Use of Fibrin Sealant as a Hemostatic Agent after Liver Biopsy in Swine

Erik K. Paulson, MD  
G. Robert Stephenson, MD  
Meg C. Neal, RN, BSN  
Victor Rossin, BS  
Jeffrey H. Lawson, MD, PhD

PURPOSE: To determine whether fibrin sealant injected into the tract created by liver biopsy can be used to decrease postprocedural bleeding. An innovative delivery system was used to deploy the fibrin sealant.

MATERIALS AND METHODS: Fibrin sealant is a hemostatic agent consisting of a suspension of fibrinogen and thrombin. A delivery system was devised whereby fibrin sealant could be injected into the tract created by liver biopsy. Thirty swine were randomized into three groups: control (n = 10), heparin (n = 10), and warfarin (n = 10). Each swine underwent laparotomy and was randomized to undergo three to five open liver biopsies with either a 14-gauge cutting needle in conjunction with the fibrin sealant device or a standard 14-gauge cutting needle alone. Forty-seven biopsy procedures were performed with the device; 64 biopsy procedures were performed without the device. Immediate blood loss per biopsy (mL) was estimated based on the size of the blood stain on a sponge. Specimens were assessed for sample size.

RESULTS: Immediate blood loss with and without the device, respectively, was: control, 0.1 mL, 5.4 mL; heparin, 0 mL, 7 mL; warfarin, 0.1 mL, 9.3 mL. These differences were significant (P < .01) for each group of swine. In 43 of 47 biopsies (91%), the device functioned without difficulty. There was no difference in sample size when the device was used.

CONCLUSIONS: The fibrin sealant device is effective in reducing bleeding after open liver biopsy in anticoagulated and nonanticoagulated swine. The promising results suggest that a trial of percutaneous liver biopsy in swine should be considered.

PERCUTANEOUS liver biopsy is an indispensable procedure in the evaluation of patients with diffuse hepatocellular disease or focal lesions (1,2). In patients with normal hemostatic function, the percutaneous approach is generally safe, with a complication rate of 0.1%–3.6% (3–9). However, the rate of complications from hemorrhage is higher in patients with coagulopathy, ascites, portal hypertension, or capsular-based tumors (10–14). In such high-risk patients, alternatives to percutaneous biopsy include an open or laparoscopic surgical approach, a transcatheter approach, or a percutaneous approach with tract embolization (12–15).

A new human-derived biologic product, fibrin sealant (Tisseel; Baxter Healthcare Corporation, Glendale, CA), was recently approved by the Food and Drug Administration as a hemostatic agent. This material consists of a suspension of fibrinogen and thrombin. When the liquid suspensions are mixed at 37°C, the thrombin hydrolyzes the fibrinogen to form a solid fibrin polymer.

In this report, we describe the use of an innovative device that permits fibrin sealant to be de-

---

1 From the Departments of Radiology (E.K.P.) and Surgery (G.R.S., M.C.N., J.H.L.), Duke University Medical Center, Durham, North Carolina, and Allegiance Healthcare Corporation (V.R.), McGaw Park, Illinois. Received October 15, 1999; revision requested November 26; revision received and accepted January 12. Address correspondence to E.K.P., Duke University Medical Center, Department of Radiology, Box 3808, Durham, NC 27710; E-mail: pauls003@mc.duke.edu

© SCVIR, 2000
ployed along the needle tract immediately after biopsy. The fibrin forms quickly and serves as a plug to decrease bleeding after biopsy.

**MATERIALS AND METHODS**

This protocol was approved by the Institutional Animal Care and Use Committee.

Fibrin sealant is packaged as a kit. The kit contains one vial of freeze-dried thrombin (1,000 U) derived from human pooled plasma, a 2-mL vial of calcium chloride solution (40 μmol/mL), one vial of freeze-dried fibrinogen derived from human pooled plasma, and a vial of a fibrinolysis inhibitor solution containing 3,000 inactivator units of aprotinin. Before use, the thrombin must be suspended in the calcium chloride solution and warmed to 37°C. Similarly, the fibrinogen must be suspended in the aprotinin solution and mixed, according to manufacturer recommendations.

The biopsy system consists of three components: the fibrin sealant delivery kit, a 14-gauge Tru-Cut needle (Allegiance Healthcare Corporation, McGaw Park, IL), and a newly designed fibrin sealant delivery sheath (Fig 1). The fibrin sealant delivery system consists of two identical 2-mL syringes attached to a plastic clip with a common plunger to ensure deployment of equal volumes of the two suspensions. The two syringes feed through a “Y” adapter before mixing in the sheath.

The Tru-Cut needle is a 14-gauge, 15-cm-long needle with an outer cutting cannula and an inner cannula with a 20-mm specimen notch.

The delivery sheath consists of a 14-cm, 13-gauge blunt metal alloy needle with a beveled tip and an attached plastic “Y” adapter (Fig 2). The fibrin sealant kit attaches snuggly to one arm of the adapter. The other arm of the adapter has a one-way valve that accepts the 14-gauge Tru-Cut needle in a coaxial fashion. The valve provides backflow control so the injection of fibrin sealant into the tract can be well directed. When used with a cutting needle (in which the specimen is covered by the outer cutting cannula), the fibrin sealant will not mix with the specimen. The sheath can also be used with automated cutting needles or aspirating needles.

The sheath used in this study was custom-designed and is not currently commercially available. In theory, such a sheath could be designed in a variety of lengths and diameters. The fibrin sealant delivery kit used in this study is commercially available and can be attached to the hubs of standard needles or vascular sheaths.

Thirty outbred swine were randomized into three groups: control (n = 10), heparin (n = 10), and warfarin (n = 10). Heparin antico-
Agulation was achieved with 100 U/kg of heparin as an intravenous bolus immediately before surgery. To insure adequate anticoagulation, prothrombin time and partial thromboplastin time of peripheral blood were determined before biopsy. In the swine in the heparin group with a partial thromboplastin time less than 150% of the control value, a second bolus of 100 U/kg of heparin was administered intravenously. Warfarin anticoagulation was achieved with 10 mg of warfarin administered by mouth for 3 days before biopsy. As in the heparin group, prothrombin time and partial thromboplastin time were measured before each biopsy. Table 1 summarizes the laboratory values of the animals before biopsy.

The swine were administered general anesthetic. Their abdomens were draped and midline laparotomy was performed with care to coagulate all sites of bleeding. The liver was adequately exposed for biopsy. The needle of the fully assembled fibrin sealant device was advanced 1–3 cm into the parenchyma of the exposed liver and a biopsy specimen was obtained. After the biopsy specimen was obtained, the cutting needle was removed and fibrin sealant was administered by simultaneously depressing the plungers while removing the sheath. Fibrin sealant was deployed until the sheath was removed from the liver. This action deploys the stream of fibrin sealant along the needle tract to the capsular surface. After approximately 13 seconds, the fibrin sealant polymerizes into a solid fibrin plug. For each biopsy, approximately 2 mL of fibrin sealant were deployed.

In each group of 10 swine, five were randomized to undergo biopsies with use of the fibrin sealant device and five were randomized to undergo biopsies with use of the Tru-Cut needle without the fibrin sealant. Three to five biopsy specimens were obtained from each animal. The numbers of biopsies performed with and without the fibrin sealant device were: control group, 15 with and 22 without; heparin group, 16 with and 21 without; warfarin group, 16 with and 21 without. Biopsy specimens were obtained from the peripheral aspect of the liver to avoid central vessels. Each biopsy site chosen was at least 5 cm away from other sites.

After each biopsy, the site was observed for approximately 3 minutes to assess immediate bleeding (Figs 2, 3). The immediate blood loss was estimated based on the size of the blood stain on a 4-inch-square sponge. The blood loss estimation was made by a nurse skilled in operating room procedures.

The size of each biopsy specimen was estimated. Specimen size was scored 1–5 as follows: no tissue = 1, scant tissue = 2, tissue core less than one third the length of the specimen notch = 3, tissue core one third to two thirds the length of the specimen notch = 4, and tissue core greater than two thirds the length of the specimen notch = 5.

Approximately 30 minutes after completing all the biopsies in each animal, the liver and peritoneal cavities were inspected for the presence of delayed bleeding. After delayed bleeding was estimated, the animals were killed with use of intravenous pentobarbital sodium at a dose of 150 mg/kg.

Because of the generally discrete nature of the biopsies, nonparametric methods were used to compare the biopsies performed with and without fibrin sealant. The effect of fibrin sealant was determined with use of the Wilcoxon signed rank test.

### RESULTS

The fibrin sealant device was extremely effective in reducing or eliminating immediate blood loss after biopsy, as shown in Table 2.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>With Fibrin Sealant</th>
<th>Without Fibrin Sealant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Mean prothrombin time (sec) 14.2 (12.4–15.5)</td>
<td>14.9 (13.5–16.3)</td>
</tr>
<tr>
<td></td>
<td>Mean partial thromboplastin time (sec) 28.8 (17.3–62.2)</td>
<td>34.5 (28–48)</td>
</tr>
<tr>
<td></td>
<td>Platelets           411 (282–734)</td>
<td>462 (276–551)</td>
</tr>
<tr>
<td>Heparin</td>
<td>Mean prothrombin time (sec) 14.6 (13.5–16)</td>
<td>15 (12.7–17.7)</td>
</tr>
<tr>
<td></td>
<td>Mean partial thromboplastin time (sec) 108 (20–150)</td>
<td>94.8 (53.5–156)</td>
</tr>
<tr>
<td></td>
<td>Platelets           561 (495–674)</td>
<td>434 (282–612)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Mean prothrombin time (sec) 33.3 (24–54)</td>
<td>37.2 (17.2–56)</td>
</tr>
<tr>
<td></td>
<td>Mean partial thromboplastin time (sec) 62.4 (51–92)</td>
<td>92.4 (28–139)</td>
</tr>
<tr>
<td></td>
<td>Platelets           492 (345–631)</td>
<td>447 (154–625)</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses refer to range.

The immediate blood loss was significantly less when the fibrin sealant device was used. In the control and warfarin groups, the mean blood loss was 50–90 times less when the device was used than when it was not used. In the heparin group, there was no immediate bleeding in any of the 16 biopsies in which fibrin sealant was used. However, without the fibrin sealant device, mean blood loss was 7 mL per biopsy.

There was no difference in specimen size when the fibrin sealant device was used, suggesting uniformity of technique (Table 2). Similar specimen size also suggests that the sheath itself does not interfere with the function of the Tru-Cut needle.

There was no evidence of signifi-
Percutaneous liver biopsy is an invaluable procedure in the diagnosis of diffuse or focal liver disease. Although the procedure is generally safe, hemorrhagic complications may occur with rates reported from 0.1% to 3.6% (3–10). In fact, in a large retrospective series of complications from liver biopsy, a majority of deaths were caused by hemorrhage (7,8). Unfortunately, patients with diffuse hepatocellular disease, who may require liver biopsy to obtain a specific diagnosis, are the very patients at greatest risk because of coexistent coagulopathy, ascites, and portal hypertension (1,10–14). Even the healthy outpatient with no risk factors could experience a life-threatening hemorrhagic complication from liver biopsy. Methods to decrease the risk of bleeding would be welcome. One such method is to deploy fibrin sealant along the biopsy tract. Our purpose was to determine if fibrin sealant could reduce bleeding after a liver biopsy in an open swine model.

With the innovative coaxial system described herein, it is feasible to deploy fibrin sealant along the tract created in a liver biopsy procedure. The fibrin sealant polymerizes to fibrin to create a plug that effectively eliminates bleeding. Not only was the device effective in the swine with normal hemostatic function, but it was effective in anticoagulated swine as well. The device reduced and, in most cases, eliminated postbiopsy bleeding.

Falstrom et al (16) recently described a similar fibrin sealant delivery system based on a modified 8-F sheath through which fibrin sealant could be deployed after removal of the Tru-Cut device. In eight dogs anticoagulated with heparin, the device eliminated immediate bleeding and delayed postbiopsy bleeding. Our work corroborates their results. Our work differs in that Falstrom and colleagues injected 4 mL of fibrin sealant compared to the 2 mL used in our model. In addition, our device included a one-way valve to prevent the possibility of back-bleeding after removal of the Tru-Cut needle. In addition, we used a commercially available product whereas Falstrom et al used an autologous product obtained from a blood bank.

Fibrin sealant has been available in Europe since 1978 and was approved for commercial sale in the United States in May 1998. Fibrin sealant may be derived from either pooled human plasma or single autologous donors. There are advantages and disadvantages of each product. The commercial form is convenient, readily available, and requires a few minutes of mixing before use. However, the autologous product is prepared from approximately 45 mL of the patient’s own blood and requires a blood bank and local expertise in hematology and cryoprecipitation methods. Typically, the autologous technique requires 24–48 hours (16–18).

Because the commercial product is derived from pooled human plasma, there is a potential risk for transmission of viruses, including hepatitis and HIV. Approval of this product by the Food and Drug Administration may have been delayed in part because of concerns regarding the potential risk of viral transmission. However, commercially produced fibrin sealant undergoes extensive viral deactivation steps, including, but not limited to, nanofiltration, two-step vapor heating, and use of solvent detergents, as outlined by Jackson et al (18). In a survey of patients who were treated...
with fibrin sealant in Europe, there were no cases of viral hepatitis or HIV reported after administration of fibrin sealant (19–20). The current estimate of the risk of viral transmission with virally inactivated fibrin sealant is one in 1,000,000,000. With the autologous product, the risk of viral transmission should be eliminated altogether. An additional risk associated with the commercial fibrin sealant is an allergic reaction to the apoprotin, which is derived from a bovine source. However, the fibrinogen and thrombin are derived from human sources and should therefore carry little risk of allergic reaction.

Detailed cost comparisons of the commercial product to the autologous product have yet to be performed. The commercial product is more concentrated than the autologous product, suggesting that a lower volume may suffice (16).

Fibrin sealant may be applied with use of various techniques, including a spray, a syringe with a “Y” adapter, in combination with other agents, such as a cellulose or gelatin sponge, or through endoscopes or vascular sheaths (18,21,22). The material has been widely used in open surgical procedures as a hemostatic agent along suture lines to control operative site oozing, to achieve hemostasis from blunt and penetrating abdominal trauma, and to close and promote healing of fistula tracts. It is biodegradable.

For high-risk patients, alternatives to percutaneous liver biopsy have been advocated, including the transjugular approach (13,23–25). The appeal of the transjugular approach is the decreased likelihood of transgressing the liver capsule. In theory, blood that oozes from a transjugular biopsy tract should remain within the intravascular volume. In addition, this approach allows additional information to be obtained, including indirect portal venous pressure determinations and access for hepatic venography. Although the jugular approach has been shown to be effective in some studies, the procedure requires considerable expertise and has been associated with hemorrhagic complications from capsular penetration. In addition, the biopsy specimen, when retrieved via the sheath, may be inadequate for histologic analysis. Early work by Corr et al (26,27) and others report an inadequate sample rate of as high as 22%. However, with technologic improvements in transjugular biopsy systems, including automated devices, this technique has recently been proven efficacious and safe in the majority of cases. In addition, the transjugular technique is contraindicated in patients with vascular thrombosis or altered neck anatomy caused by previous surgery. Finally, the transjugular technique is not suitable for biopsy of a focal liver lesion; its use is restricted to patients with diffuse liver disease.

An alternative to the transjugular approach is percutaneous biopsy with tract embolization with use of gelatin sponge, a coil, gelatin sponge coated with thrombin, or an autologous blood clot (12,13,28).

The fibrin sealant device used in this research was easy to use and reliably deployed fibrin sealant along the biopsy tract. The device was quick to set up, simply requiring loading of the syringes and assembling the fibrin sealant kit with the sheath. The deployment itself can be completed within 3–10 seconds after removing the Tru-cut needle from the sheath. However, some fibrin sealant may adhere to the inside of the sheath, which may be a cause of device malfunction. We therefore suggest the use of a new sheath for each biopsy procedure.

As shown in Figure 4, the liquid fibrin sealant insinuates along the tract, penetrating and plugging the irregular margins of the cut liver. With fixed material, such as gelatin sponge or a coil, such uniform filling is not possible.

It is reasonable to assume that this device could be used percutaneously. With use of computed tomographic or ultrasound guidance, the fibrin sealant could easily be deployed as the sheath is withdrawn from the skin. Further research is needed to test the feasibility and efficacy of this device used with a percutaneous approach. In addition, although our work suggests that 2 mL is an adequate dose, a lower dose may prove equally efficacious. Use of this device need not be restricted to core biopsies to assess diffuse hepatocellular disease. It could also be used for directed biopsies of focal liver lesions, and in other areas, including the breast, kidney, and spleen.

There are limitations of this project which should be discussed. First, our open animal model is ar-

---

Table 2
Biopsies Performed with and without Fibrin Sealant: Immediate Blood Loss and Specimen Size

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>With Fibrin Sealant</th>
<th>Without Fibrin Sealant</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of biopsies</td>
<td>15</td>
<td>22</td>
<td>–</td>
</tr>
<tr>
<td>Mean blood loss (mL)</td>
<td>0.1 (0–0.5)</td>
<td>5.4 (2–10.3)</td>
<td>.008</td>
</tr>
<tr>
<td>Size score</td>
<td>2.4</td>
<td>2.8</td>
<td>.4</td>
</tr>
<tr>
<td>Heparin (n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of biopsies</td>
<td>16</td>
<td>21</td>
<td>–</td>
</tr>
<tr>
<td>Mean blood loss (mL)</td>
<td>0 (0)</td>
<td>7 (3–15)</td>
<td>.005</td>
</tr>
<tr>
<td>Size score</td>
<td>2.3</td>
<td>2.8</td>
<td>.34</td>
</tr>
<tr>
<td>Warfarin (n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of biopsies</td>
<td>16</td>
<td>21</td>
<td>–</td>
</tr>
<tr>
<td>Mean blood loss (mL)</td>
<td>0.1 (0–0.5)</td>
<td>9.3 (2–15)</td>
<td>.008</td>
</tr>
<tr>
<td>Size score</td>
<td>3.2</td>
<td>3.3</td>
<td>.68</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses refer to range. P value based on Wilcoxon rank sum test.
Artificial. We have not yet documented the safety and efficacy of this technique in a true clinical setting. Second, because of inherent limitations of our experimental design, it was not possible to blind investigators to the use of the device. To decrease this inherent bias, the biopsies were performed by one physician using a similar technique. In addition, measurements of immediate and delayed bleeding and biopsy quality were performed by a single investigator. Third, a detailed histologic analysis of the liver after injection was not performed. Although it was our impression that the polymerized fibrin sealant was limited to the biopsy tract alone, it is conceivable that the fibrin sealant may have entered bile ducts or portal or hepatic vein branches. Fourth, although our anticoagulated animals were at increased risk of bleeding, altering platelet function or inducing thrombocytopenia would be even more deleterious to hemostasis, which should be considered for further investigations. Fifth, estimating blood loss based on the stain on a surgical sponge is imperfect. To reduce bias, this technique was consistently applied throughout the experiment by a single observer.

In conclusion, the fibrin sealant device is feasible for open liver biopsy. It was extremely effective in reducing immediate and delayed bleeding in the anticoagulated and nonanticoagulated swine. Drawbacks include the possibility of device malfunction, the risk (albeit low) of allergic reaction, and the theoretical risk of viral transmission. Our promising results suggest that the use of fibrin sealant during percutaneous liver biopsy should be further investigated.

Acknowledgment: We thank Luther Milton for his outstanding technical assistance during the surgical procedures.

References