

# The Advantages and Disadvantages of Methods Used to Control Liver Bleeding: A Review

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## Abstract

**Context:** Despite advancements in the science of surgery, minimizing bleeding from parenchymal tissue of the liver continues to be one of the challenges surgeons are facing to protect patients' lives. However, the number of surgeries needing incisions in the liver tissue, e.g. metastectomy, is constantly increasing.

**Evidence Acquisition:** A MEDLINE and conventional search of the past 50 years of the medical literature was performed to identify relevant articles on hemostasis in the liver parenchymal tissue.

**Results:** The studies that have been published on hemostasis in the liver parenchymal tissue can be classified into 3 categories: 1. surgical procedures; 2. methods affecting body hemodynamic; 3. pharmacological methods. The purpose of these studies are to identify the best therapeutic approaches that not only minimize the bleeding, but also save the maximum amount of the liver tissue and minimize the use of partial liver resections.

**Conclusions:** The excessive blood loss and the long time needed to control the bleeding during liver surgery impose several side effects and complications on patients. Topical hemostatic agents such as ferric chloride, potassium aluminum sulfate (alum) and aluminum chloride are safely applicable in patients. These agents might be used along with other current methods to minimize the blood loss and the need for blood products during liver surgeries.

**Keywords:** Liver, Surgical Procedures, Hemodynamic, Pharmacology

## 1. Context

Despite advancements in the science of surgery, minimizing bleeding from parenchymal tissue of the liver continues to be one of the challenges surgeons are facing to protect patients' lives. Massive blood loss may necessitate the transfusion of blood or blood products, which consequently are associated with increased rates of morbidity and mortality (1-5). The sinusoidal structure of liver causes the main difficulty in maintaining the liver tissue hemostasis (6). The blood vessels in these sinusoids are so small that cannot be occluded through the hemostatic techniques commonly used in surgeries (7, 8). However, the number of surgeries needing incisions in the liver tissue, e.g. metastectomy, is constantly increasing (9). In recent years, the incidence of liver injuries has dramatically increased due to an increase in the incidence of abdominal traumas related to traffic accidents. Bleeding is still the leading cause of mortality in patients with liver trauma (6-10).

A laceration with 3 cm of depth in the liver parenchyma is accompanied with a mortality rate of 19%, and if the rupture exceeds 25% - 50% of a liver lobe, the mortality rate may

exceed 28% (11). The high morbidity and mortality rates may not only be attributed to the extensive blood loss but also to the long time needed to control bleeding (12). This issue has led to numerous studies be conducted on the methods of hemostasis in liver surgeries. The purpose of these studies are to identify the best therapeutic approaches that not only minimize the bleeding, but also save the maximum amount of the liver tissue and minimize the use of partial liver resections (13-16). The studies that have been published on hemostasis in the liver parenchymal tissue can be classified into 3 categories: 1. surgical procedures; 2. methods affecting body hemodynamic; 3. pharmacological methods (Box 1). The advantages and disadvantages of some of these methods are reviewed in the present study.

## 2. Evidence Acquisition

A MEDLINE and conventional search of the past 50 years of the medical literature was performed. In order to identify relevant articles on hemostasis in the liver parenchymal tissue, we first performed a MEDLINE search of articles

from 1973 onward. Secondly, we searched the reference lists of the articles initially retrieved for additional studies. This method of cross-checking was continued until no further publications were found. In case of multiple publications on the same study population, we used the most recent publication. With regards to representative animal studies, epidemiological investigations, case reports and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature were reviewed. Material provision was conducted independently by each author, and any discrepancies among reviewers were resolved by consensus. Eligible material was selected for evaluation. Language other than English was not an exclusion criterion.

### 2.1. Surgical Methods to Reduce Bleeding From Liver Parenchymal Tissue

At present, the surgeon's preference and experiences and facilities available in medical centers are among the most important factors affecting the technique used to minimize bleeding during liver surgery. Currently, occlusion of the bleeding vessels through deep sutures or packing the site of bleeding are the most common meth-

ods used to minimize blood loss from a ruptured liver (17-19). It should be remembered that suturing may exacerbate the liver tissue damage and extend the ischemic injury to the unaffected liver parenchyma. However, the liver parenchyma is very delicate and an inexperienced surgeon may exacerbate the parenchymal laceration during the suturing technique. The packing method is also associated with the risks of rebleeding and abdominal compartment syndrome, which may impose the patient the risks and costs of additional surgeries.

Other surgical techniques used to stop bleeding from parenchymal tissues such as liver, are complete resection of the injured tissue (in severe hemorrhage), selective ligation of the bleeding vessels (Pringle's maneuver, to close the main liver arteries) and electrocoagulation (electrical cauterization) (20, 21). Although several mechanisms are involved in bleeding during liver surgeries, the surgical technique used is the most frequent cause of intraoperative and postoperative liver bleeding (22). In addition to surgical related factors, abnormalities in the patients' hemostatic system can also contribute to bleeding during liver surgery. The normal hemostasis is a result of the interaction of the vascular walls, platelets, coagulation factors, and fibrinolytic function (23, 24).

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#### Box 1. Methods Used to Reduce Blood Loss in Liver Surgery

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##### Methods Used to Reduce Blood Loss in Liver Surgery

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##### Surgical

Vascular clamping techniques

Inflow occlusion

Continuous Pringle maneuver

Continuous Pringle maneuver after ischemic preconditioning

Intermittent Pringle maneuver

Total vascular occlusion

Dissection devices for transection of liver parenchyma

Classic methods

##### Scalpel

“Finger-fracture” method

##### Clamp crushing

Ultrasonic dissection

Hydro-jet dissection

Electro coagulation (Argon coagulation)

Radiofrequency ablation-based devices

##### Anesthesiologic

Maintaining low central venous pressure by using

Blood products

##### pharmacologic agents

Antifibrinolytics

Recombinant factor VIIa

Topic hemostatic agents

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Today, all efforts are focused on finding new therapeutic methods to minimize blood loss during liver surgery (in patients with various conditions, including patients with an impaired hemostatic system) and minimize the need for transfusion of blood and blood products in these patients (24). In Europe, selective vascular occlusion techniques are the most common method used to control liver bleeding (25). However, these techniques would increase the likelihood of liver tissue ischemia. To solve this problem, some researchers have suggested that the vessels be clamped intermittently. Although this approach reduces the risk of liver ischemia, it is not an effective method in controlling liver bleeding (26). In a survey, van der Bilt et al. investigated the opinion of 621 European surgeons on the application of selective vascular clamping in liver surgery. They reported that most of surgeons believed that clamping the liver vessels would be useful only when excessive bleeding occurs during liver surgeries. Surgeons believed that complete liver inflow occlusion (i.e. the Pringle's maneuver) should be used only in such conditions (25). Nakajima et al. also studied the same issue in 231 hospitals in Japan and achieved the same result (27). In addition to the selective vascular clamping techniques, new methods have been introduced to incise the liver parenchyma. Although all of these methods try to minimize bleeding during liver surgery, some of them are very time consuming and some others had disappointing results (26-28). In a clinical trial, Lesurtel et al. compared four new techniques to make incisions in liver parenchyma in 100 patients undergoing liver surgeries. They compared the conventional clamping technique with three new techniques including the cavitron ultrasonic surgical aspiration, Hydro-jet, and dissecting sealer methods and reported that the conventional clamping technique was associated with less bleeding, shorter parenchymal incision time, and lower costs compared to the three newer techniques (29). Therefore, the beneficial effects of these new techniques are not fully understood and further studies are needed to determine the role of these techniques in liver surgery (30). However, the high costs of new methods have limited the usage of these methods in some researches and prevented them to be commercialized.

Currently no consensus exists on the using of blood products such as fresh frozen plasma in prevention of bleeding in liver surgery (31-33). Although blood products such as fresh frozen plasma and platelet concentrate should be used in controlling sever bleeding (34), no agreement exists among researchers on the use and the amount of consumption of these products in liver surgery. Further studies on the establishment of hemostasis and improvement of prognosis in patients with liver bleeding are essential and have always been emphasized by researchers (30). The high-intensity focused ultrasound (HIFU) technique is another new technology, which is used to control liver bleeding. The technique affects through a sudden increasing in the liver tissue temperature and also creates cavities in the

liver tissue. These two events would result in formation of thrombosis and activation of platelets (35). However, using HIFU may result in irreversible damages to the liver parenchymal tissue and vasculature. Therefore, the side effects and the high cost of this technique have limited its usage in liver surgeries. Using hemostatic bandages during surgery is another technique for controlling liver bleeding. The beneficial effects of these new methods are not entirely clear and more studies will be needed to assess the role of this method in liver surgery (36, 37). Clamping blood vessels and thrombosis formation are also among the methods used to control liver bleeding (38-40). However, these methods are associated with high risks of ischemic damage to the remnant liver tissue.

Recent studies have also shown that short pulsed electrical stimulation can induce temporary vasoconstriction and thrombosis formation with minimal thermal effects. Palanker et al. in a study examined the effect of pulsed electrical stimulation on liver bleeding and reported that vasoconstriction started at 10 seconds after electrical stimulation while thrombosis formation take-placed in about 3 minutes (41). This method is currently very expensive and is still under investigation.

## 2.2. Blood Loss Controlling Methods Affecting Hemodynamic

Lowering the central venous pressure (CVP) is another way to reduce the liver bleeding during surgery (42-45). Bismuth et al. (33) and Jones et al. (32) in their studies have shown that the amount of blood loss during liver surgery is directly associated with patient's CVP. The higher the CVP, the higher the volume of blood loss from the liver would be. Reducing the CVP is usually performed using vasodilator drugs or by reducing intravascular volume. Although lowering the CVP may decrease the blood loss, this method is associated with high risks for air embolism, systemic tissue hypoperfusion and acute renal failure (46, 47). In a study, Schroeder et al. investigated the effects of a low CVP in patients undergoing liver surgery. Using two homogenous groups, they showed that the group with a low CVP had higher serum creatinine levels (a marker for renal failure), more needs for dialysis, and higher mortality in 30 postoperative days compared to the group with a normal CVP (34). In another clinical trial, 79 liver donors who underwent partial liver resection were studied. The researchers found that patients with a low CVP had significantly less blood loss than patients with a normal CVP (47). It seems that although lowering the CVP can be very helpful in controlling bleeding from the liver tissue, the side effects of this method have made it less attractive.

## 2.3. Pharmacological Methods to Reduce Bleeding From Liver Parenchymal Tissue

Few pharmacological agents have been introduced to prevent or treat bleeding during liver surgery. These

agents should be used as supplementary to other methods to stop bleeding from the liver parenchymal tissue. These agents can be categorized into three main groups: 1. topical hemostatic agents, 2. Anti-fibrinolytic drugs, and 3. Accelerators of coagulation (procoagulant agents).

### 2.3.1. Topical Hemostatic Agents

Topical hemostatic agents used to establish hemostasis in liver tissue, stimulates the liver parenchymal tissue homeostasis in the cutting surface. In fact, these materials require the natural body's homeostatic system for their performance. This is a disadvantage for these agents because in many cases that require liver surgery, such as cirrhosis of the liver, the body's homeostatic function is impaired due to liver dysfunction. Based on their mechanisms of action, these agents are divided into three categories: 1. Substances that mimic coagulation (e.g. fibrin coatings); 2. Materials that provide a substrate for endogenous coagulation (e.g. collagen, gelatin and cellulose sponges); 3. The combination products that provide a substrate for working of exogenous and endogenous coagulation factors (37, 38).

Current evidence indicates the usefulness of the topical agents in reducing the time to hemostasis and decreasing the need for transfusion of blood and blood products in patients undergoing liver surgery. As a result, the prognosis of patients would be improved after liver surgery (48-52). However, the studies on topical hemostatic agents are somewhat contradictory. In a systematic review on the effectiveness of fibrin in controlling the liver parenchymal hemorrhage, Carless et al. concluded that, although fibrin is effective in controlling nonliver bleeding (53), its efficacy in stopping the bleeding from parenchymal tissues such as liver is doubtful (54). In a clinical trial on 300 patients who underwent partial liver resection, no significant differences were found in the amount of blood loss, the need for blood products and surgical complications between the groups treated with fibrin for controlling the liver bleeding and a control group that treated without fibrin (54).

Collagen is also a topical hemostatic agent which its effect on the bleeding from parenchymal tissues has been examined. Collagen, as a local hemostatic agent, was first discovered in 1970 (55). It has been shown that collagen helps hemostasis through induction of platelet aggregation (56, 57). In several studies, collagen was effective in controlling blood loss from parenchymal tissues (58-61). However, to start its hemostatic effects, collagen should be in direct contact with the bleeding tissue (56, 57). Pathological evaluation of inflammatory reactions and fibrosis toward topical hemostatic agents as foreign bodies showed that collagen stimulates lymphoid hyperplasia, fibrosis and granuloma tissue formation (62).

### 2.3.2. Antifibrinolytic Drugs

Antifibrinolytic agents can be categorized into two groups: 1. plasminogen inhibitors (such as tranexamic acid and aminocaproic acid); 2. plasmin inhibitors (such

as serine protease aprotinin inhibitors). Recently, several studies have been conducted on the efficacy and side effects of antifibrinolytic drugs (63-67). In a study conducted by Molenaar et al. the concurrent use of aprotinin and tranexamic acid could not only reduce the amount of blood loss, but also lead to 30% to 40% reduction in need for blood products (55). However, the use of aprotinin has been limited due to the high risk for renal failure and death in patients who received it (55, 67). Although several studies have been done on the effectiveness of antifibrinolytics, few studies have been published on the effectiveness of these drugs in liver parenchymal bleeding. In general, it seems that improvements in surgical techniques and methods such as reduction of CVP - despite all the complications- are yet more effective than antifibrinolytic drugs (58, 68). Further studies seem to be needed for better understanding of the effectiveness of antifibrinolytics in controlling the liver bleeding (59).

### 2.3.3. Accelerators of Coagulation (Procoagulant Agents)

The recombinant factor VII is newly proposed to be used as a procoagulant agent to control liver bleeding. Several studies have investigated the efficacy and safety of recombinant factor VII in controlling liver bleeding (60, 62, 63, 69, 70). Although no important side effect is documented in using of the recombinant factor VII (65, 66, 71), none of the studies showed a significant difference in blood loss or needing to blood products between patients who received recombinant factor VII and the patients who did not receive it. In all of these studies, the recombinant factor VII was used as a prophylactic agent and further studies are recommended to determine the role of this agent in controlling acute liver bleeding.

## 3. Results

The studies that have been published on hemostasis in the liver parenchymal tissue can be classified into 3 categories: 1. surgical procedures; 2. methods affecting body hemodynamic; 3. pharmacological methods. Surgical procedures used to reduce blood can be classified into 2 general categories: 1. Vascular clamping techniques; 2. Dissection devices for transection of liver parenchyma. The impact of anesthesiologic (methods affecting body hemodynamic) care on blood loss and transfusion requirement in patients undergoing major liver surgery is mainly determined by 1) intraoperative fluid management, 2) the transfusion triggers used, and 3) the use of pharmacologic agents.

Based on their working mechanism, topical agents can be divided into three groups: agents that mimic coagulation (e.g., fibrin sealants), agents that provide a matrix for endogenous coagulation (e.g. collagen, gelatin, and cellulose sponges), and combined products that work as a matrix for endogenous and exogenous coagulation factors.

In general, surgical technique and experience are key factors determining the amount of blood loss in liver surgery. Inflow occlusion (the Pringle maneuver) and the use

of low central vein pressure are simple and effective measures of reducing blood loss during parenchyma transection. No superiority of one dissection device has been shown above the others, and their use depends mainly on the quality of the liver parenchyma and personal preference and experience.

According to recent studies hemostatic agents (that do not need the normal functioning of the body's hemostatic system or the normal liver function) could be highly efficient in controlling bleeding from the liver tissue along with other current methods.

#### 4. Conclusions

Due to the detrimental effects of perioperative blood loss and blood transfusion in patients who undergo liver surgeries, researchers are trying to find new effective methods and materials to minimize the blood loss and to reduce the need for transfusion of blood products during the liver surgeries and especially in patients with impaired normal hemostasis. In fact, the excessive blood loss and the long time needed to control the bleeding during liver surgery impose several side effects and complications on patients. Since most of the topical hemostatic agents which are used to control bleeding from the liver parenchymal tissue require normal homeostatic function of the body to exert their effects, and the liver is a key organ in normal homeostasis, these agents are not appropriate in controlling liver bleeding in patients with abnormal liver function such as liver cirrhosis. For this reason, recently, studies have focused on hemostatic agents that do not need the normal functioning of the body's hemostatic system. Ferric chloride (72), potassium aluminum sulfate or alum  $[KAl(SO_4)_2]$  (73) and aluminum chloride (74) are among these new agents. These agents have acidic property and exert their haemostatic effects through rapid coagulation of blood proteins. The blood contains a considerable amount of proteins that would rapidly react with the ions in these acidic agents. Then the proteins are being coagulated and would close the openings of small capillaries (18). In fact, this new group of hemostatic agents (that do not need the normal functioning of the body's hemostatic system or the normal liver function) affects through chemical reaction with the blood. This property makes them highly efficient in controlling bleeding from the liver tissue. These agents might be used along with other current methods to minimize the blood loss and the need for blood products during liver surgeries.

#### Footnote

**Authors' Contribution:** Saeed Nouri: acquisition and interpretation of data, study supervision, study concept and design. Mohammad Reza Sharif: drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Hasan Afzali: drafting of the manuscript, and critical revision of the manuscript for

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