Perioperative Outcomes of Major Hepatic Resections under Low Central Venous Pressure Anesthesia: Blood Loss, Blood Transfusion, and the Risk of Postoperative Renal Dysfunction

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Background: We have previously demonstrated that maintenance of a low central venous pressure (LCVP) combined with extrabiliary control of venous outflow reduced the overall blood loss during major hepatic resections. This study examined the overall outcomes and, in particular, renal morbidity associated with a large series of consecutive major liver resections performed with this approach. In addition, the rationale for the anesthetic management to maintain LCVP was carefully reviewed.

Study Design: All major hepatectomies performed between December 1991 and April 1997 were reviewed. The prospective Hepatobiliary Surgical Service database was merged with the Memorial Hospital Laboratory and Blood Bank databases to yield the nature of the operation, blood loss, blood product transfusions, outcomes, and levels of preoperative, postoperative, and discharge serum creatinine and blood urea nitrogen.

Results: A total of 496 LCVP-assisted major liver resections were performed, with no intraoperative deaths and an in-hospital mortality rate of 3.8%. The median blood loss was 645 mL. Sixty-seven percent of the patients did not require perioperative blood transfusion during surgery and the immediate 12 hours after surgery. The median number of blood transfusions was 2. Only 3% of the patients experienced a persistent and clinically significant increase in serum creatinine possibly attributable to the anesthetic technique. Renal failure directly attributable to the anesthetic technique did not occur.

Conclusions: Major resection with LCVP allowed easy control of the hepatic veins before and during parenchymal transection. The anesthetic technique, designed to maintain LCVP during the critical stages of hepatic resection, not only helped to minimize blood loss and mortality but also preserved renal function. (J Am Coll Surg 1998;187:620–625. © 1998 by the American College of Surgeons)

The risk of major hemorrhage is of principal concern during major liver resection. Blood loss of up to 10 L has been reported. Excessive bleeding and subsequent transfusions correlate with postoperative morbidity. Although substantial blood loss may arise during vascular control at the portal delta, injury to the hepatic veins during parenchymal dissection or at their junction with the vena cava is the most common cause of life-threatening intraoperative hemorrhage.

Because of the increased risk of hemorrhage and subsequent hemodynamic instability, hepatic surgery is commonly performed under anesthetic and fluid conditions consistent with euoleemia and, in some cases, hypervolemia. Before parenchymal transection, often during and shortly after anesthetic induction, the intravascular volume is expanded with crystalloid or blood products to provide a safety cushion for the anticipated blood loss. The added volume increases CVP and distends the central veins. The resulting condition augments the difficulty in controlling blood loss from the major hepatic veins.

This is particularly true for resections performed for large tumors compromising the vena cava or the major hepatic veins or, by their size, limiting access for precise intrahepatic control of veins.

In recent years, hepatic vascular exclusion has been developed to circumvent this difficulty. This approach has the disadvantage of being complex and not well tolerated by some patients, and may be hazardous to those with jaundice or cirrhosis. In addition, although blood loss is controlled during the resectional phase of the operation, release of the
clamps and restoration of blood flow may be followed by hemorrhage from vessels transected but undetected during the resectional phase, which are then subject to the high CVP engendered by the fluid load necessary to maintain hemodynamics during vascular exclusion.

We previously described a technique for hepatectomy based on precise dissection of the arterial and portal inflow and of the hepatic veins performed using an anesthetic technique that maintained low CVP (LCVP) during extrhepatic dissection and parenchymal transection.14 This review of 496 LCVP-assisted hepatectomies was undertaken to confirm the preliminary findings of reduced blood loss, low transfusion rate, and minimal risk. In addition, we evaluated whether there is any adverse effect of this technique on renal function. We also reviewed the rationale for and the anesthetic approach used to provide anesthesia with maintenance of LCVP (less than 5 mmHg).

METHODS

All patients who underwent major hepatic resection between December 1991 and April 1997 were included. Patients having wedge resection were excluded. The surgical aspects of the resectional technique have been described previously.14,15 Inflow control was obtained by extrhepatic dissection or by pedicle ligation.7 The hepatic veins were generally controlled extrhepatically. Transection of the liver parenchyma was performed by a crushing technique with intermittent inflow occlusion (Pringle maneuver). Inflow was occluded for 5-minute periods with 1-minute intervals, and no patient had occlusion for more than 20 minutes.

Anesthetic management

Patients were premedicated with midazolam and glycopyrrolate. Intraoperative monitors included ECG (II & V3), noninvasive blood pressure, and mass spectrometry. Anesthesia was induced with sodium thiopental and succinylcholine. After the induction of general anesthesia, the patients were positioned in 15 degree head-down tilt, IV fluids were reduced to 1 mL/kg/h, and surgery was begun. All patients underwent central venous and arterial catheterization: 2 large-bore vein catheters and at least one 8.5F internal jugular introducer. General anesthesia was maintained with a combination of narcotic (fentanyl or morphine), muscle relaxant (pancuronium or vecuronium), and isoflurane in oxygen. IV nitroglycerin was not routinely used to reduce intraoperative CVP.

Neither mannitol nor low-dose dopamine was used to protect renal function.

Intraoperative fluid management was divided into 2 phases. 1) The prehepatic resection phase began at induction of anesthesia and ended at the completion of parenchymal transection and hemostasis. During this phase, inflow control of the portal vein and hepatic artery was achieved, and the vena cava and hepatic veins were dissected. Hepatic parenchymal transection was performed, during which intermittent inflow occlusion was applied. During the prehepatic resection phase, the administration of maintenance fluids was generally reduced to 75 mL/h. Intermittent fluid boluses were administered to maintain urine output above 25 mL/h and systolic blood pressure greater than 90 mmHg while keeping CVP at less than 5 mmHg. During this phase, the administration of blood products was limited to catastrophic events in which blood loss was greater than 25% of blood volume.

2) The posthepatic resection phase began after the removal of the specimen and the completion of hemostasis. During this phase, an attempt was made to render the patients euolemic with the aid of crystalloid and 6% hetastarch. Packed cells and autologous units were transfused to achieve a hemoglobin greater than 10 g/dL in patients with evidence of either coronary or cerebrovascular disease and above 8 g/dL in the rest of the population. The Woods Pump (Statlabs, Inc., Franklin, TN) and the P-50 Level I System (Level I System Technologies Inc., Rockland, MA) were routinely used in patients requiring extensive transfusion.

Upon the completion of the operation, all patients were transferred intubated to the postanesthesia care unit for overnight care. All patients were ventilated postoperatively until deemed stable for extubation and transfer to the Hepatobiliary Surgical floor.

Statistical analysis

The prospective Hepatobiliary Surgical Service database was merged with the Memorial Hospital Laboratory and Blood Bank databases to yield the nature of the operation, preoperative creatinine, preoperative BUN, postoperative creatinine, postoperative BUN, discharge creatinine, discharge BUN, blood loss, transfusion data, and operative outcomes. When applicable, the results were expressed as median or as mean ± SD. Paired t-tests were performed to identify any significant change in renal indices. A
Table 1. Distribution of Operations Performed

<table>
<thead>
<tr>
<th>Operation</th>
<th>Segments</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lobectomy*</td>
<td>V, VI, VII, VIII</td>
<td>83</td>
</tr>
<tr>
<td>Left lobectomy*</td>
<td>III, IV</td>
<td>43</td>
</tr>
<tr>
<td>Right trisegmentectomy*</td>
<td>IV, V, VI, VII, VIII</td>
<td>190</td>
</tr>
<tr>
<td>Left trisegmentectomy*</td>
<td>III, IV, V, VIII</td>
<td>37</td>
</tr>
<tr>
<td>Left lateral segmentectomy</td>
<td>II, III</td>
<td>37</td>
</tr>
<tr>
<td>Right posterior sectorectomy</td>
<td>VI, VII</td>
<td>13</td>
</tr>
<tr>
<td>Segmentectomy (including caudate)</td>
<td>Any single segment</td>
<td>54</td>
</tr>
<tr>
<td>Bisegmentectomy</td>
<td>Any two segments</td>
<td>19</td>
</tr>
<tr>
<td>Atypical resection (major)</td>
<td>Three segments or more</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>496</td>
</tr>
</tbody>
</table>

*With or without concomitant resection of Segment I.

**Note**: Mode of operations used is according to that commonly in use in the United States. Segments resected are according to the anatomic description of Couinaud.15

serum creatinine increase greater than 0.5 mg/dL was considered clinically significant.

RESULTS

A total of 496 LCVP-aided hepatic resections15 were performed (Table 1). The distribution of pathologic diagnoses is shown in Table 2. Seventy-two percent of the patients had resection of a lobe or more. Extended resections were performed in 229 patients (46%). No patient was returned to the operating room for postoperative hemorrhage. There were no deaths within 96 hours of operation. The in-hospital mortality rate was 3.8%. The causes of death are outlined in Table 3.

The anesthetic and fluid management provided excellent operative conditions in the majority of patients. IV nitroglycerin was required in only 5 patients to reduce the intraoperative CVP to desired levels. Minor hemodynamically significant air emboli were identified in 2 patients with the aid of end-tidal $\mathrm{N}_2$. Both were associated with limited hypotension of brief duration; both patients experienced no other sequelae.

Blood loss and transfusion

The median blood loss was 645 mL. The mean blood loss was 848 ± 972 mL, ranging from 40 to 9,000 mL. Only 68 or 13.7% of all patients experienced intraoperative blood loss of more than 1,225 mL, or 25% of the estimated blood volume for a 70-kg individual. Twenty-five percent of the patients were transfused with allogeneic blood components during or within 24 hours of operation: 119 patients received RBCs (2.6 ± 2.2 U), 44 patients received fresh frozen plasma (FFP, 3.1 ± 1.8 U), and 4 patients received platelets (2.25 ± 2.5 concentrates). An additional 13% of the patients had transfusion with only autologous blood units. Review of all in-hospital transfusion records revealed that only 47% of the patients required allogeneic blood components during hospitalization: 227 patients received RBCs (3.4 ± 3.5 U), 119 patients received FFP (8.1 ± 11 U), and 16 patients received platelets (7.6 ± 6.3 concentrates). An additional 5.6% of the patients had transfusion with only autologous RBC units.

Renal dysfunction

There was no overall statistical change in either creatinine or BUN after LCVP-aided heptectomy. Fifty patients had either an early (within 24 hours, 31 patients) or a late (after 24 hours, 19 patients) serum creatinine increase of at least 0.5 mg/dL. This resolved in all but 27 patients. Eleven patients were discharged with a median increase in serum creatinine of 0.6 mg/dL (0.6 ± 0.1 mg/dL). One patient

Table 2. Distribution of Pathologic Diagnoses

<table>
<thead>
<tr>
<th>Pathologic Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hepatocellular carcinoma</td>
<td>78</td>
</tr>
<tr>
<td>Primary biliary malignancy</td>
<td>56</td>
</tr>
<tr>
<td>Metastatic colorectal carcinoma</td>
<td>271</td>
</tr>
<tr>
<td>Other metastatic malignancies</td>
<td>59</td>
</tr>
<tr>
<td>Benign</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 3. Causes of In-Hospital Mortality

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal sepsis</td>
<td>8</td>
</tr>
<tr>
<td>Hepatorenal failure</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Drug-induced renal failure</td>
<td>1</td>
</tr>
<tr>
<td>Sudden death*</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>1</td>
</tr>
</tbody>
</table>

*Identifies patients with normal serum creatinine at the time of death.
Table 4. Comparison of Operative Indices Between Hepatic Vascular Isolation and Low Central Venous Pressure-Aided Hepatectomy

<table>
<thead>
<tr>
<th>First author</th>
<th>Technique</th>
<th>Total patients</th>
<th>Major resections*</th>
<th>Blood loss (mL)</th>
<th>Transfusions (U or mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delva, 1989</td>
<td>HVI</td>
<td>35</td>
<td>35</td>
<td>—</td>
<td>8.0 ± 8.3</td>
</tr>
<tr>
<td>Emre, 1993</td>
<td>HVI</td>
<td>16</td>
<td>13</td>
<td>1,866 ± 1,683</td>
<td>—</td>
</tr>
<tr>
<td>Hanneu, 1993</td>
<td>HVI</td>
<td>15</td>
<td>15</td>
<td>1,325</td>
<td>—</td>
</tr>
<tr>
<td>Habib, 1994</td>
<td>HVI</td>
<td>56</td>
<td>83</td>
<td>5.8 ± 4.7</td>
<td>—</td>
</tr>
<tr>
<td>Cunningham, 1994</td>
<td>LCVP</td>
<td>100</td>
<td>69</td>
<td>1,651 ± 1,748</td>
<td>—</td>
</tr>
<tr>
<td>Emond, 1995</td>
<td>HVI</td>
<td>48</td>
<td>44</td>
<td>1,200</td>
<td>1.4 ± 2.1</td>
</tr>
<tr>
<td>Belgiti, 1996</td>
<td>HVI</td>
<td>24</td>
<td>24</td>
<td>1,125 ± 1,291</td>
<td>1.9 ± 2.6</td>
</tr>
<tr>
<td>Present series</td>
<td>LCVP</td>
<td>496</td>
<td>557</td>
<td>849 ± 972</td>
<td>2.3 ± 3.4</td>
</tr>
</tbody>
</table>

*Major resections include all lobectomies and extended lobectomies.

Values are reported as mean ± SD.

Denotes inclusion of cirrhotic patients in series.

HVI, hepatic vascular isolation; LCVP, low central venous pressure.

died of renal failure secondary to aminoglycoside toxicity. The remaining 15 patients died while experiencing renal failure as a late complication of multi-system or hepatorenal failure.

DISCUSSION

The results of this large series of liver resections compare very favorably with the operative reports of many other series, often with a lower proportion of major resections.\textsuperscript{4,16-18} The maintenance of LCVP during the operation precludes vena caval distention and facilitates mobilization of the liver and dissection of the retrohepatic and major hepatic veins. More important, the approach minimizes hepatic venous bleeding during parenchymal transection and facilitates control of inadvertent venous injury, particularly of the intrahepatic course of the middle hepatic vein. The blood loss resulting from a vascular injury is directly proportional to both the pressure gradient across the vessel wall and the fourth power of the radius of the injury. If the CVP is lowered from 15 mmHg to 3 mmHg, the blood loss through a vena caval injury will consequently fall by a factor greater than 5. Lowering CVP not only lessens the pressure component of the equation but also minimizes the radial component of flow by reducing vessel distention.

In an attempt to reduce blood loss, physicians have advocated sometimes complex and costly approaches with some degree of success. Prolonged inflow occlusion with or without hepatic vascular isolation is an alternative approach for liver resection. This isolates the liver from the general circulation, allowing a bloodless field during liver transection. Extensive mobilization of the liver, to gain access to the suprahepatic and infrahepatic vena cava, is required. With the main portal and hepatic arterial inflow occluded, clamps are placed on the vena cava below and above the liver. The liver is then transected, and the major vascular and biliary structures are secured from within the parenchyma.

Hepatic vascular isolation induces important hemodynamic changes. The anesthetic management is more complex, and many patients require pulmonary artery catheters during the procedure. Hepatic vascular isolation typically causes a decrease in venous return with a resulting decrease in cardiac index and an increase in systemic vascular resistance. Mean arterial pressure is maintained by infusing large volumes of fluid to keep the CVP high. Most patients tolerate these hemodynamic changes reasonably well, although in some cases persistent hypotension or low cardiac index demands that the procedure be abandoned. Venovenous bypass may prevent some of these changes and has been advocated by some.

In the only prospective comparison of portal triad clamping versus hepatic vascular isolation, hemodynamic intolerance to the latter was noted in 14% of patients.\textsuperscript{19} In this study, vascular isolation was associated with longer operating times, longer hepatic ischemia, an increased incidence of abdominal fluid collections and pulmonary complications, and a longer hospital stay. There was also transient impairment of renal function seen only in the vascular isolation group. Operative blood loss and postoperative hepatic function were, however, similar between the groups.

Several recent studies of hepatic vascular isolation are summarized in Table 4.\textsuperscript{12,14,16-23} In these studies, blood loss and transfusion requirements were both greater than that reported by the authors using portal triad clamping with extrahepatic control of the
hepatic veins. In some series, blood loss was not documented and some patients had to be returned to the operating room for postoperative bleeding.\textsuperscript{21} Hepatic vascular isolation is more complex and has not yielded better results than portal triad clamping and extrhepatic control of the hepatic veins.\textsuperscript{14,16} This report provides evidence that major hepatic resection including extended hepatectomy can be performed safely and with minimal blood loss without the need for vascular isolation techniques.

Despite the recognition of renal failure as a serious complication of hepatic surgery, the incidence of postoperative renal dysfunction after liver surgery is not well established.\textsuperscript{25} Investigators have described short episodes of oliguria during LCVP-aided hepatic resection without the need for postoperative dialysis, but failed to address renal dysfunction.\textsuperscript{24} Our series reveals an incidence of 10\% of marked transient azotemia and an incidence of only 3.0\% of a persistent increase in serum creatinine after LCVP-aided hepatectomy. Eleven patients had an estimated 25\% to 40\% decrease in creatinine clearance, 3 patients demonstrated hepatorenal syndrome, and 1 patient suffered aminoglycoside tubular necrosis. Edwards and Blumgart\textsuperscript{6} reported a 13\% incidence of renal compromise after hepatic surgery. These results, particularly because they were obtained by one of us operating in a different environment and without the benefit of a LCVP-aided technique, suggest that the method we now describe has markedly reduced the incidence of renal morbidity when compared with standard practice.\textsuperscript{6}

Investigators have demonstrated a relation between the extent of intraoperative bleeding and morbidity.\textsuperscript{44} The overall low blood loss in this series clearly contributed to the low rate of postoperative renal morbidity. Steep head-down tilt (15 degrees) coupled with maintenance of at least a marginal intraoperative urine output of 25 mL/h and the immediate reexpansion of the intravascular volume at the completion of resection were largely responsible for the favorable renal outcomes. Head-down tilt provides the ideal condition to perform hepatic resectional surgery. By improving venous return, steep head-down tilt helped to preserve hemodynamic stability and renal function. In animals, head-down tilt has been shown to increase the glomerular filtration rate, sodium excretion, and urine output lasting up to 8 hours.\textsuperscript{25} Investigators have demonstrated that prolonged head-down tilt improved venous return and produced up to a 70\% increase in plasma atrial natriuretic protein.\textsuperscript{34,36}

Maintenance of anesthesia was accomplished with a combination of isoflurane in oxygen and narcotics. Isoflurane has been shown to provide vasodilation with minimal myocardial depression.\textsuperscript{27} In the majority of patients, fentanyl was adequate to maintain anesthesia under the conditions of the LCVP technique. Fentanyl has been shown to provide analgesia with minimal hypotension.\textsuperscript{28} In a small group of patients, we took advantage of the vasodilatory properties of morphine to aid in lowering CVP. Morphine reduced CVP by inducing venous vasodilation caused by histamine release and $\mu_3$ receptor activation.\textsuperscript{26,29} The combination of these anesthetics readily provided the favorable environment for hepatic resection. Only 5 patients required IV nitroglycerin to lower CVP below 5 mmHg. They did not require intraoperative dopamine for hemodynamic support.

Rees and associates\textsuperscript{31} achieved similar blood loss results using a more complex LCVP management technique. They used a combination of epidural blockade and IV nitroglycerin to provide LCVP. Their patients required intraoperative dopamine, possibly for systemic pressure support. This technique is cumbersome and adds an unnecessary level of complexity to an already challenging situation. The technique we report takes advantage of fluid restriction and the vasodilatory effects of standard anesthetics. On admission to the operating room, the patients did not receive overnight fluid replacement, a maneuver commonly practiced before or immediately after the induction of general anesthesia. Once anesthetized, the patients were maintained on minimal fluids until the completion of the resection. To guarantee the safety of patients, appropriate cannulation was performed and a high level of vigilance was maintained. We were equipped to handle major blood loss at a second's notice. Indeed, in our series, 16 patients experienced blood loss greater than 3 L. Transfusion equipment such as the Woods Pump coupled to a Level 1 System is an important aid for emergency fluid resuscitation occasionally needed with this anesthetic technique.

Air emboli occurring during hepatic surgery are well described. Hatano and colleagues\textsuperscript{22} reported the occurrence of air emboli in 2 of 13 patients during hepatectomy. This risk is likely to increase under LCVP anesthesia. An ideal anesthetic gas mixture should reduce the risk of a fatal air embolus. Isoflurane delivered in oxygen accomplished 2 objectives. It permitted the monitoring of expiratory nitrogen to identify air emboli and it eliminated the possibility of
increasing the size of a circulating air pocket with nitrous oxide. Transesophageal echocardiography was evaluated and abandoned as a monitor of air embolus. Although the technology easily identified air emboli, it failed to differentiate between clinically significant emboli and inconsequential echoes. Indeed, our patients experienced a very low incidence (0.4%) of clinically significant air emboli, possibly as a result of surgical vigilance with rapid occlusion of open venous channels. Only 2 patients experienced clinically significant air emboli with hypotension. Both patients were undergoing infra-atrial caval dissections; both episodes were brief and easily treated with blood pressure support.

LCVPaesthesia is a safe technique that facilitates operative control of hemorrhage, in particular from the major hepatic veins. Neither the surgical nor the anesthetic components of our approach may be applied alone. Close cooperation between the anesthesiologist and surgeon is necessary so that likely difficulties can be anticipated and appropriate measures can be taken. It is unlikely that the technique of LCPV will have any effect on a poorly done operation. Patients undergoing LCPV-aided hepatectomy have excellent outcomes as a result of low blood loss and minimal renal dysfunction.

References