Original Article

Anesthetic complications including two cases of postoperative respiratory depression in living liver donor surgery

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Abstract

Background: Living liver donation is becoming a more common means to treat patients with liver failure because of a shortage of cadaveric organs and tissues. There is a potential for morbidity and mortality, however, in patients who donate a portion of their liver. The purpose of this study is to identify anesthetic complications and morbidity resulting from living liver donor surgery.
Patients and Methods: The anesthetic records of all patients who donated a segment of their liver between January 1997 and January 2006 at University of Minnesota Medical Center-Fairview were retrospectively reviewed. The surgical and anesthesia time, blood loss, hospitalization length, complications, morbidity, and mortality were recorded. Data were reported as absolute values, mean ± SD, or percentage. Significance ($P < 0.05$) was determined using Student's paired *t* tests.
Results: Seventy-four patients (34 male, 40 female, mean age = 35.5 ± 9.8 years) donated a portion of their liver and were reviewed in the study. Fifty-seven patients (77%) donated the right hepatic lobe, while 17 (23%) donated a left hepatic segment. The average surgical time for all patients was 7.8 ± 1.5 hours, the anesthesia time was 9.0 ± 1.3 hours, and the blood loss was 423 ± 253 ml. Forty-six patients (62.2%) received autologous blood either from a cell saver or at the end of surgery following acute, normovolemic hemodilution, but none required an allogenic transfusion. Two patients were admitted to the intensive care unit due to respiratory depression. Both patients donated their right hepatic lobe. One required reintubation in the recovery room and remained intubated overnight. The other was extubated but required observation in the intensive care unit for a low respiratory rate. Twelve patients (16.2%) had complaints of nausea, and two reported nausea with vomiting during their hospital stay. There were four patients who developed complications related to positioning during the surgery: Two patients complained of numbness and tingling in the hands which resolved within two days, one patient reported a blister on the hand, and one patient complained of right elbow pain that resolved quickly. Postoperative hospitalization averaged 7.4 ± 1.5 days. There was no patient mortality.
Discussion: Living liver donation can be performed with low morbidity. However, postoperative respiratory depression is a concern and is perhaps due to altered metabolism of administered narcotics and anesthetic agents.

Key words: Anesthesia, complications, living liver donor surgery, respiratory depression

Introduction

Transplantation of a living-related liver segment was first attempted by Raia *et al.* in 1989.[1] This recipient died, but a successful transplant of the left lobe of a mother's liver to her child was performed by Strong *et al.* in 1989.[2] Initially, living liver donation was performed for infants or young children using the left lateral segment of the donor. However, with development of the use of the right donor hepatic lobe for adult recipients, adults now constitute approximately 75% of the patients who receive a living liver transplant in the United States. Currently, the graft survival at one and five years is similar in those who received organ from a living donor (86% and 70%, respectively) as those who received a cadaveric organ (82% and 67%, respectively), as is the overall patient survival.[3] Living liver donor surgery is now being performed throughout the world at major transplant centers.

Currently, there are many more patients throughout the world requiring a liver transplant than cadaveric organs available. For example, in 2006, 6 362 patients received a cadaveric

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.83683

liver transplant in the United States. Yet, there were still 12 548 patients needing liver transplantation at the end of the year.[3] Patients awaiting a liver transplant have high rates of depression as well as morbidity and mortality from their underlying liver disease.[4] Living liver donation is one means to treat patients in need of liver transplantation in an era of shortage of cadaveric donors. The use of live donor tissue is also potentially advantageous because the procedure can be planned appropriately and the condition of the recipient optimized for the operation. A live donor can provide an organ in an emergency where a cadaveric organ is not available. In addition, the use of living donors also provides a source for organs in countries such as Japan or India where custom and law makes the use of cadaveric organs difficult.[5,6]

However, living-related liver transplantation has the potential for significant morbidity in the donor from the hepatectomy and general anesthesia. Mortality from living liver donor surgery has been reported as well.[7-9] The purpose of this study was to identify the anesthetic complications and morbidity in the donor from living liver donor surgery.

Patients and Methods

After approval from the University of Minnesota Human Subjects Committee, the anesthetic records of all 74 patients who donated a portion of their liver between January 1, 1997 and January 1, 2006 at the University of Minnesota Medical Center-Fairview were retrospectively reviewed. The type of surgery (right lobe or left segment), anesthetic technique, monitors utilized, surgical and anesthetic time, blood loss, and hospitalization length were recorded. The records were specifically examined for anesthetic-related complications, morbidity and mortality for the immediate perioperative period and one year following surgery. The data were reported as the absolute values, mean ± SD, or percentage. Significance ($P < 0.05$) was determined using Student's paired *t* tests.

Results

Thirty-four men and 40 women donated a portion of their livers during this time period. The mean age and weight of the donors were 35.5 ± 9.8 years and 73.5 ± 12.8 kg, respectively. Fifty-seven patients (77%) donated their right hepatic lobe (adult recipients), while seventeen (23%) donated a left hepatic segment (child recipients). Sixty patients (81.1%) were designated as ASA physical status one and 14 patients (18.9%) were ASA physical status two.

General anesthesia was induced with either intravenous propofol (74%) or thiopental (26%), and fentanyl (97%) or sufentanil (3%). All patients were tracheally intubated. Tracheal intubation was facilitated usually with either cisatricurium (73%) or vecuronium (16%). One patient received succinylcholine for tracheal intubation. The remainder received either rocuronium or pancuronium for skeletal muscle relaxation. Anesthesia was maintained with isoflurane (68%) or desflurane (32%), a non-depolarizing skeletal muscle relaxant, and fentanyl (97%) or sufentanil (3%). Thirty-eight patients (52%) also received intravenous morphine in addition to fentanyl or sufentanil during the procedure. All patients were ventilated with an air-oxygen mixture with a FiO_2 from 40 to 60%. Controlled ventilation was used in all cases with a tidal volume of 7 to 10 ml/kg, positive end expiratory pressure of 4 to 8 mmHg, and a respiratory rate adjusted to produce an end-tidal carbon dioxide tension between 30 and 40 mmHg. Nitrous oxide was not utilized for any patient in this series.

Sixty-one donors (82%) had central venous pressures monitored through a catheter placed in the right internal jugular vein placed following induction of general anesthesia. All of the patients who donated their right hepatic lobe had their central venous pressures monitored. However, only one patient in the series had an arterial catheter placed for monitoring.

All patient received sodium mannitol (25 g) prior to beginning the hepatectomy to attempt to minimize edema formation in the hepatic specimen during dissection. All patients also received heparin (70 IU/kg) prior to ligation of the blood vessels in the specimen. The heparin was reversed with protamine following resection of the hepatic segment in all patients.

Most of the patients who underwent right hepatectomy, where more blood loss was anticipated than with the left segmentectomy, underwent acute normovolemic hemodilution to reduce loss of red blood cells, platelets, and clotting factors. In this procedure, the patients had 1 to 2 units (approximately 450 ml each) of whole blood withdrawn and stored in an Anticoagulant Citrate Phosphate Dextrose Solution, USP (CPD) Blood-Pack Unit® storage bag designed for this purpose (Baxter Healthcare Corporation, Deerfield, Illinois). The blood removed was replaced with either 5% albumin or Ringers' Lactate in an equal or greater volume as that removed as necessary to maintain hemodynamic stability. Blood lost during the hepatectomy therefore contained fewer red blood cells, platelets, and clotting factors. The blood removed was reinfused in all cases at the end of the hepatectomy prior to closure.

The blood lost during surgery was collected through suction during surgery and processed using a Cell Saver® device (Haemonetics Corporation, Braintree MA, USA). This

device collected blood lost and washed the cells to remove the potassium, plasma, and cell fragments in shed blood. The remaining red blood cells were suspended in normal saline and had a hematocrit of approximately 60%. The red blood cells collected in this manner were reinfused at the end of surgery. However, in most cases, there was not enough blood salvaged to be processed and reinfused [Table 1].

The average intraoperative blood loss was 423 ± 253 ml (range: 50-1 200 ml) and urine output was 870 ± 540 ml (range: 205-2 625 ml), respectively. Fluids and blood products administered during the operation are detailed in Table 1.

Though 46 patients (62.2%) required autologous blood from either a cell saver or intraoperatively following acute, normovolemic hemodilution, autologous predonation, and/or the cell saver, no patient needed an allogenic transfusion in the perioperative period. As might be expected, the hemoglobin level was lower in the recovery room (12.6 ± 2 g/dl) than prior to surgery (14.1 ± 1.4 g/dl; $P < 0.0001$).

Patients were under general anesthesia for an average of 9.0 ± 1.3 hours with an average surgical time of 7.8 ± 1.5 hours. The average total intraoperative fentanyl and sufentanil doses administered were 1 447 ± 602 μg (range: 100-2 900 μg) and 205 ± 21 μg (range: 190-220 μg), respectively. The average total morphine dose administered to the 38 patients who received morphine in addition to fentanyl or sufentanil was 10 ± 6.2 mg (range: 3-30 mg).

Following the surgery, 40 patients (54%) were extubated in the operating room and 34 (46%) were extubated after being moved to the recovery room. For the patients extubated in the recovery room, the average time they remained intubated prior to extubation, was 40 ± 37 minutes.

Most patients (66%) received intravenous fentanyl in the recovery room for postoperative analgesia (average dose: 145 ± 88 μg, range: 25-350 μg). Many patients received intravenous morphine instead or in addition to fentanyl (44%, average total dose: 7.8 ± 4 mg, range: 2-20 mg). Several other patients received hydromorphone (27%, average total dose: 1.17 ± 0.57 mg, range: 0.2-2 mg) and meperidine (5.5%, average total dose: 18.75 ± 7.22 mg, range: 12.5-25 mg). In addition, 29 patients (40%) received intravenous ketorolac for postoperative analgesia in the recovery room (average dose: 19.5 ± 6.6 mg, range: 10-30 mg).

The postoperative complications are listed on Table 2. Of special note was that one patient who had undergone a right donor hepatic lobectomy required reintubation in the recovery room following extubation in the operating room because of excessive sedation and a low respiratory rate. A second patient who also underwent a right hepatic donor lobectomy was successfully extubated in the recovery room but had to be transferred to the surgical intensive care unit to help manage prolonged sedation and respiratory depression. The patient maintained a spontaneous respiratory rate of only 2 to 3 breaths/minute for several hours after surgery and required constant encouragement by the nurses to ventilate adequately. However, this patient did not require reintubation.

Examination of the patient records revealed that both patients received doses of narcotics intraoperatively and in the recovery room that were similar to the other patients in the study. The first patient received total dose of 190 μg of sufentanil and 10 mg of morphine intraoperatively as well as 50 μg of fentanyl and 15 mg of ketorolac in the recovery room. The second patient received a total dose of 1 500 μg of fentanyl intraoperatively plus 10 mg of morphine. The patient later received 12.5 mg of meperidine in the recovery room.

The average postoperative stay was 7.4 ± 1.5 days (range:

Table 1: Perioperative fluids and blood products

Fluid type	Number of patients	Average volume administered (ml)
Normal saline or lactated ringer	74 (all patients)	3 972 ± 1 730 ml (Range: 1 200-9 600 ml)
5% Albumin	30	760 ± 489 ml (Range: 200-2 500 ml)
Cell saver	25	209 ± 105 ml (Range: 100-475 ml)
Autologous blood from acute, normovolemic hemodilution	38	452 ± 123 ml (Range: 150-700 ml)
Autologous blood from prior donation	1	350 ml

Table 2: Postoperative complications

Complication	Number of patients (%)	Treatment/resolution
Postoperative respiratory depression	2 (2.7)	One patient required reintubation and overnight ventilation. One patient required respiratory monitoring overnight in ICU
Postoperative nausea and vomiting	12 (16.2)	Resolved with anti-emetics
Paresthesias in hands	2 (2.7)	Resolved without treatment
Blister on hand	1 (1.3)	Resolved without treatment
Right elbow pain	1 (1.3)	Resolved without treatment
Abdominal pain and recurrent vomiting posthospital discharge	2 (2.7)	Resolved following readmission and intravenous analgesics

5-14 days). There was no patient mortality in this study.

Discussion

For living liver donation to have a major beneficial impact on the treatment of hepatic failure, the operation must be performed with low morbidity and no mortality. It is important that both the anesthetic and surgical complications related to this operation are identified and, if possible, prevented. Similar to other recent reviews, our study demonstrated that living liver donation could be performed safely without the need for allogeneic blood transfusion. The complications in our series such as nausea and vomiting and transient paresthesias from prolonged positioning have been described previously in other studies reviewing living liver donation.[7-11]

However, one complication noted that has not to our knowledge been described previously in living liver donors was the development of respiratory depression following surgery. Two patients required management in the intensive care unit because of prolonged sedation and a low respiratory rate. One patient required reintubation and postoperative ventilation. Both patients appeared to be suffering from a narcotic overdose, although excessive narcotics were not given intraoperatively or in the recovery room. This suggests that narcotic metabolism may be altered in patients undergoing living liver donation and may place living liver donors at risk for postoperative respiratory depression.

Rudin *et al.*[12] described higher plasma concentrations of morphine in 15 adult patients undergoing a resection of hepatic segments for tumors as well as prolonged clearance of morphine compared with 15 similar patients who underwent colon resection alone. The level of sedation was also higher in those patients who received liver resection than those who had colon surgery. The level of sedation was noted as well to be higher in the six patients who had more than 50 percent of their livers resected than those who had less removed. Similar to our experience, two of the 15 patients who underwent liver resection in Rudin *et al.*'s study developed significant respiratory depression following surgery. One of these patients had to be administered naloxone and monitored overnight in the postanesthesia care unit. Rudin *et al.* hypothesized that the reduction in morphine clearance was related to the acute reduction of liver function following surgery following hepatic resection, resulting in higher circulating morphine levels.[12] The same acute reduction in narcotic clearance might have caused the respiratory depression seen in the two patients in our series.

In contrast to the cancer patients reported in the series by Rudin *et al.*, patients undergoing hepatic resection for donation have healthy livers. However, there is some evidence that liver function may be acutely reduced following living liver donation. Niemann *et al.*[13] used indocyanine green to measure the hepatic function in 12 healthy adult living donors undergoing right hepatic lobectomy, similar to the two patients who developed respiratory depression in our study. The authors measured indocyanine green deposition during the dissection phase and immediately after removal of the hepatic lobe. The measurements were then repeated on postoperative day five. The average elimination constant for indocyanine green was reduced by 50% from baseline immediately following right hepatic lobectomy, and was still reduced by 25% from baseline on postoperative day five.[13] It is likely that the clearance of narcotics and other anesthetic agents are similarly reduced acutely following living liver donation.

Other pulmonary complications that have been reported following living liver surgery include pleural effusion and empyema, pneumothorax, bacterial pneumonia, and pulmonary embolism. Respiratory complications appear to occur most often after right hepatic lobectomy.[7] Adequate analgesia is essential to allow pulmonary toilet and early ambulation to prevent these respiratory complications, but may be difficult to safely provide if the metabolism of intravenous narcotics has been altered by the hepatic resection. Our study suggests that one must be cautious with the use of intravenous narcotics in patients who undergo hepatic resection of living liver donation, probably due to the reduced clearance of these agents.

An anesthetic technique utilizing nonopioid analgesia has been described by Feld *et al.*[14] for patients undergoing gastric bypass surgery for morbid obesity, where postoperative respiratory depression following narcotic administration is also a significant problem. In their technique, ketorolac, clonidine, lidocaine, ketamine, magnesium sulfate, and methylprednisolone were used in place of fentanyl intraoperatively, although narcotics are administered in the postoperative period. They studied 30 patients undergoing gastric bypass surgery for morbid obesity. Fifteen patients received the nonopioid regimen along with the inhaled agent, sevoflurane. The other 15 patients received intravenous fentanyl as 50 μg bolus doses as needed up to a maximum of 6 μg/kg of ideal body weight. The visual analogue pain scores and postoperative morphine consumption measured using patient-controlled analgesia devices were similar among the groups, but the level of sedation in the recovery room was significantly less in the patients who received the nonnarcotic technique.[14] Whether a similar nonnarcotic technique could prevent postoperative respiratory depression in living liver donor surgery needs to be studied.

Other means that have been suggested to provide analgesia to living liver donors include epidural analgesia and intrathecal narcotics. One recent study showed that epidural analgesia provided better analgesia with less sedation than patient-controlled analgesia for living liver donors.[15] However, an earlier study by Borromeo *et al.*[16] demonstrated a prolonged prothrombin time in five patients who donated a segment of their liver that persisted up to five days postsurgery. The authors hypothesized that the coagulation function of the liver is impaired following living liver donation. They suggested that the prothrombin time be used to guide removal of the epidural catheter to prevent the formation of an epidural hematoma. Borromeo *et al.* also recommended that anesthesiologists should be very cautious about using an epidural catheter for postoperative analgesia for living liver donation because of the impairment of coagulation following living liver donation and the risk of an epidural hematoma.[16]

Ko *et al.*[17] suggested that intrathecal morphine be utilized to provide analgesia for living liver donor surgery. Administration of the intrathecal morphine at the beginning of surgery at a time prior to beginning the liver resection when the patients' coagulation profile is normal is very unlikely to result in an epidural hematoma formation. Intrathecal morphine avoids the complications associated with placement and management of an epidural catheter in patients who eventually may develop a coagulopathy. They studied 40 patients undergoing living liver donor surgery, half of whom they administered 0.4 mg of intrathecal morphine prior to surgery. The patients who received the intrathecal morphine had significantly less pain at rest and with coughing 24 hours after surgery and required significantly less narcotics intravenously than those who received intravenous patient-controlled analgesia alone. There was no evidence of respiratory depression in either group, but there was a trend toward less sedation in the group that received intrathecal morphine. However, delayed respiratory depression has been associated with intrathecal narcotics use. Ko *et al.* recommended living donors who receive intrathecal morphine should receive monitoring of the oxygen saturation and respiratory rate for 24 hours after surgery.[17] On the other hand, our study illustrated that respiratory depression occurred in living liver donors who received intravenous narcotics alone. This suggests that all patients who donate a portion of their livers receive similar respiratory monitoring on the first day following surgery, regardless of the type of analgesia they receive.

In summary, our study demonstrates that patients can safely undergo living liver donation with little blood loss and few complications. However, there is potential for postoperative respiratory depression, perhaps due to altered metabolism of narcotics and anesthetic agents following liver resection. Anesthesiologists should ensure that patients undergoing living liver donation receive careful respiratory monitoring in the postoperative period to keep postoperative complications from living liver donation low and benefit both living liver donors and recipients.

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How to cite this article: Beebe D, Singh H, Jochman J, Luikart P, Gruessner R, Gruessner A. Anesthetic complications including two cases of postoperative respiratory depression in living liver donor surgery. J Anaesth Clin Pharmacol 2011;27:362-6.
Source of Support: Nil, **Conflict of Interest:** None declared.