

# The Development of Perioperative Practices for Liver Transplantation: Advances and Current Trends

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Transplantation is a young medical specialty that has grown rapidly over the past 50 years. Anesthesiologists, surgeons and hepatologists are all essential partners in the process of determining patient outcome. Each specialty has made landmark improvements in patient outcome. However, there is still variability in practice patterns in each of the 3 major specialties. This review will use a historic perspective to explore the unique forces that shaped specific transplant practices and those that gave rise to differences in perioperative practices. Anesthesiologists and surgeons have made significant improvements in the management of blood loss, and coagulation monitoring and intervention. This has improved operative survival and early patient outcome. Perioperative survival has improved despite a worldwide shortage of donor organs and a trend to transplant sicker patients. A smaller pool of donor organs is required to meet the needs of an expanding waiting list. The innovations to reduce deaths on the transplant wait list are reviewed along with their impact on overall patient outcome. The evolving organ shortage is the pinnacle point in shaping future transplant practices. Currently, institutional-specific practices may be reinforced by the informal "tutorship" that is used to train physicians and by the resources available at each site of practice. However, there is evidence that specific intraoperative practices such as the use of a low central venous pressure, selection of vasopressors and certain surgical techniques can modify patient outcome. Further investigation is needed to determine whether the good or the bad associated with each practice prevails and in what unique circumstance. [*J Chin Med Assoc* 2008;71(9):435–441]

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## Introduction

Transplantation is a relatively new medical specialty, dating back to only 1954 when Dr Joseph Murray took a kidney from a living identical twin and placed it into the other.<sup>1</sup> A period of 8 years elapsed before the first successful cadaveric transplant was performed by Dr Murray in 1962.<sup>2</sup> After this landmark cadaveric kidney transplant, there was a rapid development in the number and type of transplant procedures. The first successful single lung transplant was performed by James Hardy at the University of Mississippi in 1963, while Thomas Starzl and Christian Barnard performed successful liver and heart transplants in 1967.<sup>3,4</sup> However, the medical community did not initially accept transplantation as a viable treatment for end-stage organ

disease because postoperative outcomes were poor due to organ rejection. The introduction of cyclosporine in 1983 changed how the medical community viewed transplantation.<sup>5</sup> As postoperative survival steadily improved, the field of solid organ transplantation entered into modern medical care.

The field of transplantation rapidly developed a solid scientific compendium of evidence over the last 50 years to support its medical practice patterns. The cumulative scientific knowledge became so extensive and diverse that physicians had to specialize in specific organ systems. Medical specialties such as surgery, cardiology, pulmonary medicine and hepatology created separate credentialed programs in the field of transplantation to ensure that physicians had reached a documented level of competence. The knowledge



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required for perioperative care was also unique even though these specialists have never established specific credentials.<sup>6</sup>

The first anesthesiologists to care for transplant recipients in the operating room were trained in the field of intensive care. These physicians had a broad experience caring for the critically ill. They also had a diverse knowledge and skill set that made them more comfortable caring for critically ill liver transplant recipients in the operating room. As postoperative outcomes improved, intensive care training was no longer considered essential for the intraoperative care of transplant recipients and new generations of liver transplant anesthesiologists were most often informally trained by their predecessors. This approach propagated a tradition of perioperative practices that tend to be center-specific, with local, regional and even national differences in practice patterns between transplant centers worldwide.<sup>7</sup> The significant differences observed in perioperative resource utilization are easily explained by the diverse approach to patient management.<sup>8</sup> Adhering to institution-specific practices may explain why the evidence to support specific perioperative practices continue to lag behind the other transplant-related specialties. However, there is a new interest in sharing information about anesthesia-related practices across institutional boundaries.<sup>9</sup> As a result, studies that assess the risks and benefits of the different perioperative practices are now emerging. This review will explore the unique forces that created differences in perioperative practices using a historic perspective. We will track the evolution of specific anesthesia transplant practices and examine some of the scientific challenges that transplant anesthesiologist continue to face as their specialty matures.

## The Control of Blood Loss in Liver Transplantation

The clinical practice of liver transplantation is built upon the scientific evidence from multiple medical specialties. Advances in 1 subspecialty of liver transplantation have wide reaching effects on practice patterns in the other related specialties. This is particularly true for surgery and anesthesia. This is clearly seen in the early history of transplantation when surgeons were developing their technical approach. Surgeons initially constructed a portocaval shunt to maintain venous return during the anhepatic stage and they performed a splenectomy to assist in immunosuppression.<sup>10</sup> These procedures were performed in patients who were so

ill that they were close to death. The combination of extensive surgery in critically ill patients caused bleeding that was so severe that it was almost considered an insurmountable obstacle to survival. In response, anesthesiologists developed tools that rapidly administered warm blood to prevent exsanguinations during surgery. They modified cardiopulmonary bypass pumps to create the first rapid infusion devices.<sup>11</sup> These “new pumps” were able to meet the transfusion needs of most patients while preventing hypothermia. This step alone made the surgical procedure possible because it significantly improved a patient’s chance of intraoperative survival.

Blood loss has always been a central issue in liver transplantation.<sup>12</sup> It remains a major cause of morbidity and mortality even though death due to intraoperative hemorrhage is increasingly rare. This is because blood transfusion is independently correlated with negative outcomes in liver transplantation, an observation that occurs in other types of surgery.<sup>13</sup> The risks associated with transfusion have always been the principal factor that motivated technical refinements in surgical technique.<sup>14</sup> Two major events significantly reduced intraoperative blood loss. First, surgeons abandoned the construction of portocaval shunts in favor of the use of venovenous bypass circuits.<sup>15</sup> This essentially “externalized” the portocaval shunt and reduced the amount of tissue trauma and therefore bleeding. Second, the introduction of cyclosporine reduced the need for splenectomy.<sup>16</sup> The resulting fall in blood transfusion translated directly into better outcomes for the patients.

The average blood loss can be used to track the historical changes in surgical technique. In the late 1980s, an average transfusion of 20 units of packed red blood cells were used for each procedure compared to the average of 2 units of blood used in 2003.<sup>13</sup> Investigators from a single institution reported a significant reduction in the use of blood products.<sup>17</sup> In fact, they reported that up to 79% of their patient population did not need any red cell transfusion during surgery.<sup>18</sup> However, there has always been a large variability in the amount and type of blood products used between transplant centers for patients with similar demographics and intraoperative characteristics.<sup>18</sup> The amount of blood used is determined by the amount lost due to surgical technique and transfusion triggers used by anesthesiologists. It is difficult to separate the effects of these 2 important factors. However, it is likely that institution-specific anesthesia practices explain some of the variability in blood utilization.<sup>19</sup> This suggests that evidence-based protocols that specifically guide intraoperative transfusion

during transplantation could minimize some of the institutional variation and improve outcome.<sup>12</sup>

The next wave of changes that reduced blood loss and improved patient outcomes came from advances in the anesthesia management of the systemic circulation during surgery.<sup>20,21</sup> Circulatory instability was common during surgery and placed patients at risk of ischemic injury. Anesthesiologists found that they could use vasoconstrictors to increase systemic vascular resistance during surgery, which in turn improved blood pressure and organ perfusion.<sup>22</sup> Anesthesiologists also borrowed techniques from the field of hepatology that specifically controlled splanchnic blood flow.<sup>23</sup> Anesthesiologists discovered that intra-abdominal blood loss would be reduced by limiting splanchnic blood flow during surgery.<sup>20</sup> Drugs used to control variceal bleeding such as vasopressin are now commonly used during surgery to selectively limit blood flow to the gut in order to reduce surgical bleeding.<sup>24</sup> Control of the circulatory system made the use of venovenous bypass optional.<sup>25</sup> This reduced the anhepatic time, along with the cold ischemic and total surgical time—factors that are strongly correlated with outcome.<sup>26</sup> These changes should improve outcome; however, there is still no consensus on the surgical management of the anhepatic stage, whether it is beneficial or not to use venovenous bypass with the piggyback technique or total vascular exclusion because large randomized studies have not yet been performed. Thus, while a large number of centers have abandoned venovenous bypass circuits, some centers continue to use them.

There is clear evidence from studies of elective hepatic resection that anesthesia manipulation of central venous pressure during surgery can reduce blood loss.<sup>27</sup> Investigators have presented convincing evidence that lowering the central venous pressure by restricting fluid administration or inducing diuresis can decrease transfusion requirements.<sup>28,29</sup> Investigators also think that a lower central venous pressure can improve oxygen delivery to the donor graft. A low central venous pressure would create a venous pressure gradient between the portal and central venous circulation that draws blood through the donor graft. Despite this convincing evidence, individual centers still debate the benefits and risks of lowering central venous pressure because there are no outcomes studies with a matched control group to evaluate the specific effects on liver transplant recipients. Some also point out that there is no evidence to help the anesthesiologist identify an actual pressure measurement that constitutes a low central venous pressure or whether I value works equally well in a diverse population. Concerns are expressed about what central

venous pressure is beneficial and what value could place a patient at an increased risk of organ injury.<sup>17,30</sup>

There is least agreement between anesthesiologists about how to manage coagulation in the operating room. Early in the history of liver transplantation, anesthesiologists adapted coagulation monitoring for use inside the operating room so that they could rapidly obtain objective data to make impartial decisions about blood transfusion.<sup>31</sup> Many anticipated that routine monitoring of the coagulation system during surgery would standardize the transfusion of all blood products and therefore reduce the variability in blood administration between institutions.<sup>32</sup> To date however, anesthesiologists are still seeking a “gold standard” to monitor coagulation. Consequently there is little agreement about what laboratory values should trigger an intervention. There are proponents for the use of different coagulation monitoring modalities including thromboelastography (TEG), Sonoclot analysis, and standard laboratory tests including prothrombin time and partial thromboplastin time.<sup>31,33,34</sup> Their impact on transfusion management has not yet been reported for either single institutions or compared across institutions.

In a similar manner, there have always been proponents for and against the prophylactic use of pharmacological agents that are thought to stabilize clot formation and therefore reduce blood loss.<sup>35,36</sup> The routine use of prophylactic antifibrinolytic drugs was common in the early history of transplantation, but many care providers no longer adhere to this practice because of recent reports of thrombotic complications.<sup>37,38</sup> Physicians question if the number of thrombotic episodes is increasing. However, the context in which physicians view the balance of the risks and benefits of such drugs has been tipped by the changes in transfusion practices. Massive transfusion is associated with a high mortality and thus any risk associated with the prophylactic use of antifibrinolytic agents appears small. However, these risks appear magnified in patients who use very little blood since thrombotic complications become a larger proportion of the negative outcomes. The relative blood loss each center experiences will thus influence the decision of whether to use drugs prophylactically that stabilize blood clots.

## The Effects of Organ Availability on Transplant Practices

The number of liver transplants performed worldwide increased significantly from 1988 to 2006. The lack of donor organs is the single factor that controls the

growth of transplantation worldwide. This single issue is 1 of the most influential determinants of how transplant practices adapt and develop.<sup>39</sup> Physicians identified at least 3 novel ways to expand the organ pool in order to reduce the number of deaths on the transplant waiting list. All 3 approaches had a significant influence on how transplant practices developed. The first change was to create an objective method to allocate organs to patients on the waiting list. The second approach was to expand the donor pool by using donor organs that have a higher risk of graft failure. And the third was to use organs from living donors.<sup>40,41</sup>

Policies that administer organ allocation are 1 of the most important factors that have affected anesthesia liver transplant practices.<sup>42</sup> Waiting time was an important factor in organ allocation in many countries during the latter half of the 1990s.<sup>43</sup> This allowed patients who were less ill to reach the top of the waiting list. During this time, there was a fall in total resource utilization coupled with an increase in 1- and 5-year life expectancy.<sup>44</sup> Studies showed that the majority of resources had previously been consumed in high acuity care following liver transplantation.<sup>45</sup> In fact, intensive care unit charges accounted for up to 1 quarter of all costs for a transplant admission. The fall in severity of patient illness coupled with advances in fluid and coagulation management opened a window of opportunity that allowed anesthesiologists to specifically reduce the use of costly perioperative resources. Investigators were able to contain costs by introducing paradigms that reduced the use of routine postoperative ventilation.<sup>46</sup> This in turn reduced intensive care unit length of stay.<sup>47,48</sup> Of these protocols, immediate postoperative extubation proved to be very cost-effective and has been a growing trend amongst transplant centers throughout the world.

In February of 2002, the *model for end-stage liver disease* (MELD) and its pediatric equivalent (PELD) replaced previous policies for donor organ allocation in the United States.<sup>49</sup> Prior allocation policies included patient variables that required subjective assessment. Factors such as the severity of ascites or encephalopathy were subject to varying impression between observers. The MELD score aimed to objectify the criteria used to prioritize candidates for liver transplantation by generating a numerical score from the 3 standard laboratory values of international normalized ratio (INR), serum bilirubin and creatinine.<sup>50</sup> And, the sole aim of MELD was to transplant the patient with the highest score, i.e. patients with the greatest mortality risk. Although the intent of MELD is to transplant the sickest patients first, the actual MELD score does not necessarily correlate with the severity of illness due to

liver disease. For example, patients can receive additional MELD points for conditions such as hepatocellular cancer and hepatopulmonary syndrome. The number of points given is based on the predicted mortality without transplantation. Many countries have not adopted the formal use of MELD as an allocation tool, but it has become an international currency to exchange information about outcomes. Further, there is a trend in the international liver transplant community to adopt the practice of transplanting patients with a greater severity of illness, similar to the aim of MELD.

Deaths on the waiting list have fallen by 10% in the United States since MELD was implemented,<sup>51</sup> but the patients who present for liver transplant have a much greater severity of illness and consume significantly more resources.<sup>52</sup> This is shown by the correlation between the MELD score, blood use and the need for vasopressor support in the operating room; factors that are all associated with negative outcomes.<sup>53,54</sup> In addition, the inclusion of creatinine in the MELD score has shifted the priority for transplantation to patients with renal insufficiency or failure. Physicians have elected simultaneous liver-kidney transplantation (SLK) more often since the introduction of MELD<sup>55</sup> because long-term outcomes are inferior in patients who need dialysis following liver transplantation.<sup>56,57</sup> However, a recent analysis showed that outcomes from SLK are not always better than liver transplantation alone.<sup>58</sup> Investigators think that the preferential allocation of kidneys to older and more critically ill patients with renal dysfunction explain the poor long-term outcomes observed following SLK.<sup>58</sup> Anesthesiologists therefore now care for more critically ill patients with renal dysfunction. There is no evidence-based consensus on how to manage fluid and electrolyte abnormalities in patients with renal dysfunction or frank failure. Investigators have described successful intraoperative management with ultrafiltration and hemodialysis.<sup>59,60</sup> In a study of 11 SLK patients, 4 received hemodialysis, 1 ultrafiltration and both techniques were used in 3 patients.<sup>60</sup> No form of renal replacement therapy was used in 3 patients. This study clearly showed that renal dysfunction can be managed in the operating room by more than 1 approach. However, it is still not clear what the indications for renal replacement therapy are, what the goals of therapy are, and which therapy will benefit the patient the most. Further evidence is needed to address these issues.

Investigators continue to adapt the MELD score to the changing pattern of indication for transplantation. The most current proposal adds serum sodium to the MELD formula since a value < 126 mmol/L at the time

of listing is associated with a 6.3–7.8 fold increased risk of death.<sup>61</sup> The higher priority of patients with renal failure and low serum sodium challenges anesthesiologists to identify the best ways to preserve renal function. Although the MELD score continues to evolve, the philosophy is consistent: transplant the sickest patient. This is a significant factor that will continue to shape perioperative practices in the USA.

The second approach to solving the organ shortage uses organs from donors who have a higher risk of graft failure in the recipient. Studies have identified a number of donor risk factors that predict a greater risk of organ failure.<sup>62</sup> These include donor age > 60, death due to cerebrovascular disease or comorbid systemic illness such as diabetes.<sup>63</sup> There is also a greater risk of donor graft failure associated with organs that are split between 2 recipients and those recovered from donors who have died a cardiac death. The collective group of characteristics that increase the risk of graft failure is called extended criteria donors (ECD). The expansion in the use of ECD donors occurred at the same time that the severity of patient illness increased. This has created a situation of double jeopardy. Investigators are just beginning to weigh the full effects of combining high-risk recipients with high-risk donor organs.<sup>64</sup> There is compelling evidence that both higher MELD scores and the use of ECD are associated with greater perioperative cost. The trend to stretch the donor pool farther in sicker patients may therefore impact total resource utilization. The increased risk of delayed donor graft function or even primary non-function will have its greatest impact on the type of care and resources used for perioperative care.

Recovering the right or left lobe of the liver from living donors is the third practice that has eased the organ shortage. Most adult living donor transplants done in the USA use the right lobe of the liver. In contrast, the left lobe is commonly used in small adults in Asia and in most pediatric patients. There was very little interest in living liver donation in the USA after the first procedure was performed in 1991.<sup>65</sup> The enthusiasm for living liver donation, however, increased as cadaveric donor organs became increasingly scarce. The growth of living donor liver transplantation peaked in the USA in 2001 with 522 cases performed and has steadily declined with only 265 cases complete in 2007.<sup>66</sup> In contrast, living donation is a primary source of organs for patients in Asia.<sup>67,68</sup> The number of cases in Japan and Taiwan alone far exceeds those performed in the United States. The decline in living donor liver transplantation coincided with the death of a living liver donor in 2005. In the USA, over 1,700 living donor liver transplants have

been performed with 2 early deaths and 2 liver transplants in adult donors.<sup>69</sup> However, other factors have played a role in causing the decline of living liver donation. These include: changes in organ allocation that prioritize medical urgency; exhaustion of the initial pool of eligible patients on the waiting list, leaving only new additions to the waiting list as potential living donor transplant candidates; and the increasing use of extended criteria (marginal) donors.<sup>69</sup> The use of alternate donor sources has forced anesthesiologists to step out of their traditional role where they only focus upon the recipient. They now must take on new responsibilities to facilitate the unique interaction between the live organ donor and transplant recipient.

## Conclusion

The art and science of perioperative liver transplantation has undergone a remarkable evolution since its humble beginnings in 1967. Perioperative physicians have been instrumental in improving liver transplant recipient outcome and adapting their practice to the progress in other aspects of transplant practice. But there is still considerable debate about the relative benefits and risks of many anesthesia-based practices. The informal apprenticeship that anesthesiologists use to train their successors may inadvertently reinforce the difference in practice patterns between institutions. This creates a widening gap between institutional preferences and evidence-based practices. The trend in the USA and other countries is to transplant the sickest patients while using organs at risk for graft failure. With impending constraints on resource utilization worldwide, anesthesiologists have to examine their practices beyond the limits of institutional boundaries to identify those that are associated with the best outcome while being cost-effective.

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