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Hemostasis after Liver Resection Improves after Single Application of Albumin and Argon Beam Coagulation

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Abstract
Background Bleeding from the liver surface is common after hepatic resection. Animal studies have demonstrated superiority of argon beam coagulation (ABC) and 38% human serum albumin when applied together after partial liver resection when compared to ABC alone. There are no data addressing the combination of albumin and argon beam coagulation (ABCA) applied to the bleeding liver after resection in humans. The aim of this study was to evaluate the safety and efficacy of ABCA on hemostasis when applied to the surface of the liver remnant post-hepatic resection.
Methods Ten patients underwent liver resection and were treated with ABCA immediately after the liver was divided. The liver surface was coated with albumin and ABC applied simultaneously, the liver was covered with gauze for 3 min, and ABCA was repeated if necessary. Number of rebleeding episodes requiring re-application of ABCA, time of ABCA application, overall blood loss, and liver functions were monitored. Patients were followed for at least 6 months.
Results Nine of 10 patients required a single application of ABCA, and one patient required two treatments. Average time of ABC use was 5±3 min. Median blood loss was 230 ml. Liver functions returned to near normal within 4 days of resection.
Conclusions ABCA performed well with respect to hemostatic properties, much like previous observations in animal studies. Further clinical trials are justified using this technique.

Keywords Liver · Hemostasis · Albumin · Argon beam coagulation

Background/Introduction

The liver is the most common site of metastases for many tumors, especially those originating in the gastrointestinal tract. A more common problem worldwide is primary hepatocellular carcinoma, the third leading cause of cancer death overall which accounts for nearly 700,000 deaths worldwide.[1] In the USA, most liver resections are done for colorectal metastases followed by resections for primary hepatocellular carcinoma. Approximately 160,000 patients present with colorectal cancer each year in the USA, and 40,000 will develop liver metastases.[2] Overall, 30,000 patients will have liver only disease during some of their disease course and may be candidates for resection. Patients with other tumors metastatic to the liver will be offered surgery; these tumors include soft tissue sarcoma, melanoma, gynecologic tumors, neuroendocrine tumors, and others.[3] With disease limited to the liver, patients undergoing complete resection of primary or metastatic tumor may be cured. Typically, series report 5-year survival of 20% to 60% following such resections.[4–7] Median survival for patients with unresected primary liver tumor or colorectal metastases is closer to 6 to 12 months.

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Major risks associated with liver resection are related mainly to intraoperative bleeding, bile leak, infectious complications, and liver failure.[8–10] Typical blood loss in major hepatic resection ranges from 800–3,000 ml, although novel instrumentation and division of liver parenchyma with decreased central venous pressure has lead to decreased intraoperative bleeding.[11–16] Up to 80% of patients undergoing resection will require transfusion.[9] Operative time is a significant risk factor for perioperative complications associated with resection.[17] Liver injuries from blunt or penetrating trauma or iatrogenic liver injuries may produce similar complications.[6] 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 not be sufficient. Increased serum levels of tissue plasminogen activator are associated with surgery and this can be problematic in situations associated with significant bleeding such as liver transplantation.[18] In these instances, diffuse oozing from the liver will not stop spontaneously and normal hemostatic mechanisms are inadequate.

Surgery of visceral organs such as liver, spleen, and kidney can be challenging, not only in controlling hemorrhage but also in preventing complications following surgery. Rapid, hemostatic and durable sealing of the injury site is the key to successful soft tissue surgery. Traditional surgical techniques such as gauze packing, mesh sutures, and staples can fail to seal the resected surface initially.[11] Patients most vulnerable are those with diffuse bleeding caused by hypothermia, coagulopathy, extreme blood loss, electrolyte disturbance, or acidosis.[19] Fibrin glue seals wound surfaces, but it sometimes performs poorly when bonded to a liver surface with active bleeding.[20] Data regarding fibrin sealants and liver surgery are mixed; some authors report superior results with fibrin glue[12], but one large randomized controlled trial of 300 patients found no difference with respect to blood loss or bile leak when fibrin glue was compared to controls.[21] Suture is inadequate for diffuse bleeding, seen sometimes after prolonged resection or in cirrhotic patients. Packing is an effective but temporary solution. Most superficial applications to the liver are not effective during active bleeding because flow of blood prevents contact of the agent to the liver surface.[22]

Thermal techniques have been used in surgery for many years by coagulating tissue and fusing small vessels. The extracellular collagen in the coagulated tissue acts as a biologic glue that bonds the contiguous tissues. Chemical cautery and electrocautery have been found to control bleeding, but neither are particularity efficacious in stopping moderate active bleeding from the liver. The argon beam coagulator (ABC) is frequently used in surgery for hemorrhage control of solid visceral organs[23–26] and is more effective for mild to moderate rates of bleeding. The bond strength from ABC application can be improved significantly by adding exogenous protein before heating. This concept has been studied extensively in our laboratory. We have heated liver and other organ surfaces coated with albumin using a 800 nm Diomed laser or ABC, resulting in tissue welding in which albumin is used as a solder to join tissues.[22,23,27,28] Laser energy applied to tissue surfaces coated with albumin (Fig. 1) in this manor results in a durable coating with considerable strength and resistance to disruption, with burst strength comparable to the liver itself.[27] This technique relies on heating of the albumin, unraveling of some of the extracellular matrix proteins, followed by cooling and adherence of albumin with adjacent tissue proteins.[29]

A series of pre-clinical animal studies have been performed in order to optimize bonding, by adjusting the energy source, the concentration of albumin and method of application. We have established that administration of topically applied 38% albumin to the resected liver surface along with argon beam coagulation significantly reduces bleeding from the liver.[22,23] Albumin applied in this fashion is well tolerated and appeared to add no specific toxicity, with acute and long-term animal data demonstrating equivalence to argon beam coagulation alone, with respect to complications, histology, and adhesion formation.[29] Both methods readily stop bleeding of the liver, leave residual coagulated albumin remnants, and encapsulate and these remnants up to a year postoperatively. A study was designed to evaluate the efficacy of argon beam coagulation either with 38% albumin applied to the resected liver (ABCA) or without albumin (ABC) as previously described.[22] Animals treated with ABCA had significantly fewer rebleeding episodes when compared to the control group (0.5 vs. 1.5 average rebleeds per surgery, respectively). Although blood loss in the two groups was not significantly

Fig. 1 38% HSA application on resected surface of liver post right hepatectomy.

different, a trend toward less blood loss in the ABCA group was apparent.[22,23]

Based on the success of the acute study, a chronic preclinical study was performed to compare healing responses between ABC and ABCA repairs at one and three months. Histology and adhesions observed in the two animal groups were not different at 12 months.[23]

We hypothesize that ABCA applied to human patients undergoing major hepatic resection will have benefits similar to those observed in our animal patients. To assess safety and feasibility of ABCA application in this setting, we report a series of patients treated prospectively with the similar methodology as outlined in our preliminary studies.

Materials and Methods

Study Population

Patients from two centers, Providence St. Vincent Medical Center and Providence Portland Medical Center, enrolled in the study between November 2006 and December 2008. Participating patients were undergoing major liver resections, either formal lobectomy, segmentectomy, or equivalent non-anatomic wedge resection. Previous chemotherapy (usually FOLFOX) or antibody therapy (Bevacizumab, Genentech, South San Fransisco) was allowed. Patients were considered not eligible for the study if they were less than 18 years of age, had a history of allergic reactions to albumin or were at risk for significant coagulopathy. All patients gave written informed consent to participate. The protocol and informed consent form were reviewed and approved by our institutional review board prior to recruitment of subjects for the study.

Study Design

The study design required evaluation and treatment of patients using albumin with argon beam coagulation to control liver surface bleeding after hepatic resection. Eligibility and screening procedures, including physician evaluation and blood samples, were performed at the pretreatment visit and the day of procedure. On the day of procedure, immediately following hepatic resection, 38% human serum albumin (HSA) applied through a syringe and 18-gauge blunt tip needle to the resected hepatic surface and cauterized using ABC. Lap sponges were then applied and pressure held for 3 min. Hemostasis was evaluated immediately following the 3-min hold. Patient blood test follow-up was done at 1 day post-op, 4 days post-op, discharge, 1 month, and 6 months.

Albumin

The albumin used in this study was concentrated to 38% on two separate occasions. Two separate lots of 25% HSA were purchased from Baxter CORP (Deerfield, IL), Buminate 25% USB Lot # 1123451 and Buminate 25% USB #11234442 expiration date 08242006 and 08062008, respectively. The 25% HSA was then concentrated to 38% on two occasions using passive diffusion in a good manufacturing practices (GMP) facility in accordance with FDA standards. Samples were sent to NAMSA for bactericidal and fungicidal sterility testing. All samples were found to be sterile.

Argon Beam Coagulator

An ABC is a non-contact device that conducts radiofrequency current to tissue along a jet of inert, nonflammable argon gas. The ABC used in this study was a ConMed System 7500 (ConMed, Utica, NY). For open applications the settings were as follows: power of 120 W, Argon gas flow rate of 9.0 L/min, and spark setting of 70. For laparoscopic applications, the settings were as follows: power of 80 W, argon gas flow rate of 4.5 L/min, and spark setting of 70.

Surgery

Eligible patients were offered entry into the study and receive the informed consent prior to surgery. Blood was drawn to measure preoperative serum AST, ALT, alkaline phosphatase, and albumin were drawn if not available or not performed within 30 days prior to surgery. The operation proceeded with an incision appropriate for planned intervention. Both open and laparoscopic resections were included. The technique of liver resection and method of parenchymal division, vascular isolation, and wedge vs. segment or sector resection was at the discretion of the attending surgeon.

For open surgical resections, crush/clamp technique, linear stapler, and harmonic scalpel (Ethicon, Cincinnati, OH) were utilized to divide liver tissue, and vessels larger than 5 mm within the liver were ligated. Intraoperative ultrasound and cholecystectomy were performed when appropriate. For laparoscopic resections, the liver was divided using the harmonic scalpel, linear stapler, and 38% albumin was applied through an 18-gauge spinal needle. In both open and laparoscopic procedures, the bleeding liver surface was packed with gauze sponges prior to argon beam coagulation with albumin. The bleeding 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 coagulator in the fulgurate setting at up to 125 W with an argon flow rate of between 4–9 L/min. The volume of albumin used and the total seconds of argon beam coagulator use were recorded. Once gross hemostasis was achieved, the resected surface was packed with gauze for three minutes. The resected surface was then inspected. If hemostasis was not complete, a reapplication of albumin with argon beam coagulation was performed. The liver surface was then packed with lap pads for three minutes. This process was repeated until hemostasis was complete. Once hemostasis was complete, the surgery proceeded as directed by the attending surgeon.

Results

Thirteen patients were registered for the study and underwent elective laparotomy or laparoscopy followed by liver resection unless contraindicated by initial findings at surgery (Fig. 2). Three patients did not complete the study due to lack of liver resection secondary to benign findings at surgery (one patient) or advanced disease despite initially more favorable clinical impression (two patients). Characteristics of the patient population are summarized in Table 1. Indications for surgery include colorectal carcinoma (five patients), gall bladder carcinoma (three patients), adenoma (one patient), and cholangiocarcinoma (one patient). Comorbidities were typical for this patient population and notable only for significant obesity and fatty liver in patient 1 and advanced aged with relatively small remnant liver in patient 3.

Results of ABCA are detailed in Table 2. Average time for ABCA application was just over 3 min, with one patient requiring over 10 min of post-resection hemostasis time. Amount of albumin applied was between 20 and 40 ml. ABCA treatment was immediately efficacious in nine out of 10 patients. The patient in which ABCA treatment did not achieve immediate hemostasis underwent repeat application of ABCA and pressure application for 3 min, and hemostasis was then achieved. Blood loss, operative times, and length of stay are listed. Morbidity observed included a postoperative abscess near the remaining liver in patient 4 and death from multisystem organ failure (patient 1) and liver failure (patient 3).

Discussion

Albumin concentrated to 38% and added to the resected liver surface with argon beam coagulation (ABCA) was found to be safe and efficacious with respect to providing hemostasis during liver surgery in a group of 10 patients. Significant blood loss was not observed during or after application of ABCA. We are not aware of other reports documenting this novel technique of hemostasis. The design of this study was essentially a phase 1 study, demonstrating the treatment was well tolerated and effective with respect to stopping bleeding after major liver resection.

Patient selection for this trial was essentially consecutive recruitment of eligible patients at the two study sites, by the

Fig. 2 Study flow chart.

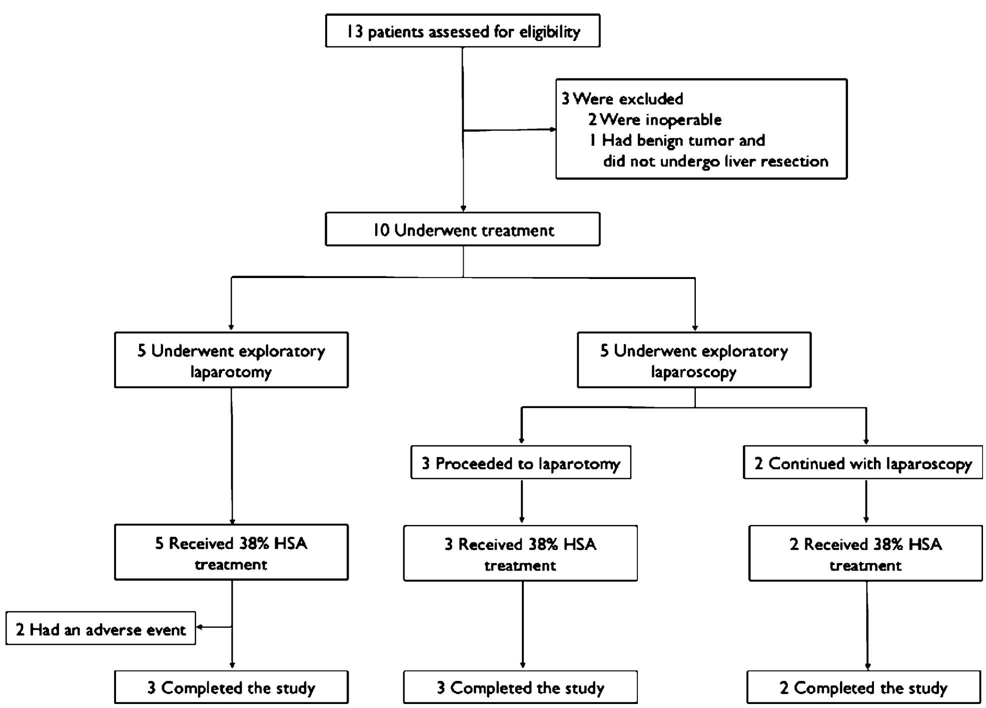

Table 1 Demographics, Presentations, and Co-Morbidities for Study Patient Population

Patient	Sex	Age (years)	BMI (Kg/m^2)	Presentation	Co-Morbidity
1	M	66	36.5	Cholangiocarcinoma	Type 2 diabetes mellitus, osteoarthritis, obesity, hypertension
2	F	49	28.7	Colorectal carcinoma, hepatic metastases	
3	M	81	24.3	Colorectal carcinoma, hepatic metastases	Hypertension, gout, prostate cancer, weight loss
4	F	50	28.3	Gallbladder carcinoma	
5	M	70	28.7	Gallbladder carcinoma	Hypertension
6	F	37	18.4	Giant central hepatic adenoma	
7	M	60	26.6	Gallbladder carcinoma	
8	M	74	24.4	Colorectal carcinoma, hepatic metastases	Diverticular disease, coronary artery disease, renal insufficiency
9	M	58	22.4	Colorectal carcinoma, hepatic metastases	
10	M	74	30.8	Colorectal carcinoma, hepatic metastases	Hepatitis C, cirrhosis, bradycardia
MEAN		62	26.9		
STDEV		14	5.0		

two surgeons involved in the study. Relatively high risk patients were accepted, including patient 3 with abutment of tumor along a long segment of inferior vena cava adjacent to segment 8. Earlier treatment with FOLFOX chemotherapy had lead to complete response of hepatic metastases and resection was performed for rapidly growing late recurrence, not amenable to radiofrequency ablation secondary to size and location. Blood loss was significant and the patient developed liver failure postoperatively. In retrospect, remnant liver size and patient age were relative contraindications for resection. Patient #1 had cholangiocarcinoma and had portal vein involvement, requiring vein resection and re-anastomosis at the bifurcation. Multiple co-morbidities and major hepatic steatosis were present, and the patient died after surgery from multiple system organ failure, with portal venous and hepatic inflow present on several studies post operatively. In both cases, infectious complications related to the albumin were not present. The only other complication was associated with an otherwise event free liver resection. Patient #4 returned 30 days postoperatively with inflammatory signs, and a perihepatic abscess was seen and drained with CT guidance. Gram negative bacteria were found in culture; it is relatively unlikely that the abscess was related to the presence of coagulated albumin. The patient did well, and all other patients had treatment without known complications. The postoperative rate for all perihepatic abscess at Providence Portland Medical Center is 6.8%.

The present study demonstrates results as favorable or better than our animal data using ABCA, with respect to

Table 2 Surgical Summaries for Study Patients

	Time of ABCA (min:s)	Amount of albumin applied (mL)	Incidence of rebleed	Resected surface (cm^2)	Blood loss (mL)	Surgical time (hr:min)	Time in hospital (days)
1	4:40	40	0	195	6,300	14:30	10
2	3:12	20	0	36	450	3:43	5
3	13:00	30	1	145	2,100	7:40	31
4	3:40	20	0	42	450	4:36	4
5	3:54	40	0	40	1,700	4:45	4
6	3:42	30	0	54	1,300	9:45	4
7	5:38	30	0	96	800	4:55	4
8	7:32	40	0	108	1,300	7:10	8
9	2:15	30	0	46	100	2:30	2
10	3:45	30	0	60	900	5:13	8
MEAN	5:08	31	0	82	1,540	6:28	8
STDEV ±	3:07	7	0	53	1,780	3:30	8

blood loss. We reported that one half of animals needed repeat albumin/argon application after the initial treatment, whereas one of 10 patients needed reapplication of ABCA in this study. Other potential advantages of ABCA include more effective sealing of bile leaks, cost savings (compared to fibrin glue or radiofrequency probes) and shorter operative times. None of these issues could be assessed with a study of this size and design. ABCA applications times were short, ranging from 2 to 13 min, with volume of albumin no greater that 40 ml per patient. Observed mean length of stay of 8 days is typical for major hepatectomy. Results of the present study are comparable to a much larger trial examining FLOSEAL (Baxter) application after liver resection reported by Izzo and others.[30] In this series, 367 of 375 sites were hemostatic and the remaining sites had reduced bleeding after fibrin glue application. Average time to hemostasis was 2.9 min.[30] Another report of fibrin glue after liver resection mentions bile leak present in 10% of the patients.[19] We did not observe bile leaks in this series.

In conclusion, ABCA application was effective at promoting hemostasis after major liver resection. Further studies are warranted to document equivalence or superiority to other hemostatic methods, including fibrin glue preparations in the setting of a larger, randomized Phases II or III study.

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