90% Hepatectomy with a Porto-hepatic Shunt in a Canine Model: A Feasibility Study

Shawn Steen, Charles Conway, Catalina Guerra, Hamed Kargozaran, and Singh Gagandeep

All authors are from the Department of Gastrointestinal Surgery, John Wayne Cancer Institute at Saint John’s Health Center, Santa Monica, CA. Charles Conway, MD, is in the Department of Surgical Oncology, Ochsner Medical Center, New Orleans, LA. Shawn Steen, MD, is in the Department of Surgical Oncology, General and Oncologic Surgical Associates, Thousand Oaks, CA. Catalina Guerra, DVM, is the Director, Biological Resource Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA. Hamed Kargozaran, MD, is in the Department of Surgical Oncology, Kaiser Permanente West Los Angeles Medical Center, Los Angeles, CA. Singh Gagandeep, MD, is the Chief, Division of Surgical Oncology, and the Head, Hepatobiliary and Pancreatic Surgery, City of Hope National Comprehensive Cancer Center, Duarte, CA.

Address correspondence and reprint requests to Gagandeep Singh, MD, Division of Surgical Oncology, City of Hope National Comprehensive Medical Center, 1500 East Duarte Road, Duarte, CA 91010, telephone 626-471-7388, or email: gsingh@coh.org.

The information in this article was presented in March 2010 at the 63rd Annual Cancer Symposium Society of Surgical Oncology, St. Louis, MO.

Abstract

Background

We postulated that a surgical shunt between the portal and hepatic veins (portohepatic shunt) could improve the function and regeneration of the liver remnant after extensive hepatic resection. Using a canine model, we designed a survival study to test the feasibility of 90% hepatectomy with a portohepatic shunt. Of eight mixed-hound canines, it was necessary to sacrifice two animals for postmortem study of hepatic anatomy; we used the results to design a procedure for removing all of the liver except portions of two lobes. We tested this 90% hepatectomy procedure under general anesthesia in the remaining animals, with (N=3) or without (N=3) a portohepatic shunt. We monitored animals postoperatively with serial liver biochemical testing, and sacrificed on postoperative day 48. Assessment of liver regeneration was by weight after complete postmortem hepatectomy. Extended hepatectomy removed four complete lobes and portions of the right lateral and caudate lobes. For the portohepatic shunt, we anastomosed the left portal vein branch to the left hepatic vein branch. All procedures were performed successfully. One no-shunt animal expired on the second postoperative day. We thus confirmed the feasibility of 90% hepatectomy with portohepatic shunt in the canine model. If the efficacy of shunting is validated in a larger study population, it may increase the indications for extensive resection in patients with advanced hepatic malignancy.

Key Words: canine; hepatectomy; liver resection; porto-hepatic shunt

Introduction

Surgical resection is the standard of care for many primary and metastatic tumors in the liver, and it can be successful even when 80% of the liver is removed (Abdalla et al. 2002; Szawlowski et al. 1987). However, preoperative estimation of remnant liver function is difficult when a liver has been previously damaged by cholestasis, chemotherapy, or tumor-associated biliary/vascular obstruction. In these cases, extensive resection may not leave enough functional tissue to avoid hepatic insufficiency (Truant et al. 2007).

Operative techniques that preserve remnant liver function after extensive hepatectomy could significantly reduce the risk of postoperative liver failure, but their development requires an accurate in vivo model. Murine models are not adequate because the physiology, anatomy, and regenerative ability of the rat liver are not strictly comparable to those of the human liver (Court et al. 2004).
In the rat, survival after 90% hepatectomy is less than 40 hours, with an overwhelming steatosis found postmortem in the remnant liver (Szawlowski et al. 1987). A large-animal model may have more clinical relevance for study of extensive liver resection and regeneration in subjects with marginal hepatic function. Porcine models do not function well for studies using liver vasculature because the hepatic arteries, portal veins, and hepatic veins have multiple small branches that divide outside the liver parenchyma and have minimal correlation to human anatomy. Additionally, the hepatic veins enter the liver parenchyma immediately and cannot be dissected out for any length (author’s previous experience, data not shown).

To date, the literature does not include a canine 90% extended hepatectomy model that results in long-term survival (Covey et al. 2009). We postulated that we could develop a technique to remove 90% of the canine liver. We also hypothesized that the construction of a shunt between the portal vein and hepatic vein (portohepatic shunt) would decrease postsurgical injury to the 10% liver remnant. Previous studies performed in living donor liver transplants have shown decreased portal pressures and improved survival after portohepatic shunts (Ku et al. 1995). Creation of the shunt after 90% hepatectomy in our study was performed to decrease pressure in the portal venous system with the expectation that it might lead to less liver remnant dysfunction, improved liver regeneration, and improved survival.

Materials and Methods

Animals

We obtain eight dogs from Antech Inc. (Barnhart, MO); all were mixed-hound canines weighing 24 to 26 kg, ages 8-12 months. Upon arrival at LA BioMed at Harbor-UCLA Medical Center, we examined the animals, drew blood, and tested for heart worms, complete blood count, and chemistry profiles including liver function testing. We then kept the animals in strict quarantine for 15 days in accordance with institutional protocols. At the time of study, all animals were maintaining normal diets and physiological functions. The study protocol, reviewed and approved by the Institutional Animal Care and Use Committee at LA BioMed, met institutional and national standards for the humane care of research animals for minimization of pain and discomfort to the animals.

Development of Surgical Technique

On day 16, it was necessary to sacrifice two animals, and we undertook detailed postmortem dissection to study the basic anatomy of the canine liver and develop the steps needed to perform an extended hepatectomy. Postmortem anatomic study demonstrated the six lobes of the canine liver (Figure 1a). Each of the lobes was divided by deep fissures, giving the canine liver a much more lobar appearance than the human liver. The right liver consisted of three lobes: the right lateral lobe and the right medial lobe were to the right side of the porta hepatis; the quadrate lobe was just inferior to the gallbladder. The left side of the liver comprised a left lateral lobe and left medial lobe. The sixth lobe was the caudate lobe. This lobe was divided into the caudate process, which was in contact with the right kidney, and the papillary process, which was in contact with the lesser curve of the stomach (Figure 1a).

Figure 1. (a) In vivo canine liver consisting of six lobes: right lateral lobe (RLL), right medial lobe (RML), quadrate lobe (QL), caudate lobe (papillary process (PP) visualized, caudate process (CP) not visualized), left medial
lobe (LML), and left lateral lobe (LLL). Gallbladder (GB). (b) Porta hepatis with sutures encircling the portal vein (PV), common bile duct (CBD), and hepatic artery (HA) from lateral to medial showing branching of structures outside of hilum. (c) Ex vivo 90% hepatectomy specimen containing the LML, LLL, QL, PP of caudate lobe, GB, RML, and ventral portions of the RLL and CP of caudate lobe. (d) In vivo liver remnant after 90% hepatectomy comprises portions of the CP of the caudate lobe and medial RLL. The completed porto-hepatic shunt is seen to the left of the liver remnant.

These findings were consistent with postmortem studies that used corrosion casts to examine intrahepatic portal vein and hepatic artery anatomy in dogs (Covey et al. 2009; Ursic et al. 2007). The right portal branch feeds the caudate process and both right lobes. The left portal branch supplies the remaining liver. The hepatic artery has right lateral, right medial, and left branches, the course of which follows that of the portal vein branches (Ursic et al. 2007). We found that the hepatic artery and portal vein invariably branched into main right and left branches outside the liver hilum (Figure 1b).

We used these results to design a 90% hepatectomy procedure that removed all of the liver except portions of the right lateral and caudate lobes. We selected the portions of the right lateral and caudate lobes used for the remnant because the liver parenchyma nearly envelops the vena cava in those areas. In the postmortem study of liver anatomy, we weighed nonremnant and remnant portions of the liver separately to confirm a 90:10 nonremnant:remnant ratio by weight. We used the anatomic boundaries corresponding to the remnant portion as a guideline for the extent of resection during testing of 90% hepatectomy in live animals. At the conclusion of the live-animal study, it was necessary to sacrifice each animal so that the regenerated remnant liver could be removed and weighed for comparison among animals.

Testing of Surgical Technique

We undertook the 90% hepatectomy procedure in six live animals. Three animals underwent 90% hepatectomy without a portohepatic shunt (no-shunt group), and three animals underwent 90% hepatectomy with a portohepatic shunt between the left portal vein and the left hepatic vein (shunt group).

Each dog was sedated with acepromazine 0.1-0.5 mg/kg IM followed by ketamine 5 mg/kg and diazepam 0.25 mg/kg IV. General anesthesia was maintained with 2% inhaled isoflurane via endotracheal tube. Animals were placed in lithotomy, and midline incisions were used. After the liver was mobilized by dividing the coronary and triangular ligaments, dissection was carried to the level of the hepatic veins superiorly and the vena cava inferolaterally. The portal structures were identified within the hepatoduodenal ligament, and the portal vein branches to the left and right lobes were individually dissected free and encircled. The canine portal vein branches outside the hilar plate and the main left portal branch were easy to identify. The left main portal vein branch was dissected carefully into the liver parenchyma to preserve as much length as possible, controlled with a vascular clamp, and divided.

Hepatic veins approaching the liver parenchyma tend to be shorter in dogs than humans. We carefully ligated the middle hepatic vein without narrowing the left hepatic vein. We then dissected the left hepatic vein into the liver parenchyma to provide as much length as possible. We controlled the dissection with a vascular clamp and divided the area sharply. We preserved the right hepatic vein to drain the remaining liver remnant.

We then divided the liver parenchyma itself with the use of a LigaSure™ device (Covidien™); we removed the quadrate lobe, left lateral lobe, left medial lobe, and papillary process of the caudate lobe. In order to complete the 90% hepatectomy model, we used the LigaSure™ device to remove the entire right medial lobe, the ventral and lateral portions of the right lateral lobe, and caudate processes of the caudate lobe. The remaining 10% of liver parenchyma included portions of the caudate lobe and the right lateral liver lobe encircling the vena cava. We preserved blood flow to this remnant through the right portal vein, right hepatic artery, and right bile ducts. The hepatic venous outflow was through the right hepatic vein and the direct branches of the remaining liver into the vena cava.

Next, we constructed the portohepatic shunt by anastomosing the left portal vein branch to the left hepatic vein with a running 6-0 Prolene suture using standard vascular surgery techniques. We compensated for size discrepancy between the smaller portal vein and the larger hepatic vein by beveling the anastomosis slightly.
Recovery

At the conclusion of surgery, the animals remained in isolated recovery for 8 hours. Every 4 hours for the first 24 hours, they received 400 mL of lactated Ringer’s solution, administered intravenously or subcutaneously. Food and water were available ad libitum. For the first 7 postoperative days, personnel fed them canned and dry Hill’s prescription low-fat diet. From postoperative day 8 through the third week, they received only dry Hills diet. From the third week until the end of study at postoperative day 48, the animals ate a standard laboratory canine diet containing 25% protein and 9% fat at 20-30 g/kg of body weight.

We assessed the biochemical response of the remaining liver parenchyma during the postoperative period by serial sampling of blood for measurement of transaminases, alkaline phosphatase, and bilirubin. At the end of the study period on postoperative day 48, it was necessary to sacrifice the animals using pentobarbital sodium at a 100 mg/kg lethal dose. After sacrifice, we removed the liver by dividing the portal structures and the vena-cava above and below the hepatic veins. We then compared the regenerated livers in the shunt and no-shunt study animals by total ex vivo weight.

Results

Our 90% resection technique removed the left medial and lateral lobes, quadrate lobe, right medial lobe, papillary process of the caudate lobe, ventral and lateral portions of the right lateral lobe, and caudate process of the caudate lobe (Figure 1c). This removal left a portion of the right lateral lobe and caudate process of the caudate lobe, both of which were supplied by the intact right portal branch.

In the three animals that underwent the shunt procedure, we dissected the left portal vein and preserved it for an average of 3-4 cm of length, whereas we were able to dissect only the left hepatic vein for a length of 1-2 cm on average. We constructed the portohepatic shunt easily and without tension (Figure 1d).

Average blood loss during surgery in all animals was less than 200 mL. No animals received a blood transfusion, and no effort was made to lower central venous pressure intraoperatively. Five of the six survived until the study endpoint at postoperative day 48. One no-shunt animal expired on postoperative day 1 from an unknown cause that might have been related to hepatic insufficiency. All remaining animals recovered to full activity and diet within 10 days from initial surgery.

![Figure 2. Postoperative trends for total bilirubin (TBili), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) for the five surviving animals. No significant difference was found when the animals that underwent surgical porto-hepatic shunt after 90% extended hepatectomy were compared with those who underwent 90% extended hepatectomy without porto-hepatic shunt.](image-url)
Postoperative blood tests for the five dogs that survived to the study’s endpoint are shown in Figure 2. The peak increase in the transaminases generally occurred on postoperative days 1 or 2 and decreased to normal by 2 weeks. Alkaline phosphatase peaked between postoperative days 1-6 and stayed elevated longer but approached normal by 2 weeks. Total bilirubin levels peaked quickly after surgery (between postoperative days 1-3) and normalized by 2 weeks after surgery. There was no significant difference in postoperative biochemical tests between the shunt and no-shunt groups (Figure 2). After sacrifice on postoperative day 48, the liver weights did not differ significantly between the shunt and no-shunt groups, indicating that the presence of a portohepatic shunt did not influence regeneration (Figure 3).

![Regenerated Liver Weights at Sacrifice](image)

Figure 3. No difference in weight of the regenerated liver was found after sacrifice on postoperative day 48.

Discussion

Liver failure is primarily responsible for mortality after major hepatectomy (Shirabe et al. 1999). The reasons for postoperative liver failure are multifactorial. At the biochemical level, microcirculatory disturbances, vascular pressure, hyperendotoxinemia, Kupffer cell activation, and cytokine-induced apoptosis contribute to hepatocellular death (Nagao et al. 2000). At the clinical level, preoperative liver function, remnant liver volume, and blood loss during surgery can affect postoperative outcomes. Among these, the most important risk factor for liver failure after a major hepatectomy is remnant liver volume (Shirabe et al. 1999). High portal and hepatic artery flow to small liver remnants leads to portal congestion, which damages remaining hepatic parenchyma (Bogetti et al. 2004; Man et al. 2003; Mitsumoto et al. 1999). Additionally, increased portal pressure can lead to congestion and edema of the bowel wall, allowing translocation of bacteria and thereby increasing postoperative morbidity and mortality (Mitsumoto et al. 1999). The abrupt regenerative response of a small remnant liver (Ninomiya et al. 2010) could exacerbate these problems, further increasing the risk of liver failure.

Studies of living-donor liver transplantation have attempted to decrease portal venous inflow by using portal bypass, splenic artery ligation, or splenectomy (Bogetti et al. 2004; Jabbour et al. 2003; Troisi et al. 2003, 2005). Portal bypass techniques include portal vein to hepatic vein, inferior mesenteric vein to left renal vein, and splenic vein to renal vein shunts (Bogetti et al. 2004; Yagi et al. 2006). In one Japanese study, splenectomy or splenorenal shunt decreased pressure in the portal vein and thereby improved living-donor liver transplantation graft survival and liver biochemical function based on serum bilirubin, transaminases, and coagulation studies (Yagi et al. 2006). Another group in Japan performed a 28% orthotopic liver transplant in dogs by constructing a portohepatic shunt from the left portal vein to the left hepatic vein. In their study of seven animals, all subjects without the portohepatic shunt died within 3 days. Those animals with the shunt survived more than 3 days and had improved graft function as measured by bile production and serum bilirubin and transaminase levels (Ku et al. 1995).

However, we cannot apply results of living-donor liver transplantation studies directly to resection of native liver, and the literature on extended hepatectomy is limited. In 1963, Sigel first described a 70% hepatectomy in the canine model (Siegel 1963). In 1978, Francavilla and colleagues studied the biochemical constituents of portal blood after a 72% hepatectomy with good survival for 6 days after surgery (Francavilla et al. 1978). In 2000, a group from Japan described an 84% hepatectomy that preserved only the right lateral lobe (Nagao et al. 2000). It was necessary to sacrifice all animals 6 hours after surgery, however, and long-term survival data were not available. Earlier a French group had obtained survival after 95% hepatectomy in canines, but only by performing a staged
procedure: 65% initial hepatectomy followed 6-10 weeks later by a resection that left only the papillary process of the caudate lobe (Szawlowski et al. 1987).

To our knowledge, there are no reports of survival after an initial 90% hepatectomy in canines, nor are there many studies reporting the construction of portal shunts after extensive resection of native liver tissue. Mitumoto and coworkers reported significantly improved 7-day survival in canines that underwent 80% hepatectomy with a side-to-side porto-caval shunt that lowered portal venous pressure (Mitumoto et al. 1999). However, when 90% hepatectomy removed all liver except the caudate lobe, no canines survived even with the porto-caval shunt (Mitumoto et al. 1999). Another study from Japan reported lower portal pressures and improved liver function tests in canines after a 70% hepatectomy with resection of the jejenum (Kawano et al. 2006). Nonindicated bowel resection, however, has a limited place in clinical medicine.

In our model, one factor possibly contributing to survival after 90% hepatectomy was a remnant that comprised portions of both the caudate process and the right lateral lobe located along the vena cava. Our postmortem studies demonstrated multiple direct short hepatic veins entering the vena cava from portions of adjacent caudate and right lateral lobes (Figure 4). The literature on canine hepatic anatomy confirms that the right lateral lobar hepatic veins directly drain into the caudal vena cava via one to three branches (Covey et al. 2009). Likewise, the caudate process has one to two hepatic veins that drain directly into the vena cava (Covey et al. 2009). Although these accessory veins might not be relevant in a partial orthotopic liver transplant, they could be important for survival of a native liver remnant. By preserving the hepatic parenchyma along the vena cava, our technique might have decreased the outflow resistance and the portal pressure of the liver remnant enough to allow its survival and regeneration. Because both the shunt and no-shunt groups had similar hepatectomy procedures, the native venous outflow may have also lowered the portal pressures enough that the portohepatic shunt had less impact on outcomes.

![Figure 4. Postmortem picture of hepatic venous drainage showing multiple direct hepatic vein branches from the caudate and right lateral lobes into the vena cava.](image)

**Conclusion**

Our technique for 90% hepatectomy with or without construction of a portohepatic shunt was technically feasible and reproducible in this canine study. All six dogs survived the procedure, and the three shunted animals survived the full 48 days without complications and with normalization of liver biochemical testing within 2 weeks. Two of three no-shunt animals also survived 48 days, with similar normalization of liver biochemical testing. Although we did not show a significant benefit in postoperative liver biochemical tests or regeneration with a portohepatic shunt, application of our technique in a larger group of dogs may show a statistically significant improvement in postoperative recovery with the use of a portohepatic shunt. In addition, future studies could use pressure monitoring to demonstrate a quantifiable decrease in the amount of pressure in the portal venous system. Finally, in view of the similar hepatic anatomy between dogs and humans, our technique for 90% hepatectomy with a portohepatic shunt has potential for clinical translation.
Acknowledgment:

Funding from the following individuals and institutions supported this research: the Davidow Charitable Fund (Los Angeles, CA),; the William Randolph Hearst Foundations (San Francisco, CA),; the Rod Fasone Memorial Cancer Fund (Indianapolis, IN),; the Ruth and Martin H. Weil Fund (Los Angeles, CA),; Mrs. Lois Rosen,; the Lance Armstrong Foundation (Austin, TX),; the John Wayne Cancer Foundation (Newport Beach, CA)); and the Wrather Family Foundation (Los Alamos, CA). The authors also thank CovidienTM for providing the LigaSure™ units for this study.

Dr. Steen is the Carolyn Dirks Fellow (Los Angeles, CA).

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