Damage Control as a Strategy to Manage Postreperfusion Hemodynamic Instability and Coagulopathy in Liver Transplant

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IMPORTANCE Damage control (DC) with intra-abdominal packing and delayed reconstruction is an accepted strategy in trauma and acute care surgery but has not been evaluated in liver transplant.

OBJECTIVE To evaluate the incidence, effect on survival, and predictors of the need for DC using intra-abdominal packing and delayed biliary reconstruction in patients with coagulopathy or hemodynamic instability after liver allograft reperfusion.

DESIGN, SETTING, AND PARTICIPANTS We performed a retrospective analysis of adults undergoing liver transplant at a large transplant center from February 1, 2002, through July 31, 2012.

MAIN OUTCOMES AND MEASURES Predictors of DC, effects on graft, and patient survival.

RESULTS Of 1813 patients, 150 (8.3%) underwent DC during liver transplant, with 84 (56.0%) requiring a single additional operation for biliary reconstruction and abdominal closure and 57 (38.0%) requiring multiple additional operations. Compared with recipients without DC, patients requiring DC had greater Model for End-stage Liver Disease scores (33 vs 27; \( P < .001 \)); more frequent pretransplant hospitalization (72.0% vs 47.9%; \( P < .001 \)), intubation (33.3% vs 19.9%; \( P < .001 \)), vasopressors (23.2% vs 10.9%; \( P < .001 \)), renal replacement therapy (49.6% vs 30.3%; \( P < .001 \)), and prior major abdominal operations (48.3% vs 21.9%; \( P < .001 \)), including prior liver transplant (29.3% vs 8.9%; \( P < .001 \)); greater operative transfusion requirements (37 vs 13 units of packed red blood cells; \( P < .001 \)); worse intraoperative base deficit (10.3 vs 8.4; \( P = .03 \)); more frequent postreperfusion syndrome (56.2% vs 27.3%; \( P < .001 \)); and longer cold (430 vs 404 minutes; \( P = .04 \)) and warm (46 vs 41 minutes; \( P < .001 \)) ischemia times. Patients who underwent DC followed by a single additional operation for biliary reconstruction and abdominal closure had similar 1-, 3-, and 5-year graft survival (71%, 62%, and 62% vs 81%, 71%, and 67%; \( P = .26 \)) and patient survival (72%, 64%, and 64% vs 84%, 75%, and 70%; \( P = .15 \)) compared with recipients not requiring DC. Multivariate predictors of DC included prior liver transplant or major abdominal operation, longer pretransplant recipient and donor length of stay, greater Model for End-stage Liver Disease score, and longer warm and cold ischemia times (C statistic, 0.75).

CONCLUSIONS AND RELEVANCE To our knowledge, this study represents the first large report of DC as a viable strategy for liver transplant recipients with coagulopathy or hemodynamic instability after allograft reperfusion. In DC recipients not requiring additional operations, outcomes are excellent and comparable to 1-stage liver transplant.
Damage control (DC) is an accepted strategy to treat seriously injured patients\(^\text{14-16}\) and is increasingly used to manage critically ill patients with nontraumatic abdominal emergencies.\(^\text{5-7}\) The principles of DC include abbreviated laparotomy to control blood loss and contamination, resuscitation in the intensive care unit, and planned additional operation.\(^\text{8-10}\) Damage control avoids the vicious cycle perpetuated by hypothermia, acidosis, and coagulopathy and allows for the restoration of normal physiologic mechanisms before definitive surgical management.\(^\text{11-12}\) Although associated with significant morbidity, DC provides indisputable benefit to properly selected patients, with reported survival rates after severe trauma ranging from 58% to 90%.\(^\text{13}\)

Patients undergoing orthotopic liver transplant (OLT) experience varying degrees of hypothermia, acidosis, and coagulopathy after reperfusion depending on the difficulty of the hepatectomy, volume of blood transfusions, presence of postreperfusion syndrome (PRS), and function of the allograft.\(^\text{14-17}\) In routine cases, the physiologic derangements are corrected intraoperatively, and the transplant is completed in a single operation; in challenging cases, the physiologic derangements may persist, leading to worsening hemodynamic instability, bleeding, and coagulopathy.

Damage control is a valuable option for the challenging liver transplant. The strategy includes completion of portal venous and hepatic arterial anastomoses for allograft reperfusion, deferral of biliary reconstruction, intra-abdominal packing, and resuscitation in the intensive care unit before packing removal, biliary reconstruction, and closure of the abdomen within 48 hours. Although DC is widely used in trauma and acute care surgery, it has not been reported in liver transplantation. The specific aims of this study were to evaluate the use of DC, effects on survival, and predictors of need for DC in a large series of patients undergoing OLT in the post-Model for End-stage Liver Disease (MELD) era.

**Methods**

We retrospectively reviewed a prospectively maintained transplant database and identified all adult patients (aged ≥18 years) who underwent OLT (primary and additional transplants) from February 1, 2002, through July 31, 2012, at the University of California, Los Angeles (UCLA). The UCLA Institutional Review Board approved the study. Informed consent was not required.

Recipient variables analyzed included age, sex, medical and surgical comorbidities, MELD score, pretransplant hospitalization status and length of hospital stay (LOS), pretransplant need for mechanical ventilation, vasopressor support, and renal replacement therapy (RRT). Medical comorbidities included hypertension, diabetes mellitus, coronary artery disease, and presence of ascites. Coronary artery disease was defined as a history of myocardial infarction, prior percutaneous or open revascularization, or nonocclusive coronary atherosclerosis detected on angiography. Surgical comorbidities included prior abdominal operations, categorized as minor (pelvic or gynecologic surgery, laparoscopic cholecystectomy, appendectomy, and inguinal or ventral hernia repairs) and major (any exploratory laparotomy, gastric, small or large intestinal operation, open cholecystectomy, and liver surgery, including prior OLT).

Donor variables included age, sex, serum sodium level, number of vasopressors, LOS, and graft type (such as whole or split cadaveric, donation after cardiac death, living donor grafts, and expanded criteria donor (ECD) grafts based on criteria published previously).\(^\text{18}\) Donor LOS was calculated from the day of hospital admission to the day of organ procurement. Operative variables included cold ischemia time (CIT), warm ischemia time (WIT), transfusion of packed red blood cells (PRBCs), worst base deficit, PRS, use of venovenous bypass, and need for bolus or infusion of vasopressors. Postreperfusion syndrome was defined as a decrease in the mean arterial pressure greater than 30% below baseline, lasting at least 1 minute and occurring within the first 5 minutes of reperfusion.\(^\text{19}\)

Variables collected as measures of postoperative morbidity included the development of graft nonfunction, hepatic artery thrombosis, portal vein thrombosis, and biliary and infectious complications. Graft nonfunction was defined as the need for additional transplant during the index admission or recipient death due to all-cause graft failure and included true primary nonfunction and graft loss due to hepatic artery thrombosis, portal vein thrombosis, and other perioperative factors. Outcome measures included posttransplant LOS, 30-day mortality, and overall graft and patient survival. Pretransplant LOS was calculated from the day of admission to the day of transplant; posttransplant LOS was calculated from transplant to the day of discharge from the hospital.

A DC strategy with deferral of biliary reconstruction and intra-abdominal packing was based on a joint decision between the surgeon and anesthesiologist in critically ill patients with ongoing hypothermia, acidosis, coagulopathy, transfusion requirements, and/or hemodynamic instability that required vasopressor support after arterial reperfusion. After meticulous hemostasis, ongoing coagulopathy was treated with antifibrinolytic agents, including tranexamic acid and aminocaproic acid. The abdomen was temporarily packed with laparotomy pads, and the patient was warmed to a goal temperature greater than 35°C. If the physiologic derangements persisted beyond 60 minutes despite hemostasis and resuscitation, then biliary reconstruction was deferred, the abdomen was packed with laparotomy pads, the fascia was left open, and the skin was closed. The patient was brought to the intensive care unit for resuscitation and stabilization. A blood transfusion requirement greater than 6 to 8 units of PRBCs in 24 hours prompted consideration for urgent additional laparotomy.\(^\text{20}\) Otherwise, additional operation for packing removal, biliary reconstruction, and closure was planned within 48 hours when normal physiologic mechanism was restored.

Patients requiring DC were further categorized as needing one planned additional operation for delayed biliary reconstruction or having had multiple complications, includ-
ing a single unplanned additional operation for ongoing bleeding during which biliary reconstruction was performed, multiple subsequent operations, or graft failure with additional transplant or death.

Comparisons were made between patients with and without DC at the time of OLT. Continuous variables were compared using the Mann-Whitney test and summarized as medians and interquartile ranges. Categorical variables were compared using χ² or Fisher exact tests and summarized as percentages. Graft and patient survival curves were computed using Kaplan-Meier methods and compared using log-rank tests. To allow comparison of similarly challenging cohorts, propensity analyses using logistic regression were performed by matching patients requiring DC with controls not requiring DC on both preoperative factors (1:2 on recipient MELD score, LOS, and prior abdominal surgery) and intraoperative factors (1:1 on units of PRBCs, worst base deficit, and PRS). A multivariable logistic regression model was used to evaluate the effect of 14 recipient (age, sex, hypertension, diabetes, coronary artery disease, ascites, prior major abdominal operation, prior OLT, MELD score, pretransplant hospitalization and LOS, intubation, vasopressors, and RRT), 6 donor (age, sex, terminal serum sodium, number of vasopressors, LOS, and graft type), and 2 operative variables (CIT and WIT) on the need for DC. Missing values were singly imputed using the Markov Chain Monte Carlo regression method. The final model was selected using the backward procedure for variable selection with a liberal P < .15 as the retention criterion. Linearity was evaluated by fitting splines. Variables that did not conform to the linearity assumption were modeled using best thresholds. The best threshold for a given continuous predictor was defined as the value of the predictor that maximized the χ² statistic for the odds ratio (OR) under the final logistic model. All effects were assumed to be additive on the log odds scale. Results are summarized as ORs and 95% CIs. P ≤ .05 was considered statistically significant. Model accuracy was summarized using the concordance C statistic.

Results

Of 1813 adult patients who underwent OLT during the study period, 150 (8.3%) required DC during OLT (Figure 1). Of these 150, 84 (56.0%) required a single additional operation for removal of packing and completion of the biliary anastomosis, with 58 (38.7%) as a planned procedure when the patient was stabilized and 26 (17.3%) as an unplanned additional operation due to ongoing bleeding and hemodynamic instability. Multiple subsequent additional operations were required in 57 patients (38.0%), 5 patients (3.3%) died before any additional operation, and 4 patients (2.7%) underwent additional transplant at the second laparotomy. The median time to the first additional operation was 2 days.

Recipient Characteristics and Pretransplant Acuity

Baseline recipient characteristics and pretransplant acuity are listed in eTable 1 and eTable 2 in the Supplement. Compared with recipients not requiring DC, patients undergoing DC were significantly more likely to have prior major abdominal operations (48.3% vs 21.9%; P < .001), including prior OLT (29.3% vs 8.9%; P < .001); greater MELD scores (33 vs 27; P < .001); more frequent pretransplant hospitalization (72.0% vs 47.9%; P < .001); longer pretransplant LOS (19 vs 8 days; P < .001); and greater need for mechanical ventilation (33.3% vs 19.9%; P < .001), vasopressors (23.2% vs 10.9%; P < .001), and RRT (49.6% vs 30.3%; P < .001) before OLT. No significant differences were found in age, sex, medical comorbidities, or presence of ascites among the groups.

Donor and Operative Characteristics

Donor and operative characteristics are listed in eTable 3 in the Supplement. Compared with recipients without DC, recipients requiring DC had significantly longer CIT (430 vs 404 minutes; P = .04) and WIT (46 vs 41 minutes; P < .001), greater blood transfusion requirements (37 vs 13 units of PRBCs; P < .001), greater base deficit (10.3 vs 8.4; P = .03), more frequent PRS (56.2% vs 27.3%; P < .001), and more frequent use of venovenous bypass (64.7% vs 36.3%; P < .001), vasopressor boluses (72.4% vs 29.8%; P < .001), and infusions (85.9% vs 60.2%; P < .001). No significant differences were found in donor age, sex, terminal serum sodium level, number of vasopressors, LOS, or graft type, with a trend toward increased need for DC for grafts with greater ECD scores (ECD score 0, 5.9% DC; ECD score 1: 8.3% DC; ECD score 2: 10.5% DC; and ECD score 3 or 4: 17.3% DC).

Postoperative Outcomes

Postoperative outcomes are given in eTable 4 in the Supplement. Compared with patients not requiring DC, patients requiring DC had longer posttransplant LOS (53 vs 31 days; P < .001) and greater incidence of infection (49.3% vs 21.4%; P < .001), graft nonfunction (18.7% vs 3.3%; P < .001), and mortality within 30 days (15.3% vs 4.0%; P < .001). No significant differences were found in the incidence of hepatic artery thrombosis, portal vein thrombosis, or biliary complications between the groups.

Damage Control as a Strategy for Liver Transplant Recipients

Of 150 patients who underwent damage control (DC), 58 had a single, planned additional operation for delayed biliary reconstruction (DBR), 26 had a single, unplanned additional operation during which the bile duct was reconstructed, and 57 had multiple additional operations for various complications. Five patients died before any additional operation, and 4 patients underwent additional transplant at the first additional operation. OLT indicates orthotopic liver transplant.

Figure 1. Flow Diagram of Study Patients

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Graft and Patient Survival

Kaplan-Meier graft and patient survival estimates are given in Figures 2, 3, and 4. Compared with recipients undergoing standard 1-stage OLT, patients requiring DC (Figure 2) had inferior 1-, 3-, and 5-year graft survival (51%, 44%, and 43% vs 81%, 71%, and 67%; P < .001) and patient survival (62%, 55%, and 54% vs 84%, 75%, and 70%; P < .001). However, DC patients who underwent a planned, single subsequent operation for delayed biliary reconstruction had similar 1-, 3-, and 5-year graft survival (71%, 62%, and 62% vs 81%, 71%, and 67%; P = .26) and patient survival (72%, 64%, and 64% vs 84%, 75%, and 70%; P = .15) compared with 1-stage OLT recipients and significantly superior 1-, 3-, and 5-year graft survival (71%, 62%, and 62% vs 81%, 71%, and 67%; P < .001) and patient survival (72%, 64%, and 64% vs 55%, 50%, and 47%; P < .001) compared with DC recipients with multiple complications (Figure 3).

Figure 4 compares 1-, 3-, and 5-year graft survival estimates among 1-stage OLT and DC recipients based on number of additional operations. Patients undergoing DC requiring a single additional operation had equivalent graft survival compared with patients undergoing 1-stage OLT who subsequently underwent additional operations for other indications (66%, 59%, and 56% vs 73%, 64%, and 60%; P = .52); similarly, DC recipients requiring multiple additional operations had poor but equivalent graft survival compared with patients undergoing 1-stage OLT requiring multiple additional operations for other indications (35%, 29%, and 29% vs 48%, 43%, and 40%; P = .06).

Despite propensity matching to controls not requiring DC based on preoperative MELD score, LOS, and prior abdominal surgery, patients undergoing DC were significantly more likely to require venovenous bypass (65.3% vs 45.3%; P < .001), require intraoperative blood transfusions (35 vs 13 units of PRBCs; P < .001), and had greater PRS (57.3% vs 26.3%; P < .001), worse intraoperative base deficits (10.2 vs 7.8; P < .001), and significantly worse postoperative outcomes, including LOS (31.0 vs 26.0 days; P = .04), infection (49.3% vs 29.9%; P < .001), and 1-, 3-, and 5-year graft survival (52.0%, 46.0%, and 44.0% vs 73.0%, 61.0%, and 56.0%; P < .001) and patient survival (62.0%, 56.0%, and 54.0% vs 75.0%, 63.0%, and 58.0%; P = .08) compared with their matched cohort.
When matched to controls not requiring DC on intraoperative factors, patients undergoing DC had worse postoperative outcomes, including graft nonfunction, death within 7 days, need for additional unplanned additional operations, and inferior graft and patient survival.

**Multivariable Logistic Regression Analysis for Predictors of DC**

Multivariable logistic regression analysis identified 7 factors significantly associated with DC during OLT (Table). These factors included prior OLT (OR, 4.74; 95% CI, 2.90-7.75; \( P < .001 \)), prior major abdominal operation (OR, 2.53; 95% CI, 1.51-4.24; \( P < .001 \)), pretransplant LOS of 30 days or longer (OR, 2.48; 95% CI, 1.53-4.02; \( P < .001 \)), WIT of 45 minutes or longer (OR, 2.19; 95% CI, 1.53-3.15; \( P < .001 \)), donor LOS of 3 days or longer (OR, 1.76; 95% CI, 1.13-2.74; \( P = .01 \)), MELD score, per point increase (95% CI, 1.02-1.05; \( P < .001 \)), and CIT, per minute increase (1.002 (1.001-1.003) \( P = .52 \)). The C statistic for the model was 0.75 (eFigure in the Supplement).

**Table. Multivariate Predictors of Need for Damage Control**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odd Ratio (95% CI)</th>
<th>( P )</th>
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</thead>
<tbody>
<tr>
<td>Prior OLT</td>
<td>4.74 (2.90-7.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Major abdominal operation, not OLT</td>
<td>2.53 (1.51-4.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-OLT LOS ≥30 d</td>
<td>2.48 (1.53-4.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WIT ≥45 min</td>
<td>2.19 (1.53-3.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Donor LOS ≥3 d</td>
<td>1.76 (1.13-2.74)</td>
<td>.01</td>
</tr>
<tr>
<td>MELD score, per point increase</td>
<td>1.04 (1.02-1.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CIT, per minute increase</td>
<td>1.002 (1.001-1.003)</td>
<td>.52</td>
</tr>
</tbody>
</table>

Abbreviations: CIT, cold ischemia time; LOS, length of stay; MELD, Model for End-stage Liver Disease; OLT, orthotopic liver transplant; WIT, warm ischemia time.

**Discussion**

Although DC with intra-abdominal packing and temporary closure has gained popularity in the treatment of patients with multisystem trauma, hepatic trauma, and nontrauma, few data exist regarding its use in liver transplant, with the literature limited to case reports and small case series. This study is the largest contemporary single-center experience with DC in liver transplant. We report graft and patient outcomes and define predictors of the need for DC. Recipients requiring DC had significantly greater acuity of illness compared with patients not requiring DC, with greater MELD scores and need for hospitalization, mechanical ventilation, vasopressors, and RRT before transplant. Compounding the critical illness, nearly 50% of recipients requiring DC had a history of prior major abdominal surgery, including 30% with prior OLT. Adhesions from prior surgery, particularly prior OLT, increase the difficulty of dissection and bleeding during the transplant, which in part explain the more frequent use of venovenous bypass, longer CIT and WIT, and larger transfusion requirements in the recipients who required DC. In addition, patients who required DC had more profound physiologic derangement and hemodynamic instability, including greater base deficit, more frequent PRS, and greater use of vasopressors intraoperatively.

A major objective of our study was to evaluate the association of DC with posttransplant outcomes. Recipients who underwent DC had greater incidence of infection, graft nonfunction, and death within 30 days. In the literature, the DC strategy improves outcomes over prolonged definitive operations in critically ill patients, but the morbidity and mortality remain high. Further to evaluate the inferior outcomes in the DC cohort, we performed 2 propensity-matched analyses. To control for preoperative acuity, patients requiring DC were matched to patients not requiring DC on laboratory MELD score, LOS, and prior abdominal surgery. Although there was excellent matching on these preoperative acuity measures, patients not requiring DC had significantly less need for intraoperative venovenous bypass and transfusions and had less PRS and acidosis, indicating that the intraoperative environment that dictated the need for DC was not recapitulated in...
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Influence intraoperative outcomes and the need for DC. Our use of ECD livers, particularly in high-acuity recipients, may be significant in predicting DC, supporting the notion that the ECD score (donor LOS, CIT, and WIT) were independently analyzed. Our multivariate analysis revealed that 3 of the 4 factors contributing to the ECD score did not reach statistical significance, our multivariate analysis may lead to the need for DC. Although categorization by the ECD score did not use specific trigger points to initiate DC, DC was strongly considered in recipients who remained refractorily hypothermic (temperature <35°C) and acidic (pH <7.25) and who required more than 20 to 25 units of PRBCs with ongoing raw surface bleeding. Ultimately, consideration for DC for an individual patient required the collective decision between the surgeon and anesthesiologist, assessing the patient’s temperature, acid-base and volume status, transfusion requirement, coagulopathy, and hemodynamic and cardiac stability. Defining and validating more specific perioperative parameters that might indicate when to perform DC in liver transplant are areas for future study.

Conclusions

We report, to our knowledge, the largest single-center series of DC in liver transplant. Damage control is a viable option for the management of challenging recipients with intraoperative hypothermia, acidosis, coagulopathy, and hemodynamic instability after allograft reperfusion. It may be required in up to 8% of high-acuity recipients, with favorable outcomes equivalent to 1-stage OLT in patients requiring a single additional operation. We identify important recipient and perioperative factors that accurately predict the need for DC and may help in the early identification of patients most likely to benefit from a 2-stage OLT procedure.

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Acquisition, analysis, or interpretation of data: DiNorcia, Lee, Harlander-Locke, Xia, Kaldas, Zarrinpar, Farmer, Yersiz, Hiatt, Agopian.
Drafting of the manuscript: DiNorcia, Harlander-Locke, Hiatt, Agopian.
Critical revision of the manuscript for important


