Effective Control of Hepatic Bleeding With a Novel Collagen-Based Composite Combined With Autologous Plasma

Results of a Randomized Controlled Trial

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Hypothesis: A novel collagen-based composite of bovine microfibrillar collagen and bovine thrombin combined with autologous plasma is more effective than standard hemostasis (collagen sponge applied with pressure) in controlling diffuse hepatic bleeding after hemihepatectomy or segmental resection of the liver.

Design: Randomized controlled trial.

Setting: Seven university-affiliated medical centers.

Patients: Sixty-seven adult patients scheduled for hemihepatectomy or segmental resection who received hemostatic intervention with an investigational treatment (n=38) or control (n=29).

Intervention: Bleeding hepatic tissue was managed in all control subjects with a collagen sponge with manual pressure. Subjects in the experimental group had the sprayable liquid composite intraoperatively applied to the surgical site. The liquid immediately formed a collagen-fibrin gel that was used without concomitant tamponade.

Main Outcome Measures: Hemostatic success was defined as the proportion of subjects in each treatment group who achieved complete hemostasis within 10 minutes. Success rates and median times required to achieve controlled bleeding (ie, slight oozing) and complete hemostasis were compared between treatment groups.

Results: All 38 subjects in the experimental group achieved complete hemostasis within 10 minutes compared with only 69% (20/29) of control subjects (P<.001). The median time to controlled bleeding was approximately 4 times longer (250 vs 62 seconds) for control subjects than for experimental group subjects (P<.001). The median time required to achieve complete hemostasis also favored the experimental group (150 vs 360 seconds; P<.001). No adverse events related to the use of the experimental hemostatic agent were detected.

Conclusions: The experimental composite is more effective at controlling and stopping diffuse hepatic bleeding than a collagen sponge applied with pressure; it may be a useful hemostatic agent for patients undergoing hemihepatectomy, segmental resection, and related surgical procedures.

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The liver is particularly prone to excessive hemorrhage as a result of abdominal trauma or during elective hepatic resection. The predisposition of this organ to diffuse bleeding is directly related to its extreme vascularity, particularly because of the hepatic sinusoidal structure, which does not have smooth muscle capable of contraction to induce vasoconstriction. Consequently, traumatic damage, including parenchymal lacerations and fractures, and surgical cutting during elective operative procedures (eg, tumor resection) tend to expose wide, raw surfaces with multiple bleeding sites that are often not amenable to suturing and ligation. In the case of trauma, underlying coagulopathy may further complicate the effective control of diffuse bleeding, and this sometimes requires that measures such as pericolic packing be undertaken.

Effective hemostasis during hepatic resection also can be difficult to attain and is especially troublesome in the cirrhotic patient. In these patients, marked hemorrhagic diatheses are often observed, which may make intraopera-
PATIENTS AND METHODS

SUBJECT SAMPLING

Data were gathered during a multicenter, randomized controlled trial in 4 distinct surgical indications: general, hepatic, cardiac, and orthopedic. This larger study was conducted at 10 geographically dispersed US medical centers to determine the safety and effectiveness of a novel collagen-based composite compared with standard methods of hemostasis for control of diffuse bleeding during an investigational device exemption (IDE). To qualify for inclusion in this clinical investigation, all male and nonpregnant female patients provided informed consent, supplied a medical history, and reported no history of sensitivity to bovine thrombin or collagen, or anaphylaxis from any cause. Overall, 318 patients were entered into the study and received study-specific hemostasis.

RANDOMIZATION PROCEDURES

Randomization was stratified within each clinical site and within each surgical indication. Thus, separate computer-generated randomization schedules of treatment group assignment placed in sealed envelopes were used for each clinical site and for each type of surgery. The hepatic surgical group consisted of 80 adult patients scheduled for hemi-hepatectomy or segmental resection of the liver by tangential excision. These patients were recruited from 7 of the 10 participating clinical centers and randomly assigned on a one-to-one basis in blocks of 6 to either treatment (45 patients) or control (35 patients). The slight imbalance in sample size between the 2 treatment groups resulted from several clinical centers contributing small numbers of patients to the study, leading to randomization within incomplete blocks. Patients suspected of having, or diagnosed as having, liver abscesses were ineligible for inclusion in this surgical subgroup.

Figure 1 illustrates the randomization procedure and patient throughput in addition to the specific reason(s) for excluding patients from the analyses of hemostatic effectiveness. Briefly, 6 patients in each study group never received study-specific hemostasis and 1 additional patient in the experimental group was concurrently treated with an absorbable gelatin sponge. Consequently, 67 patients (38 in the treatment group and 29 in the control group) participated as study subjects and provided complete data with respect to the time required to achieve controlled bleeding and complete hemostasis (Figure 1).

HEMOSTATIC INTERVENTIONS

The objective of this multicenter, randomized controlled trial was to determine the safety and effectiveness of a novel collagen-based composite combined with autologous plasma compared with a standard method of hemostasis for control of diffuse bleeding during hepatic surgery. The experimental hemostatic agent, CoStasis Surgical Hemostat (Cohesion Technologies Inc, Palo Alto, Calif), is a composite of bovine microfibrillar collagen and bovine thrombin that is mixed with autologous plasma at the time of surgery and is composed of a sterile suspension of bovine fibrillar collagen (20 mg/mL) and bovine thrombin (500 U/mL) in a calcium chloride buffer (40 mmol/L). The premixed collagen-thrombin suspension is supplied in a syringe and is mixed intraoperatively with an equal volume of the subject’s own plasma from a second syringe. The subject’s plasma provides the fibrinogen that is cleaved by the thrombin to form a collagen-fibrin gel matrix. This composite was applied without pressure (tamponade) to the bleeding surface(s) in all subjects assigned to the experimental group. All control subjects had bleeding of the liver parenchyma and/or associated lobar tissue managed with absorbable collagen sponges (Instat; Johnson & Johnson, New Brunswick, NJ) applied with manual pressure by the surgeon.

OUTCOMES

The duration of bleeding from the raw surface of the liver at the completion of parenchymal transection was recorded with a stopwatch by a trained study coordinator, starting at the time that the hemostatic intervention was initiated. If hemostasis had not occurred within 10 minutes, the intervention was recorded as a treatment failure. Two hemostasis points were recorded for the purposes of evaluating effectiveness. The time to controlled bleeding was defined as the time elapsed from the initial application of the treatment or control intervention until the bleeding from the exposed surfaces had slowed to a slight oozing. The time to complete hemostasis was defined as the time elapsed from the initial application of the treatment or control intervention until the investigator indicated that bleeding from the exposed surfaces had stopped completely. If a subject’s bleeding stopped completely without passing through a controlled bleeding phase, the time to controlled bleeding was set equal to the time to complete hemostasis.

STATISTICAL METHODS

The primary effectiveness end point, hemostatic success, was defined a priori as the cumulative rate for each treatment group to achieve complete hemostasis within 10 minutes of observation. These hemostatic success rates were compared between experimental and control subjects by means of Fisher exact test. The time to controlled bleeding and the time to complete hemostasis were evaluated for each treatment group by means of the Kaplan-Meier estimation. The cumulative complete hemostasis rates are displayed graphically in Figure 2 for the 2 groups, and these distributions were compared statistically by means of the log rank test. All time-to-event data are presented as median (± SE) values and are censored at 10 minutes.
The median age for all subjects in the hepatic group was 58 years (range, 21-88 years), and this group consisted of 29 men (43%) and 38 women (57%). There were no statistically significant differences between the experimental and control groups with respect to age or sex.

Twenty-five subjects underwent surgery to remove a primary cancer (hepatocellular carcinoma), 36 subjects had removal of liver metastases (mainly of colorectal origin), 2 subjects had surgical correction of trauma-induced injuries, and 4 subjects had other types of problems requiring liver resection.

The proportion of subjects achieving complete hemostasis within the 10-minute period of observation (ie, hemostatic success) is presented in the Table. All 38 experimental group subjects (100%) achieved complete hemostasis within 10 minutes. By contrast, less than 70% (20/29) of control subjects achieved complete hemostasis during the same duration of observation. These hemostatic success rates (ie, 38/38 vs 20/29) were significantly different (P < .001) (Table). The Table also shows the median times to controlled bleeding and complete hemostasis. There was an approximately 4-fold improvement in the median time to controlled bleeding among experimental group subjects (62 seconds) compared with control subjects (250 seconds), and this difference was highly significant (P < .001) (Table). The time to complete hemostasis in the experimental group was less than half that in the control group (150 vs 360 seconds; P < .001) (Table). The comparative cumulative success rates representing the time to complete hemostasis are displayed in Figure 2, demonstrating a striking difference in the percentage of subjects achieving complete hemostasis soon after initiation of hemostatic treatment. For instance, even after as little as 3 minutes of observation, more than half of subjects in the experimental group had stopped bleeding, whereas only about 10% of controls had achieved complete hemostasis (Figure 2).

Of the 7 clinical centers that contributed subjects to the hepatic group, 3 centers provided more than 80% (55/67) of the patients. There were no noteworthy or statistically significant treatment group differences among these 3 centers with respect to important baseline characteristics or hemostatic effectiveness.
outcomes. Overall, there also were no differences between treatment and control subjects regarding the transfusion of whole blood, packed cells, platelets, or plasma. Similarly, there were no differences between treatment and control subjects for change from baseline values for hemoglobin, hematocrit, or plasma fibrinogen levels. There also were no adverse events, including documented episodes of rebleeding, related to the use of the investigational hemostatic agent in this study. Two deaths occurred during 8 weeks of postoperative follow-up. Both of these were in control subjects, and neither death was considered to be related to the use of the collagen sponge. Comprehensive serology panels and antibody titers were performed before and after treatment. The results of this evaluation are being submitted for publication elsewhere.

**COMMENT**

Few controlled trials have been conducted to determine the comparative effectiveness of hemostatic agents in the control of hepatic bleeding and, thus, treatment is often based on surgeon preference. The findings of this randomized controlled trial demonstrate the advantages of the investigational collagen-based composite over a standard method of hemostasis, collagen sponges applied with manual pressure. Indeed, there were uniform and statistically significant differences between groups favoring the experimental group with respect to the proportion of subjects achieving complete hemostasis as well as the time to controlled bleeding and the time to complete hemostasis. In addition, the effectiveness demonstrated in the experimental group was realized in the absence of concurrent tamponade, which is often required with other collagen- and thrombin-based agents. The findings of the current study also compare favorably with results reported by Kohno et al\(^2^3\) of a randomized trial of microcrystalline collagen powder and fibrin glue in patients undergoing elective hepatic resection. Approximately 87% and 81% of patients treated with collagen powder and fibrin glue, respectively, achieved complete hemostasis in that study.

The analytical methods used to evaluate the results of this study included subjects who actually received protocol-specific treatment (ie, n=67) (Figure 1). Nonetheless, even if all excluded subjects were counted in a formal intention-to-treat analysis of hemostatic success and coded as treatment failures, the results continued to favor the experimental group at a highly significant level (38/45 vs 20/35; \(P=.01\)). Unfortunately, the participating surgeons in this study could not be blinded intraoperatively to treatment assignment, allowing for possible bias of results. However, the superior hemostatic effectiveness of the investigational hemostatic agent was observed consistently across all 7 clinical centers. In addition, the duration of bleeding was monitored and recorded by an independent study coordinator, which provided an extra level of verification to the data collection process and likely reduced any potential investigator bias.

The majority of patients in this study underwent elective hepatic resection of benign and malignant tumors. This setting provided a controlled clinical model to evaluate the hemostatic effectiveness where the liver had been surgically exposed and bleeding emanated from a wide, raw surface. Bleeding in these patients can be difficult to manage in a consistent and timely fashion, and it can be particularly troublesome in cirrhotic individuals with marked hemorrhagic diatheses.\(^8\) It is unclear whether these encouraging findings can be extrapolated directly to the treatment of the patient with liver trauma, as few subjects with trauma-induced bleeding were included in the current study. However, similar operative procedures (eg, hemihepatectomy, wedge resection) are used occasionally to treat complex traumatic injuries to the liver,\(^2^4\) and one grade IV liver laceration included in the current investigation was treated effectively with the investigational treatment. Although this novel collagen-based composite is not envisioned to supplant ligation and/or surgical repair of major vascular disruption in the traumatized liver, its adjunctive use may be helpful to control diffuse raw-surface bleeding that often accompanies these operative procedures.\(^4\)

Bleeding from experimental liver injuries in animal models has been reported to be effectively controlled with collagen-based hemostatic agents.\(^2^3,25,21,22,25\) Laboratory investigations confirm that these collagen-based agents trigger platelet aggregation when directly applied to bleeding tissue.\(^2^6,27\) Bovine thrombin likewise has inherent hemostatic properties via the conversion of fibrinogen to fibrin.\(^2^2\) CoStasis combines both of these materials with the patient's own plasma to form an effective, biocompatible composite in a liquid form. Importantly, obtaining the fibrinogen component from autologous plasma effectively eliminates concerns about disease transmission, commonly cited as a shortcoming of some commercial fibrin products produced from pooled human blood sources.\(^2^7\) Several collagen-based hemostatic products exist that include powders, fleeces, and lyophilized sponges. These products have somewhat unsatisfactory handling properties, and their use often requires concurrent manual tamponade.\(^9,28,29\) The sprayable characteristic of the investigational hemostatic agent offers potential advantages in the operative setting because wide surfaces can be treated instantaneously without the need for tamponade. Although such use was not evaluated in this study, the sprayable characteristics may make this investigational hemostatic agent suitable for use in minimally invasive laparoscopic procedures.

In summary, the results of this randomized controlled trial demonstrate improved hemostatic performance with CoStasis Surgical Hemostat compared with a collagen sponge in controlling diffuse hepatic bleeding among patients undergoing liver surgery. These clinical findings support consideration of the use of this investigational hemostatic agent to provide effective and timely hemostasis, especially among patients undergoing elective liver resection.

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REFERENCES

The authors of this article should be congratulated on completing a long-overdue randomized trial evaluating the effectiveness of a combined collagen and fibrin mixture in establishing hemostasis of hepatic bleeding. Previously, other investigators reported the effectiveness of collagen and fibrin glue in controlling hepatic hemorrhage in humans, and a controlled experimental comparison of fibrin glue and oxidized cellulose (Surgicel; Johnson & Johnson, New Brunswick, NJ) has been accomplished in an animal model. However, a prospective randomized trial comparing fibrin glue mixtures with conventional hemostatic agents in humans has been demanded by scientific purists for some time. Unfortunately, this study falls short of the mark in several respects.

The present prospective trial included patients who underwent hemihepatectomy or segmental resection and were randomly assigned to treatment with either CoStasis Surgical Hemostat (a collagen-based composite combined with autologous plasma) or collagen sponge applied with pressure. Thirty-eight patients received treatment with CoStasis Surgical Hemostat and 29 patients received treatment with collagen sponge. The duration of bleeding and effectiveness of both hemostatic agents were monitored by visual inspection of the surgical site for a maximum of 10 minutes.

CoStasis Surgical Hemostat was reported to be 100% effective in achieving complete hepatic hemostasis, whereas collagen sponge applied with manual pressure was only 69% effective in controlling bleeding. Moreover, the median time to controlled bleeding was approximately 4 times longer for the latter hemostatic agent than for CoStasis Surgical Hemostat. Both differences were highly statistically significant, and the authors concluded that CoStasis Surgical Hemostat was more effective in controlling liver hemorrhage than collagen sponge.

Although this study was purported to be a prospective randomized trial, it was actually part of a much larger multicenter trial designed to evaluate CoStasis Surgical Hemostat in the treatment of hemorrhage from a variety of organs. As such, the results should be interpreted with circumspection, as they may hinge on factors other than just the dissimilarity of the hemostatic agents studied. Such factors include contrasting institutional personnel, operative experience, individual case load, surgical technique (including use of the Pringle maneuver to aid in slowing hemorrhage), patients' coagulation profiles, extent of liver resection, and the desire to prove the effectiveness of CoStasis Surgical Hemostat as a hemostatic agent.

A nice touch could have been added to the treatment protocol, that is, a crossover of hemostatic agents in which the effectiveness of CoStasis Surgical Hemostat would have been examined in patients in whom collagen sponge was ineffective in controlling bleeding immediately after failure of the latter hemostatic agent. It is unfortunate that the investigators missed this opportunity to complete a prospective randomized crossover trial. Nevertheless, the fact that CoStasis Surgical Hemostat was found to be 100% effective in establishing hepatic hemostasis in this study deserves special attention and should be confirmed by further scientific trials.

Some critics might consider the group of patients treated with collagen sponge as a “straw man designed to be easily toppled” when compared with the group of patients treated with CoStasis Surgical Hemostat because the latter intervention included bovine thrombin (500 U/mL) as one of its main components, whereas the collagen sponge was not combined with thrombin. Thrombin-soaked hemostatic agents are generally much more effective in controlling liver bleeding than the same hemostatic agents applied in their dry form.

Finally, the authors could have added more to the article had they provided a description of their techniques of achieving hepatic hemostasis with CoStasis Surgical Hemostat. Techniques of achieving hepatic hemostasis with the use of fibrin glue have been described elsewhere, but the sophisticated reader is left to assume that any new techniques important to the application of the CoStasis Surgical Hemostat are nonexistent, which is probably hardly the case. The authors do point out that there may be a place for this hemostatic agent in laparoscopic procedures, but they neglect to mention that endoscopic application may be beneficial as well.

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