The Impact of a Surgical Protocol for Enhanced Recovery on Living Donor Right Hepatectomy

A Single-Center Cohort Study

Seong Hoon Kim, MD, PhD, Young Kyu Kim, MD, Seung Duk Lee, MD, Eung Chang Lee, MD, and Sang Jae Park, MD, PhD

Abstract: The concept of surgery for enhanced recovery (SFER) program has never been an issue in the context of living donor right hepatectomy (LDRH), much less its effects. The purpose of this study was to evaluate outcomes after the establishment of an SFER protocol for LDRH in a single center.

A single-center cohort study was performed in 500 consecutive living donors who underwent right hepatectomy from January 2005 to June 2014 by analyzing the outcomes before and after an established SFER protocol that evolved with continuous refinements in surgical technique and management over 300 LDRHs, being in place on September 2011. Donor characteristics, operative outcomes, and postoperative complications divided into 2 groups (group 1, stepwise adjustment; group 2, complete adherence to the protocol) were compared.

Donor characteristics were comparable in the 2 groups. Overall complication rate was 10.0% with no mortality. In group 2, operative time, hospital stay, and overall complication rate decreased significantly, and the morbidity was 1% and confined in grade I complication without reoperation, perioperative blood transfusion, or readmission. All donors in this series recovered fully and returned to the previous functional lifestyle.

An SFER protocol on LDRH can be established by the gradual implementation of various refinements of surgical technique, and the recent outcomes achieved after the establishment of an SFER protocol could provide a current guidance on LDRH toward the ultimate goal of zero morbidity.

INTRODUCTION

Living donors are the only effective source of liver grafts in areas where deceased donor organs are in short supply. Living donor right hepatectomy (LDRH) is the most common form of donor surgery performed in adult-to-adult living donor liver transplantation (LDLT). However, this procedure exposes living donors to potential risks of morbidity and mortality.2,5 Considering placing healthy individuals at operative risk, preventing morbidity and mortality remains top-priority concern in the era of living donor surgery performed worldwide as a last-ditch effort.

The outcomes of LDRH are determined by the following variables: preoperative selection, intraoperative surgical procedure, and postoperative care. Every major complication may start out as any small mistake of the 3 variables. Enhanced recovery after surgery (ERAS) programs were reported to result in good outcomes in surgical interventions including liver resection, concentrating on the postoperative care.6,7 However, intraoperative surgical technique and procedure is the most important feature key success factor in determining the outcome of LDRH, where there is still lack of consensus about the optimal surgical technique and management.

It was previously reported from the authors’ early experience that the morbidity of LDRH can be reduced to near-zero.8 In the meantime, a surgery for enhanced recovery (SFER) protocol for LDRH was established by the gradual implementation of various refinements of surgical technique and procedure and a learning experience over 6 years. The aim of this study was to introduce an SFER protocol and evaluate outcomes after the establishment of an SFER protocol for LDRH in a single center.

METHODS

Study Design

This was a retrospective cohort study of all living donors who underwent right hepatectomy between January 2005 and June 2014 at the National Cancer Center, Korea. This study was approved by the Institutional Review Board of the National Cancer Center, Korea.

Donor characteristics, operative outcomes, and postoperative complications were reviewed from a prospectively maintained database. To assess the effects of an SFER protocol on outcomes of LDRH, a comparative analysis was done by dividing consecutive living donors into 2 groups, each prior to and after establishing and implementing the SFER protocol (group 1, January 2005 to August 2011, a period of stepwise adjustment; group 2, September 2011 to June 2014, a period of complete adherence to the protocol). All complications were recorded prospectively and stratified by grade according to Clavien classification.9
Donor Evaluation and Selection

The initial donor evaluation and selection criteria have been specified elsewhere. Since then, the preoperative evaluation has hardly changed except that magnetic resonance cholangiography (MRC) was introduced from donor no. 165. In the meantime, the selection criteria for LDRH have been extended with advanced surgical technique and improved management without compromising donor safety.

Concisely, all living donors voluntarily signed the informed consent about the items deliberated by the Ethics Group of the Vancouver Forum, and all LDRHs were approved by Korean Network for Organ Sharing (KONOS) as well as the Ethical Committee of our institution.

With regard to liver volume, a future remnant left liver volume ≥ 30% of total liver volume by computed tomography (CT) volumetry was chosen as the minimum cutoff. However, if healthy donors were less than 50 years old with no or mild fatty liver, a remnant left liver volume < 30% of total liver volume was selected carefully, in which case the middle hepatic vein (MHV) was absolutely preserved in donors.

In terms of donor age, initial acceptance criteria included adults aged 16 to 59 years. However, the criteria have been extended to include elderly donors aged 60 or older by the following selection criteria: preservation of MHV, a remnant liver volume ≥ 30%, and no or mild fatty change in healthy condition.

Surgery-For-Enhanced-Recovery (SFER) Protocol

An SFER program was completely established on September 2011 by gradual refinements in surgical technique and management over 300 LDRHs with a principle aim of standardizing the surgical procedure that could lead to improve outcomes by enhanced recovery.

The learning curve of the 1st 51 LDRHs was reported with initial experience and techniques. Since the beginning of the LDLT program, liver parenchymal transection was performed with the ultrasonic dissection device using the hanging maneuver without any vascular inflow occlusion, and autologous blood was not preserved. In the meantime, notable diverse modifications have been made in surgical technique and management. From donor no. 45 in July 2007, a drainage tube was placed by piercing the abdominal wall using an electric coagulator in order to prevent delayed bleeding caused by a pointed end connected to a closed-suction drain that had actually occurred to 2 donors. From donor no. 55 in February 2008, an upper midline incision above umbilicus has been the one and only incision method to be used without exception in all living donors, which could reduce not only the size of abdominal incision but also abdominal muscle damage. From donor no. 93 in July 2008, the dose reduction protocol from 50 to 25 IU/kg was implemented to reduce possible bleeding complication of intravenous heparin injection just prior to dividing the inflow vessels. From donor no. 112 in November 2008, the wound protector was employed to protect surgical wounds from contamination. From donor no. 165 in September 2009, Glisson approach was employed during hilar dissection and the hanging maneuver was used consistently from the start of parenchymal transection to make the surgical procedure simple and to reduce operative time, and preoperative MRC was substituted for intraoperative cholangiography for the benefit of noninvasiveness, based on the reports that MRC accurately depicts living donor biliary anatomy as correlated with intraoperative cholangiography and is superior in complete depiction of the central, right, and left hepatic ducts.

From donor no. 167, donors were discharged back to the surgical ward for nursing care after LDRH with no admission to the intensive care unit. From donor no. 169 in October 2009, no donor underwent central venous catheterization because of improved hemodynamic stability during surgery and apprehension for possible complication such as pneumothorax that had actually occurred in 1 donor. From donor no. 200 in March 2010, the bile duct was divided just 2 mm to the right side of the confluence under direct vision. For 1 donor suffered biliary stricture (donor no. 197). Before then, the bile duct division had been performed just 1 mm to the right side of the confluence. From donor no. 271 in March 2011, further dosage reduction of intravenous heparin was done from 25 to 5 IU/kg. From donor no. 299 in August 2011, the right hepatic duct was dissected and ligated just at the right side of the confluence under a clear view, and then the right side of ligature was cut.

Surgical Procedure

During the start-up period, an outside experienced surgeon supervised the 1st 17 LDRHs. Since then, a single in-house surgeon (SHK) performed more than 400 cases of LDRH, and especially, since donor no. 160, he has been the only main operator specially dedicated to living liver donor surgery. The current surgical technique is as follows.

An upper midline incision above umbilicus is made with a wound protector installed. The right liver is mobilized fully with inferior right hepatic veins larger than 5 mm saved if present. After cholecystectomy, the right Glisson pedicle is dissected. The inferior parenchyma of caudate lobe is transected up to the hepatic hilum. A tape is positioned along the anteromedian surface of inferior vena cava on the left side of the saved inferior right hepatic veins with its upper and lower ends between right and MHVs and between the right and left Glisson pedicles, respectively. Hanging maneuver is employed consistently from the beginning of parenchymal transection until the tape is exposed. All MHV tributaries > 5 mm in diameter are preserved for reconstruction. After complete parenchymal transection, the right Glisson pedicle is dissected into right hepatic artery, portal vein, and hepatic duct. The right hepatic duct is ligated just at the right side of the confluence under a clear view and the left side of ligature is cut. After injection of intravenous heparin (5 IU/kg), the right hepatic artery, portal vein, and hepatic vein are divided in the order named at each bifurcation without narrowing the remnant stumps. The graft is transferred to a basin containing histidine-tryptophan-ketoglutarate solution. The falciform ligament is anchored back to its original position to prevent rotation of the remnant left liver, and a drainage tube is placed alongside the cut liver surface.

Postoperative Care and Follow-Up

Donors were transferred to the recovery room after being exubatuated in the operating theatre. Donors were also encouraged to breathe deeply and ambulate early within the 1st day or 2 after surgery. Compressive stockings were worn up until discharge as prophylaxis for thromboembolism, and low-molecular weight heparin was administered to elderly donors over age 60 for 1 week after surgery. Feeding was started within 24 hours after operation. Postoperative routine laboratory tests were checked daily for 3 consecutive days, and then every 2nd day until discharge. For imaging follow-up, CT scans were routinely performed at 1 week, 1 month, and 1 year after LDRH. After discharge, all donors were followed up in the outpatient clinic.
with routine laboratory tests at 1 month after LDRH, then 3 months later, and thereafter every half year. Readmission was defined as any hospital readmission due to surgery-related complications after discharge.

Statistical Analysis
Categorical and continuous variables were compared using the Fisher exact test and the Mann–Whitney U-test, respectively. Linear regression analysis of the total operation time with respect to the case numbers was performed to determine the regression line described by a linear equation, and the results were depicted as lines and scatter plots. A P value less than 0.05 was considered statistically significant. All analyses were carried out using SAS version 9.1.3 for Windows (SAS Institute, Cary, NC).

RESULTS

Donor Characteristics
Over this period of 9 years and 5 months, a total of 500 consecutive LDRHs were performed for adult LDLT. Donor characteristics are listed in Table 1. There were no significant differences between the 2 groups in terms of gender ratio, age, body mass index, fatty change, and the volume ratio of remnant left liver to whole liver by CT volumetry.

Operative Outcomes
Graft type was mostly right liver (96.2%) and showed no statistically significant difference between the 2 groups. Outcome measures are shown in Table 2. The operation time became significantly shorter in group 2 than in group 1, where the shortest was 104 minutes and the longest was 305 minutes. Total operation time had a positive correlation with the case numbers (Figure 1, \( P < 0.001; R^2 = 0.505 \)).

The operative blood loss was significantly reduced in group 2. Three donors in group 1 and no one in group 2 received postoperative transfusions, all of which resulted from postoperative bleeding. The trend toward shorter hospital and intensive care unit stays in group 2 was obvious and statistically significant. Three donors in group 1 were readmitted for pleural effusion, diaphragmatic hernia, and biliary stricture, respectively, while no one was readmitted in group 2.

The donor liver functions showed transient liver enzyme elevation and hyperbilirubinemia in the immediate postoperative period, but these indices declined smoothly over a week in all donors (data not shown).

Morbidity and Mortality
The median postoperative follow-up of all donors was 60.7 months (range; 12.9–118.0 months). According to the Clavien classification, the overall complication rate in all living donors was 10.0% (50/500) (Table 3). The complication rates in various grades were 4.6% (23/500, grade I), 1.6% (8/500, grade II), 1.0% (5/500, grade IIIa), 2.6% (13/500, grade IIIb), and 0.2% (1/500, grade IVa). There was no complication of grade IVb or V. The overall complication rate was 16.0% (48/300, group 1) and 1.0% (2/200, group 2). The lower incidence of overall complication was distinct and statistically significant in group 2. And the complication rate of grade III was 6.3% (19/300, group 1) and 0% (0/200, group 2), which presented a significant difference between the 2 groups (\( P = 0.001 \)).

The most common complication was wound infection (2.7%, 13/500), which required no antibiotic treatment and was thus in grade I. The 2nd most common complication was postoperative bleeding (3.3%, 10/500), which needed

| TABLE 1. Characteristics of 500 Consecutive Living Donors |
|----------------------------------------------------------|
| **Characteristic**                                      | **Group 1** (n = 300) | **Group 2** (n = 200) | **Total** (n = 500) | **P Value** |
| Sex (M:F)                                                | 186:114                | 117:83                | 303:107             | 0.456       |
| Age, years                                              |                         |                       |                     | 0.430       |
| Median                                                  | 30                     | 34                    | 31                  |             |
| Range                                                   | 16–60                  | 16–76                 | 16–76               |             |
| Body mass index, kg/m²                                   | 23.0                   | 22.8                  | 22.9                | 0.635       |
| Range                                                   | 15.2–36.0              | 15.9–30.0             | 15.9–36.0           |             |
| Steatosis, %                                            |                         |                       |                     | 0.362       |
| Macrovesicular                                          |                         |                       |                     |             |
| Median                                                  | 0                      | 0                     | 0                   |             |
| Range                                                   | 0–30                   | 0–30                  | 0–30                |             |
| Microvesicular                                          |                         |                       |                     | 0.134       |
| Median                                                  | 5                      | 5                     | 5                   |             |
| Range                                                   | 0–40                   | 0–40                  | 0–40                |             |
| Remnant left liver/whole liver, % by computed tomography|                         |                       |                     | 0.902       |
| Volumetry                                               |                         |                       |                     |             |
| Median                                                  | 34.0                   | 34.8                  | 34.3                |             |
| Range                                                   | 23.1–50.7              | 25.2–48.6             | 23.1–50.7           |             |

Group 1, stepwise adjustment; Group 2, complete adherence to the protocol. Categorical and continuous variables were compared using the Fisher exact test and the Mann–Whitney U-test, respectively.
immediate reoperation and so was classified as grade IIIb. In group 1, 10 donors (3.3%) underwent reoperation due to bleeding immediately after operation, and 3 of those were given a blood transfusion. Another 3 donors (1.0%) were readmitted for reoperation on account of grade IIIb complications. One donor suffered video-assisted thoracoscopic surgery due to lung collapse caused by pleural effusion that had lasted 2 months after LDRH. One donor had hepaticojejunostomy under the same incision due to biliary stricture that failed endoscopic intervention 2 months after LDRH. One donor underwent relaparotomy for diaphragmatic hernia detected 23 months after LDRH, which was repaired by primary closure of the diaphragmatic defect. In group 2, there were only 2 cases (1.0%) of complication confined in grade I; wound infection and biloma, both of which cured with conservative management not lasting more than 2 weeks after operation.

Ultimately all donors recovered fully and resumed their previous activities without apparent adverse sequelae. Currently, the only donor out of touch in outpatient follow-up was due to motor vehicle crash death 2 years after the operation.

### DISCUSSION

This study has demonstrated that an SFER protocol can be implemented with excellent outcomes in LDRH. This SFER protocol evolved through stepwise acquisition of specific procedures over a 6-year period and 300 cases of LDRH with regard to time and experience, respectively, and was embedded into surgical practice in the authors’ institution. Any complication that had occurred played an important role to present an opportunity for refining a surgical protocol. So, this SFER protocol was actually made 1 step closer to finding a way that does not repeat the same complications based on a process of trial and error. A full SFER program was then in place by September 2011 after 300 LDRHs. From donor no. 301 in 2011 onwards, all LDRHs were performed with strict adherence to this fixed SFER protocol.

The 2 principles of this SFER protocol were 1st, to eliminate redundancy, and 2nd, to introduce new procedures to make surgery safe, speedy, and less invasive. The former includes discontinuation of intraoperative cholangiography, central venous catheterization, and intensive care unit stay, and serial reduction of the intravenous heparin dosage administered before graft removal. The latter was best exemplified by use of liver hanging maneuver from the start of parenchymal

| Outcome                      | Group 1 (n = 300) | Group 2 (n = 200) | Total (n = 500) | P Value |
|------------------------------|-------------------|-------------------|----------------|---------|
| Graft type                   |                   |                   |                |         |
| Right liver                  | 288 (96.0)        | 193 (96.5)        | 481 (96.2)     | 0.817   |
| Right liver with MHV         | 12 (4.0)          | 7 (3.5)           | 19 (3.8)       |         |
| Operation time, minute       |                   |                   |                | <0.001  |
| Median                       | 257               | 173               | 224            |         |
| Range                        | 146–414           | 104–305           | 104–414        |         |
| Blood loss, mL               |                   |                   |                | <0.001  |
| Median                       | 300               | 200               | 300            |         |
| Range                        | 100–1400          | 100–600           | 100–1400       |         |
| Blood transfusion, n         | 3 (1.0)           | 0 (0)             | 3 (0.6)        | 0.279   |
| Intensive care unit stay, days|                   |                   |                | <0.001  |
| Median                       | 0                 | 0                 | 0              |         |
| Range                        | 0–3               | 0–0               | 0–3            |         |
| Postoperative hospital stay, days |              |                   |                | <0.001  |
| Median                       | 8                 | 7                 | 8              |         |
| Range                        | 6–34              | 6–14              | 6–34           |         |
| Readmission, n               | 3 (1.0)           | 0 (0)             | 3 (0.6)        | 0.279   |

Group 1, stepwise adjustment; Group 2, complete adherence to the protocol. Values in parentheses are percentages unless indicated otherwise. Categorical and continuous variables were compared using the Fisher exact test and the Mann–Whitney U-test, respectively. MHV = middle hepatic vein.

**FIGURE 1.** A scatter diagram illustrating the relationship between the total operation time and the case numbers shows the fitted regression line obtained by the least squares estimates of simple linear regression analysis. The \( P \) value was calculated by a linear regression \( t \)-test.
transection by Glisson approach under upper midline incision above umbilicus, use of wound protector, and the method of "ligation & cut" in bile duct division. The time-points at which these various principles were introduced coincided with the time-points when an immediate change was necessary to eliminate apparent hazards or redundancy and to protect donor safety.

Previous work on ERAS program focused on multimodal postoperative management, which showed its beneficial impact on short-term complications, hospital stay, and return to normal activities. Moreover, there has been no report supporting the use of ERAS protocol after LDRH. Living donors generally constitute a homogenous healthy adult group that pass through rigorous medical and ethical checkups. Therefore, a standardized surgical procedure is warranted to further lower operative morbidity. The modifications in surgical technique and management in this study will suffice to illustrate the efforts to make the surgical procedure standardized in detailed areas of LDRH toward achieving a better outcome. So, LDRH under the SFER protocol was safe and speedy under upper midline incision with excellent outcomes.

Over the last decade, LDRH with laparoscopic or robotic assistance has received much attention, but was performed technically in only a few selected donors while taking a long operation time despite use of expensive equipment and new technology. The mini-skin incision procedure is considered an important element of minimally invasive living donor surgery because of its definitive cosmetic advantage. However, the hazard of prolonged operation time and the high cost of the additional equipment may represent another non-negligible invasiveness, resulting in the increased overall insult in living donors. However, upper midline incision above umbilicus introduced since 2008 in this study was feasible and efficient in 445 consecutive living donors from donor no. 55. Currently, the indications of upper midline incision for liver surgery in the authors’ institution are all living donors and patients with liver tumor less than 5 cm. The incision contributed to less operative time and fast recovery.

Surgical outcome of LDRH as in other liver surgery can be appraised in a 3-fold axis: intraoperative blood loss, operating time, and postoperative morbidity. Less blood loss and less morbidity should be a matter of the highest priority to determine the safety of surgery. But as long as the 2 are secured, the operative time should be reduced, because right-liver donation and prolonged donor operation time were shown to be independent risk factors of major complications in the donors. The median blood loss was 300 mL (range, 100–1400 mL) for all donors in this study. The operative blood loss was consistently kept in low among the 2 groups, but the upper limit of range was reduced from 1400 to 600 from group 1 to group 2. The operation time gradually became shorter and shorter overtime and experience. The significant reduction of operation time in group 2 could be attributed to technical innovation and proficiency achieved over 300 cases of LDRH in group 1. The wide difference of the operative duration even in group 2, where the shortest was 104 minutes and the longest was 305 minutes, was

### Table 3. Donor Complications Graded by the Clavien System

| Grade | Group 1 (n = 300) (Donors 1–300) | Group 2 (n = 200) (Donors 301–500) | Total (n = 500) (Donors 1–500) | P Value |
|-------|-------------------------------|----------------------------------|-----------------------------|---------|
| I     | 21 (7.0)                     | 2 (1.0)                          | 23 (4.6)                    | 0.002   |
|       | 12 Wound infections           | 1 Wound infection                | 13 Wound infections         |         |
|       | 4 Bilomas                     | 1 Biloma                         | 5 Bilomas                   |         |
|       | 3 Middle hepatic vein partial thromboses | 1 Middle hepatic vein partial thromboses |         |         |
|       | 1 Left portal vein partial thrombosis | 1 Left portal vein partial thrombosis |         |         |
|       | 1 Hematoma                    |                                  | 1 Hematoma                  |         |
| II    | 8 (2.7)                      | 0 (0)                            | 8 (1.6)                     | 0.024   |
|       | 3 Transfusion                 |                                  | 3 Transfusion               |         |
|       | 3 Mechanical ileus            |                                  | 3 Mechanical ileus          |         |
|       | 1 Hypophosphatemia            |                                  | 1 Hypophosphatemia          |         |
|       | 1 Main portal vein stenosis   |                                  | 1 Main portal vein stenosis |         |
| IIIa  | 5 (1.7)                      | 0 (0)                            | 5 (1.0)                     | 0.410   |
|       | 3 Bilomas                     |                                  | 3 Bilomas                   |         |
|       | 1 Pneumothorax                |                                  | 1 Pneumothorax              |         |
|       | 1 Biliary stricture           |                                  | 1 Biliary stricture         |         |
| IIIb  | 13 (4.3)                     | 0 (0)                            | 13 (2.6)                    | 0.002   |
|       | 10 Bleeding cases             |                                  | 10 Bleeding cases           |         |
|       | 1 Pleural effusion            |                                  | 1 Pleural effusion          |         |
|       | 1 Diaphragmatic hernia        |                                  | 1 Diaphragmatic hernia      |         |
|       | 1 Biliary stricture           |                                  | 1 Biliary stricture         |         |
| IVa   | 1 (0.3)                      | 0 (0)                            | 1 (0.2)                     | 0.999   |
|       | 1 Rhabdomyolysis              |                                  | 1 Rhabdomyolysis            |         |
| IVb   | 0 (0)                        | 0 (0)                            | 0 (0)                       | –       |
|       | 0 (0)                        | 0 (0)                            | 0 (0)                       | –       |
| Total, % | 48 (16.0)                  | 2 (1.0)                          | 50 (10.0)                   | <0.001  |

Group 1, stepwise adjustment; Group 2, complete adherence to the protocol. Values in parentheses are percentages unless indicated otherwise. 

## Footnotes

1. Fisher exact test.

## References

1. Handling of all living donors was stepwise adjustment; Group 2, complete adherence to the protocol. Values in parentheses are percentages unless indicated otherwise.
caused by the unanticipated long-waiting time for difficult recipient hepatectomy especially in patients having the history of previous liver resection, and by long operation time in living donors with intra-abdominal adhesion that were commonly related to previous abdominal surgery.

Safe and speedy surgery is a key success factor to improve the outcomes of LDRH. The SFER protocol consisting of various modifications in surgical technique and management resulted in the most recent morbidity of 1% in 200 donors without any major complications, reoperation, blood transfusions, or readmission. This is in contrast with the previous reports that the complication rates after LDRH have been in a range of 20% to 78.3% since it came into practice in 1996.26–32 The majority of LDRHs were completed less than 3 hours with the shortest at 106 minutes. This safety and stability helped build a strong foundation for stopping central venous catheterization and for bypassing intensive care unit stay, which contributed to avoid any procedure-related complication such as pneumothorax and to prevent intensive care unit-acquired infection, weakness, and delirium. Considering this whole series of 500 consecutive cases, LDRH will stand so good a chance of becoming a common procedure that it will be able to be performed safely with less morbidity in the hands of expert donor surgeons.

Donor safety, an uncompromisable issue, is ensured by 3 factors; preoperative evaluation of donor, intraoperative surgical technique, and postoperative care. This study focused mainly on intraoperative surgical procedure. Therefore, the protocols on donor selection and postoperative managements still need to be refined in keeping pace with the recent improved surgical techniques.

In conclusion, this study validated that the estimated morbidity and mortality of LDRH were 10% and 0%, respectively, and showed that an SFER protocol can be established based on continuous refinement of surgical technique and management, and that the morbidity can be reduced to 2% and confined in grade I complication under this SFER protocol. The recent outcomes reached through this SFER protocol could provide the current standard for LDRH toward the ultimate goal of zero morbidity.

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