agents in liver surgery was reviewed. Furthermore we conducted a Dutch national survey to explore the use of and belief in these agents in liver surgery.

Results: The Dutch national survey among surgeons showed that topical haemostatic agents are frequently used not only to lower intra-operative blood loss or shorten time to haemostasis, but even more importantly, to reduce resection surface related complications such as bile leakage, postoperative haemorrhage and abscess formation. Although various topical haemostatic agents have been shown to reduce intra-operative time to haemostasis at the resection surface after liver resections, there is no scientific proof that these topical haemostatic agents really reduce resection surface related complications.

Conclusion: This review highlights the need for more randomized clinical trials to investigate the efficacy of topical haemostatic agents in reducing resection surface related complications.

Keywords

liver resection, surgical technique, haemostatic agents, fibrin sealants, questionnaire

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Introduction

Worldwide, partial liver resections are being performed for primary or secondary hepatic malignancies with increasing frequency. Although recent reports have shown improvement in operative morbidity and mortality associated with hepatic resection there is no uniformity between centres in the surgical, anaesthetic and haemostatic techniques used. Specific factors contributing to the improvement in operative risks have not been clearly defined. Several studies have shown intra-operative blood loss and transfusion requirements to be risk factors for post-operative morbidity and mortality.[1–4] According to these results, a main focus in hepatic resections should be reduction of blood loss and transfusion requirements.

During liver surgery, there are several techniques to reduce blood loss. Reduction of the central venous pressure during transection of the liver parenchyma has been shown to significantly reduce blood loss.[5,6] Vascular occlusion techniques, such as inflow occlusion and total vascular occlusion, have also been shown to potentially reduce blood loss during hepatic resection.[7] The device used for transection of the liver parenchyma might also influence blood loss,[8] even although none of these devices or techniques have gained unanimous acceptance among liver surgeons.

Besides techniques applied during resection, several topical agents have been developed to improve haemostasis of the resection surface. Apart from their haemostatic potential, these haemostatic agents are also used with the aim to prevent bile leakage, which is still a clinically important complication after liver surgery. Bile leakage from the resection surface has been reported in up to 15% of the patients after partial liver resections. Only a few clinical trials on the use of haemostatic agents have focused on resection surface-related complications after liver resection. Haemostatic agents are used more and more, even although the true effects remain unclear.

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Table 1 Different topical haemostatic agents used in surgery. Examples of agents between brackets

Agents providing a matrix for coagulation	Collagen *(Tissufleece®, Novacol® Lyostipt®, Antema®, Avitene®, Duracol®)*
	Gelatine *(Gelfoam®, Spongostan® Gelita®)*
	Cellulose *(Nu-knit®, Surgicell®)*
Agents that mimic coagulation	Fibrin sealants *(Tisseel® or Tissucol®, Quixil® or Crosseal®, Vivostat®, Beriplast®, Biocol® Bolheal®, Hemaseel®)*
	Carrier-bound fibrin sealants *(FloSeal® Tachosil®, Costasis®)*

This review will focus on the use of topical haemostatic agents in liver surgery. The rationale of different topical agents will be discussed followed by the results of a Dutch national survey on the use of topical haemostatic agents by liver surgeons in The Netherlands.

Topical haemostatic agents

Topical haemostatic agents can be divided into two groups (see Table 1). The first group consists of agents that only provide a matrix for endogenous coagulation. Available matrices are those that are made of collagen, cellulose or gelatine. These agents do not contain active components. The second group consists of agents that do contain active components, the fibrin sealants. These agents mimic endogenous coagulation. A few products available combine a matrix for coagulation with active haemostatic components, the so-called 'carrier-bound fibrin sealants'.

The final step in the normal coagulation cascade, the formation of fibrin from fibrinogen under the influence of thrombin, is mimicked by fibrin sealants (see Fig. 1). These agents contain separated, virus inactivated, human fibrinogen and thrombin. The composition of the available sealants differs mainly in the concentration of fibrin and thrombin and the addition of calcium or antifibrinolytic components, such as aprotinin. When applied, for example, to a resected liver surface, the two components mix and reproduce the last step of the coagulation cascade. This leads to the gradual polymerization of fibrinogen by hydrogen bonding and electrostatic reactions into fibrin fibres. These fibres form a three-dimensional structure with the appearance of a gel. Factor XIII (fibrin-stabilizing factor), activated by thrombin in the presence of calcium ions, converts the bonds between the fibrin monomers into covalent bonds. This cross-linking leads to the formation of a stable and insoluble fibrin clot. Most fibrin sealants also contain an antifibrinolytic agents, usually aprotinin or tranexamic acid. These agents inhibit the degradation of the fibrin clot by proteolytic enzymes.[9]

Most fibrin sealants are packed in a dual syringe system. Hereby thrombin and fibrinogen are separated. They mix at the end of the syringes or in a connector just before contact with the resection surface. Another method for applying fibrin sealant is as a spray.

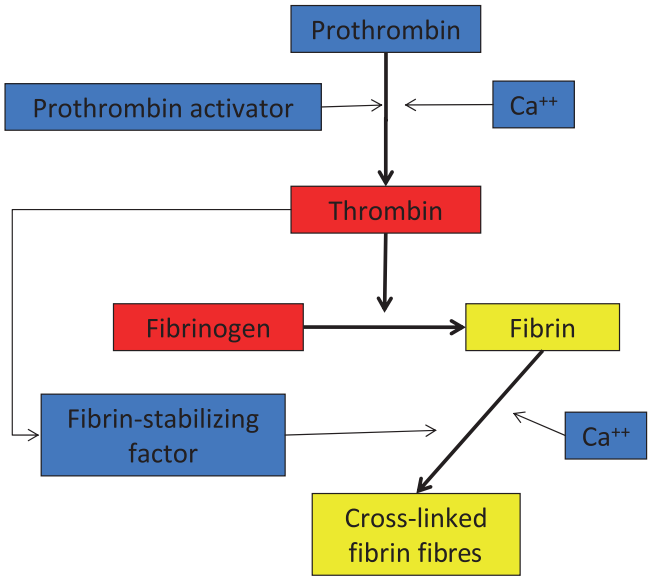

Figure 1 The final step in the normal coagulation cascade, the formation of fibrin out of fibrinogen under the influence of thrombin, is mimicked by fibrin sealants

The earlier mentioned carrier-bound fibrin sealants combine the active agents in the fibrin sealant with a matrix for coagulation. Instead of using ready-to-use carrier-bound fibrin sealants, it is also possible to combine a fibrin sealant with a matrix of choice, in this way creating a carrier-bound fibrin sealant. The ideal topical agent should have the capacity to seal small vessels and bile ducts of the resection surface, be safe and easy to use.

Little is known about the effect of bile on the active substances of topical haemostatic agents. In the past, experimental research was performed to show the effect of bile on blood clotting. These studies have shown that bile salts, especially taurocholate or desoxycholate, are responsible for delaying blood clotting by counteracting the activities of thrombin and prothrombin.[10,11]

Use of haemostatic agents in liver surgery: results of a Dutch survey

Topical haemostatic agents are increasingly used in liver surgery. A Japanese survey found that 60% of surgeons performing liver surgery routinely use haemostatic materials such as fibrin sealants.[12]

In 2004, we conducted a web-based nation-wide survey to explore the surgical attitudes and preferences regarding hepatic resections among Dutch surgeons, focusing on haemostasis. In our survey, the following parameters were assumed to be of importance: anaesthetic techniques, vascular occlusion techniques, haemostatic techniques and the use haemostatic agents. One of our goals was to determine whether surgeons believe in the effect of haemostatic agents in reducing resection surface-

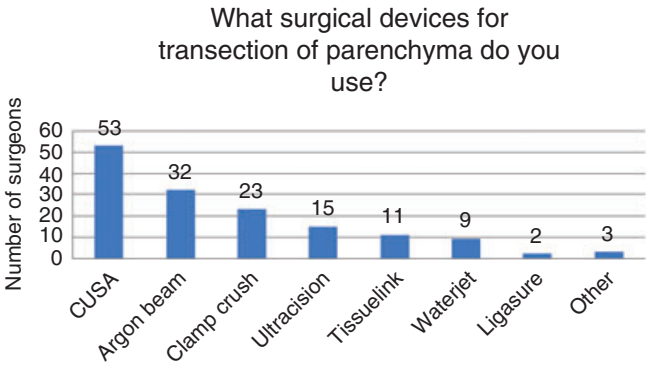

Figure 2 Results of a Dutch survey. Use of surgical devices among 67 surgeons who regularly perform major liver resections. Multiple answers were possible

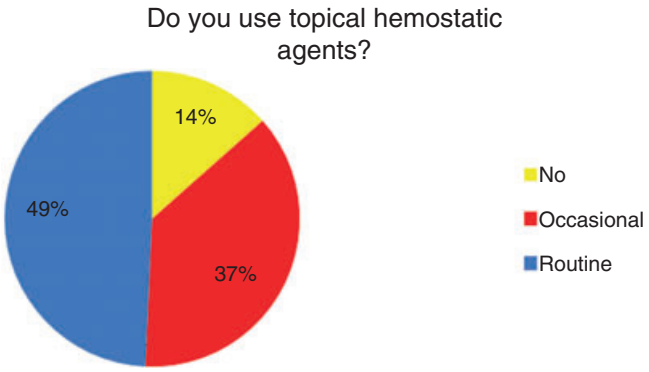

Figure 3 Results of a Dutch survey. Use of topical haemostatic agents among 67 surgeons who regularly perform major liver resections

related complications. Questionnaires were sent by e-mail to all practicing surgeons in the Netherlands. E-mail addresses were obtained from the Dutch Surgery Association ('Nederlandse Vereniging voor Heelkunde'). The response rate was 69% (590/859). Hepatic resections were performed by 96 out of the 590 respondingsurgeons, of whom 24 only performed wedge or segmental resections. Seven surgeons sometimes performed larger liver resections but never hemihepatectomies. Sixty-seven (11%) surgeons in the Netherlands reported that they regularly perform major partial liver resections (e.g. hemihepatectomies). All of these surgeons were working in a teaching hospital (n = 31) or in a university medical centre (n = 36). Here we report only on the surgical practice of those 67 surgeons performing major liver resections.

The estimated number of liver resections in the Netherlands is around 500 per year, but there are no valid data on complete numbers. In our survey, 41 (69%) surgeons performed less than 10 resections per year, whereas 26 (31%) surgeons performed more than 10 per year. Data on surgical methods used for transection of the hepatic parenchyma are presented in Fig. 2. The most frequently used methods were CUSA (Cavitron Ultrasonic Surgical Aspirator; Valley lab Inc., Boulder, CO, USA), argon beam coagulation and the clamp crush technique.

The majority of surgeons (58/67; 87%) used haemostatic agents after resection of the liver parenchyma. More than half of them used haemostatic agents routinely (57%), the rest of these surgeons used haemostatic agents only when indicated. The most frequently used products were fibrin sealants (see Figs 3,4).

Forty-five per cent of the surgeons believed that fibrin sealants reduce resection surface-related complications, 12% disagree and 43% were not sure about the effect of fibrin sealants on resection surface-related complications (see Fig. 5).

From this nation-wide survey, we conclude that haemostatic agents are frequently used in major liver surgery, not only for haemostasis, but also with the aim to reduce resection surface-related complications.

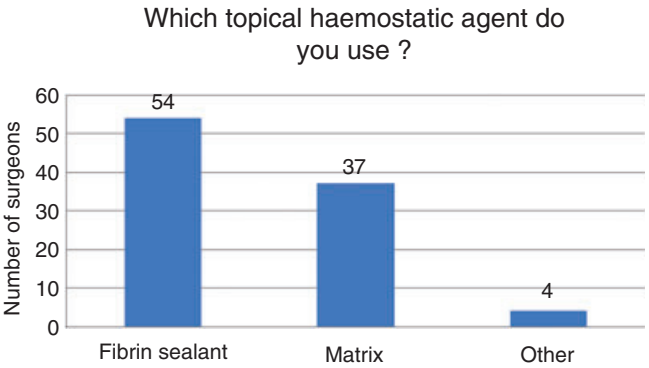

Figure 4 Results of a Dutch survey. Use of various types of topical haemostatic agents among 58 out of 67 surgeons who use topical haemostatic agents when performing liver resections. Multiple answers were possible

Evidence for the use of topical haemostatic agents in liver surgery

In 2002, a systematic review was performed to examine the efficacy of fibrin sealants in reducing intra-operative blood loss and red cell transfusion in adult elective surgery. Types of surgery involved in this study were prostatectomy, pulmonary, cardiac, vascular, arthroplasty and liver surgery. Overall these results suggested efficacy of fibrin sealants. For the trials that were conducted in the setting of liver surgery, the use of fibrin sealants did not show a significant reduction of intra- and post-operative blood loss. A lack of blinding in the majority of the studies reviewed raised concern about taking blood transfusion practice as a response variable. The authors conclude that there were inadequate data provided to draw firm conclusions about the impact of fibrin sealant use on clinically important endpoints.[13]

In liver surgery, haemostatic agents have shown to be effective in improving time to haemostasis of the resection surface. Although several products show a statistically significant reduction in time

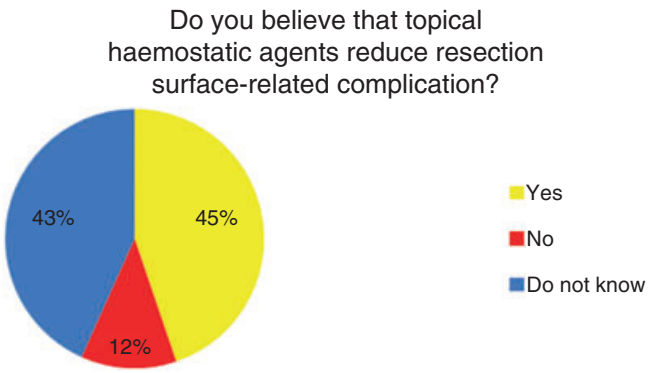

Figure 5 Results of a Dutch survey. Perception about the efficacy of topical haemostatic agents among 67 surgeons who perform liver resections

to haemostasis the question remains whether this is clinically relevant. Also in liver surgery, intra-operative blood loss or blood transfusion might not be a relevant endpoint for the use of haemostatic agents, because these agents are mainly used after transection of the parenchyma, to seal the resection surface, while blood loss is usually a problem during transection and not so much thereafter.

Apart from intra-operative haemostasis, resection surface-related complications, such as bile leakage and abscess formation, are a major concern after liver resection. Patients suffering from a biliary leakage after partial liver resection often require prolonged hospitalization, additional interventions and have a worse prognosis. The reported incidence of biliary leakage varies between 3.6% and 12%.[14–16]

In a prospective randomized trial, Frilling *et al.* compared a carrier-bound fibrin sealant (Tachosil, Nycomed, Copenhagen, Denmark) (n = 59) with argon beam coagulation (n = 62) as a haemostatic agent in liver resection. Time to haemostasis was significantly shorter in the group treated with the carrier bound fibrin sealant (3.9 min vs. 6.3 min, P = 0.0007). Although the incidence of bile leakage was slightly higher in the sealant group (7% vs. 4%), the frequency of bile leakage and other adverse events did not significantly differ between the groups.[17]

Another fibrin sealant, Crosseal (American Red Cross, Washington, DC, USA), (n = 58) was compared with other commercially available haemostatic agents (n = 63) by Schwartz *et al.* Time to haemostasis was shorter in the Crosseal group (282 vs. 468 min, P = 0.006) and significantly more patients achieved haemostasis within 10 min in this group (P = 0.003). There were significantly less abdominal fluid collections and reoperations in the Crosseal group compared with the control group, although this was a secondary endpoint.[18]

The largest prospective randomized controlled trial that compared the combination of Tissucol (Baxter Immuno, Vienna, Austria) and an absorbable collagen sponge (Johnson & Johnson) (n = 150) with a control group (n = 150) showed no differences between the two groups with regards to the need for blood transfusion, post-operative complications (such as intra-abdominal abscesses and other fluid collections or re-interventions).[19] Another randomized controlled trial compared Costasis (Cohesion Technologies Inc., Palo Alto, CA, USA) (n = 28) with a collagen matrix (n = 29). Costasis is a composite of bovine microfibrillar collagen and bovine thrombin that is mixed with autologues plasma at the time of surgery. Although the sealant was more effective in controlling bleeding than the collagen matrix, there were no differences in transfusion need or adverse events.[20]

Theoretically, fibrin sealants might seal small bile ducts, which is the rationale for surgeons to use fibrin sealants with the assumption to reduce biliary complications after partial liver resection. Only a few clinical trials have focused on the effect of topical haemostatic agents on biliary leakage after liver resection. Capusotti *et al.* performed a retrospective analysis in 610 patients to identify the risk factors associated with bile leakage after liver resection. Bile leakage was defined as the drainage of 50 ml or more of bile from the surgical drain, or from drainage of an abdominal collection, beyond the third post-operative day. After resection, fibrin sealant was applied to the raw resection surface to improve haemostasis. At multivariate analysis, use of fibrin sealant appeared to be an independent protective factor against bile leakage.[14]

Ten years earlier, a French group had similar results. In a randomized controlled trial, they compared the application of fibrin sealant on a dry resection surface after hepatic resection (n = 38) with a control group (n = 44). The fibrin sealant group had significantly less drain production after 3 days. The concentration of bilirubin in the drain fluid was also significantly lower in the fibrin sealant group.[21]

In a retrospective study by Hayashibe *et al.*, the combination of fibrin sealant and a matrix, in this case a bioabsorbable polyglicolic acid felt (n = 51), or fibrin sealant alone (n = 37) were compared. Fibrin sealant alone was used from 2001 until 2003, the combined agent was used from 2003 until 2005. The combination of the two haemostatic agents was favourable for prevention of bile leakage after hepatic resection. There was no bile leakage in the group treated with the combined agent vs. three patients (8.1%) with bile leakage in the fibrin-sealant group. Drawbacks of this study were the low number of patients, the retrospective design and the difference in treatment by time period.[22]

Directions for future research

Despite the clear effect of topical haemostatic agents on intra-operative time to haemostasis, the efficacy of these agents regarding clinically relevant post-operative outcome measures (such as bile leakage or other resection surface-related complications) remains to be demonstrated. More clinical trials are needed that focus on resection surface-related complications instead of time to haemostasis or transfusion requirements. Apart from the study by Figueras *et al.*, no previous trial was adequately powered to show a significant difference in resection surface-related complications. As fibrin sealants have proven to be more effective in

haemostasis than matrix agents, further research should focus on fibrin sealants or a combination of sealants with a matrix, the so-called carrier-bound fibrin sealants. The concern of potential viral transmission when fibrin sealants based on human plasma-derived coagulation proteins are used, has lead to the development of recombinant clotting factors. It is likely that these recombinant products will replace products based on plasma-derived human thrombin and fibrinogen in the future.

Conclusion

There is a large variety of topical haemostatic agents available for use during surgery. The most frequently used agents are fibrin sealants. Topical haemostatic agents are used on a large scale in liver surgery. Despite a lack of clear evidence in the literature, most surgeons believe that topical haemostatic agents reduce resection surface-related complications after liver resection. Several studies have been published about the use of haemostatic agents in liver resection. Most of these studies lack clinically relevant primary endpoints. When scrutinizing the literature, it is important to distinguish the studies that have time to haemostasis as primary outcome measure from those studies that focus on more clinically relevant outcome measures, such as the need for post-operative interventions to treat bleeding or resection surface-related complications (e.g. biloma or other intra-abdominal fluid collections). Fibrin sealants seem to be effective in reducing the time to haemostasis, but their impact on reducing resection surface-related complications remains contradictory. For this reason, larger, randomized controlled trials are needed to show efficacy of haemostatic agents in reducing those post-operative complications.

Conflicts of interest

M. T. de Boer and R. J. Porte are involved in clinical trials on the use of fibrin sealants in liver surgery that are partially funded by Johnson & Johnson and ProFibrix.

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