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Argon ion beam hemostasis with albumin after liver resection

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Abstract

Background: Bleeding is common after liver resection and establishing hemostasis with sutures or argon beam coagulation can be difficult. In our laboratory, concentrated albumin applied to the liver surface before argon beam coagulation improves sealing of the resected surface of the liver, including closure of blood vessels and ducts not generally seen with standard argon beam coagulation.

Methods: Domestic swine underwent heparinization, then laparotomy and wedge resection of the left medial segment of the liver, using finger fracture technique. Blood vessels and ducts 5 mm or greater were ligated. For achieving hemostasis, the animals were randomized to either a control group using argon beam coagulation alone (n = 15) or an albumin group using argon beam coagulation with concentrated 38% albumin (n = 13). After initial hemostasis, the resected liver surfaces were packed for 3 minutes. Repeated applications of argon beam coagulation with or without albumin were performed as needed, followed by 3 minutes of repacking, until complete hemostasis was achieved. Liver functions and blood counts were examined 4 days postoperatively.

Results: The albumin group was less likely to require repeat applications of argon beam coagulation than control animals (mean 0.5 versus 1.5 times, $P = 0.006$). The total time of argon beam coagulation was significantly shorter in the albumin group (mean 90 versus 154 seconds, $P = 0.001$).

Conclusions: Adding albumin to the liver surface substantially increases the durability of the repaired surface and reduces the time needed to achieve stable hemostasis when compared with standard argon beam coagulation. Further investigations using this technique are warranted.

Keywords: Liver; Bleeding; Albumin

The risks associated with liver resection are related mainly to liver function after surgery and control of bleeding during surgery. Typical blood loss in major hepatic resection ranges from 800 to 3000 mL [1]. Forty percent to 80% of patients undergoing resection will require transfusion [2]. Operative time is a significant risk factor for perioperative complications associated with resection [3]. Secondary problems include liver necrosis, bile leak, and abscess formation. Liver injuries from blunt or penetrating trauma, or iatrogenic liver injuries may produce similar complications. Multiple methodologies (packing, Pringle, suture, resection, argon beam coagulation, fibrin glue application, collagen powder, thrombin/gelfoam, infrared coagulation, electrocoagulation) have been reported to minimize bleeding after liver injury or resection. Suture application is inadequate for diffuse bleeding, seen sometimes after prolonged resection or in cirrhotic patients. Packing is effective but temporary. Most superficial applications to the bleeding liver are not effective because bleeding prevents contact of the agent to the liver surface.

Following trauma to the liver, bleeding is normally reduced by vasoconstriction, platelet activation, and adherence to the injured surface, and blood clotting occurs. If the liver injury or resection is complex, these hemostatic mechanisms may fail. Increases in serum levels of tissue plasminogen activator are associated with surgery [4] and this can be problematic in situations associated with significant bleeding such as liver transplantation [5]. In these instances,

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diffuse oozing from the liver will not stop spontaneously, and normal hemostatic mechanisms are inadequate.

The use of albumin as a tissue sealant or solder has been reported previously [6]. Laser energy applied to tissue surfaces coated with albumin results in a durable coating with considerable strength and resistance to disruption. This technique relies on heating of the albumin, unraveling of some of the extracellular matrix proteins, followed by cooling and adherence of the albumin with adjacent tissue proteins [7,8]. Bonds formed may be electrostatic or covalent. Investigators have described laser urethroplasty, enterocystoplasty, esophageal closure, corneal procedures, and internal mammary artery anastomoses using this technology [9]. Work from our laboratory has focused on optimization of albumin-associated weld strengths, application techniques, and on developing practical methods of energy activation of albumin for hemostasis of solid organs. Preliminary experiments demonstrated that a mixture of 38% albumin applied to a divided liver resulted in considerable bonding strength and more favorable application characteristics when compared with more or less concentrated solutions of albumin. We found that argon beam coagulation of the albumin alone was more efficient than using a 800 nm Diomed laser to solder albumin mixed with ICG. Further preliminary experiments demonstrated that our albumin solder provided excellent hemostasis, even on the surface of actively bleeding liver or spleen in heparinized swine. Blood vessels up to 0.5 cm in size were sealed using this technique, which seemed much more effective than applying argon beam coagulation alone. The current study was designed to determine if argon beam coagulation using albumin solder is more effective for hemostasis than application of argon beam coagulation alone.

Material and methods

All experiments were performed in accordance with the 1996 National Research Council *Guide for the Care and Use of Laboratory Animals* and applicable federal regulations. Domestic swine were numbered and correctly identified on the day of operation. Twenty minutes prior to operation, each animal was given 500 mg of intravenous cefotetan and a 250 mL fluid bolus of Ringer's lactate. Anesthesia was induced with 4 to 9 mg/kg of intramuscular tiletamine/zolazepam, followed by isoflurane by mask and endotracheal intubation. The right femoral artery was surgically isolated and cannulated with a 6-Fr catheter to facilitate continuous blood pressure monitoring and retrieval of blood for laboratory studies. Preoperative laboratory studies included a blood count, liver function tests, and an activated clotting time. The animals were then given 5,000 U of intravenous heparin. Approximately 10 minutes later, the activated clotting time was checked, and if it was longer than 200 seconds, the operation proceeded. If the activated clotting time was less than 200 seconds, additional heparin was given.

The operation proceeded with a vertical midline incision to enter the abdomen. The left medial segment of the liver was exposed. A nonanatomic resection of the inferior aspect of this segment was then performed. A level for the resection was selected such that a raw surface of liver parenchyma approximately 7 × 2 cm would remain after the resection. The liver capsule was scored with the cautery, the parenchyma was fractured with hemostats, and vessels larger than 5 mm were ligated. Imprints of the resected segment were obtained to assess surface area.

Each animal was then randomized to either argon beam coagulation alone or albumin application plus argon beam coagulation for hemostasis. Randomization was stratified to encourage animals in each group to undergo surgery on the same day. Typically, one or two animals in each group would be resected on a given day. Animals receiving argon beam coagulation alone group received coagulation (Argon Beam Coagulator; Valley Lab, Boulder, CO) in the "fulgurate" setting at 75 W with an argon flow rate of 4 L/minute. This was applied to the raw surface of the liver while proximal digital compression was applied. No hepatic vascular isolation was employed. Animals in the albumin plus argon beam coagulation group received similar application of argon beam coagulation. However, prior to argon beam coagulation, the raw hepatic parenchyma was coated with a thin layer of 38% human albumin. The albumin layer was then "soldered" to the liver surface using the argon beam coagulation. The volume of albumin used was recorded. In both groups, once gross hemostasis was initially received, the resected surface was packed with gauze for 3 minutes. The resected surface was then inspected. If hemostasis was not complete, each animal received reapplication of argon beam coagulation alone or albumin plus argon beam coagulation according to its randomization assignment. The liver surface was again packed with gauze for 3 minutes. This process was repeated until hemostasis was complete. Once hemostasis was complete, the liver was packed a final time, for 10 minutes. The liver surface was inspected and the abdomen was closed without drains. Measurements of the time of argon beam coagulation application, blood lost on gauze packs, and number of episodes of hemostasis and repacking were recorded.

Postoperatively, the animals were returned to their pens and allowed to resume *ad libitum* feeding. Fentanyl patches were applied for analgesia. They were monitored for jaundice, fever, abscess, respiratory failure, ascites, loss of appetite and wound complications. Postoperative antibiotics were not administered. Animals were euthanized at 0, 30, and 90 days after surgery for chronic studies. Albumin for this experiment was prepared from standard 25% human serum albumin. The albumin was concentrated to 38% w/v using a pressure filtration chamber. The refractive index was measured to confirm the concentration. The 38% albumin

Table 1
Characteristics of liver resections and initial hemostasis (mean ± SEM)

	Argon	Argon + albumin
Activated clotting time (sec)	305 ± 15	295 ± 25
Resection surface area (cm^2)	13 ± 1	13 ± 1
Time of resection (min)	8 ± 4	7 ± 4
Time initial hemostasis (min)	2 ± 1	2 ± 1

was drawn up into syringes, sterilized by gamma irradiation, and stored at 4°C until time of surgery. Results from comparison of parametric data were analyzed by unpaired *t* tests, and the numbers of rebleeding episodes were examined using the Mann-Whitney *U* test. All errors reported are the standard error of the mean (SEM).

Results

Hepatic resections were performed on 30 animals. One animal that received albumin and argon beam coagulation developed a fascial disruption of his abdominal closure 3 days postoperatively, and was found to have some small nodules on the serosa of his ileum; this animal was not excluded from the study. Of the 30 swine, 15 were randomized to the argon beam coagulation alone group, and 15 were randomized to the albumin plus argon beam coagulation group. Animals within the albumin plus argon beam coagulation group had similar amounts of albumin applied and soldered, with a mean applied albumin volume of 3.4 ± 1.2 mL. The animals in the two groups were comparable in terms of preoperative activated clotting time, surface area of resected liver and time of resection between the two groups (Table 1). Time spent using the ABC to attain initial hemostasis after liver resection was similar between the two groups, suggesting that the surgeons were not biased toward inferior hemostasis in one group or another, based on randomization assignment (Table 1).

The number of episodes of continued bleeding and repacking was significantly lower in the group that received albumin plus argon beam coagulation when compared with argon beam coagulation alone (Table 2, $P = 0.006$). When using albumin and argon beam coagulation, liver bleeding generally stopped after the first application with no rebleeding; whereas argon beam application alone usually lead to at least one rebleeding episode. Specifically, when albumin was used 8 animals did not rebleed, 6 rebled once, and a single animal rebled twice; when albumin was not used 2 animals did not rebleed, 6 rebled once, 6 rebled twice, and a single animal rebled four times. The overall rate of attaining hemostasis as measured by total time of argon beam coagulation application was shorter in the albumin plus argon beam coagulation group (Table 2, $P = 0.001$). Blood loss on sponges used to pack the liver was not significantly lower in the albumin plus argon beam coagulation group (Table 2, $P = 0.13$).

Table 2
Results of secondary hemostasis (mean ± SEM)

	Argon	Argon + albumin
Rebleeding episodes	1.5 ± 0.3	0.5 ± 0.2*
Time argon application (sec)	155 ± 15	90 ± 5*
Blood loss during hemostasis (mL)	17 ± 7	5 ± 2

* $P < 0.05$.

Comments

We have demonstrated that argon beam coagulation using albumin solder is more effective at providing hemostasis of bleeding liver than argon beam coagulation alone, in a porcine liver resection model. One animal died after surgery in the argon beam coagulation only group during preliminary experiments. For this reason, the experimental protocol was designed to include a 10-minute examination period, and further delayed bleeding problems were not observed. One animal in the albumin group developed intraperitoneal nodules, which unfortunately were not examined pathologically but were likely secondary to fungal infection. The nodules were seen diffusely and not in the distribution of previous albumin application. The significance of these complications is unclear.

Comparisons of albumin solder with fibrin glue or other newer hemostasis methods have not been reported. However, several advantages with the argon beam coagulation albumin technique seem apparent. The cost of albumin is relatively low, compared with fibrin glue preparations. Commercial 25% albumin can be converted to 38% or 50% solutions, as reported elsewhere [9]. Viral contamination is exceedingly rare given heating of the albumin during processing [10]. Application of albumin to tissue surfaces during surgery is efficient, adding little time to the procedure. Laparoscopic application would also be straightforward, using a long needle or similar applicator.

Clinical situations for possible use of the argon beam coagulation albumin solder are numerous. Bleeding after routine hepatic resection, or more troublesome bleeding after resection is cirrhotic patients could be controlled with albumin solder. Bleeding after laparoscopic cholecystectomy can also be problematic, and argon beam coagulation albumin application could be helpful. Studies documenting long-term safety with this technique are under way. We are examining histology of porcine liver 6 months and 1 year after argon beam coagulation albumin application. Further studies designed to improve the delivery mechanism of the albumin are planned. Regulatory approval will be necessary before human trials and possible frequent use in the clinical setting.

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