Epidural Analgesia Provides Better Pain Management After Live Liver Donation: A Retrospective Study

Hance Clarke,[1,2] **Tony Chandy,**[1,2] **Coimbatore Srinivas,**[1,2] **Salima Ladak,**[1,2] **Nobuhiko Okubo,**[1] **Nicholas Mitsakakis,**[1,2] **Susan Holtzman,**[3] **David Grant,**[4] **Stuart A. McCluskey,**[1,2] **and Joel Katz**[1,2,5]
[1]*Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, Toronto, Canada;* [2]*Department of Anesthesia, University of Toronto, Toronto, Canada;* [3]*Department of Psychology, University of British Columbia–Okanagan, Kelowna, Canada;* [4]*Multiorgan Transplant Program, University Health Network, University of Toronto, Toronto, Canada;* [5]*Department of Psychology and School of Kinesiology and Health Science, York University, Toronto, Canada*

Despite the increase in surgical volumes of live liver donation, there has been very little documentation of the postoperative pain experience. The primary aim of this study was to examine the difference in acute postoperative pain intensity and adverse effects between patients who received intravenous patient-controlled analgesia (IV PCA) or patient-controlled epidural analgesia (PCEA) for pain control after live liver donation surgery. A retrospective chart review was performed of 226 consecutive patients who underwent right living donor hepatic surgery at the Toronto General Hospital, Toronto, Canada. Patients who received as their primary postoperative analgesic modality IV PCA (n = 158) were compared to patients who received PCEA (n = 68). Demographic profiles for the 2 groups were similar with respect to age, sex, and body mass index at the time of surgery. For the first 3 postoperative days, pain intensity was significantly lower in patients who received epidural analgesia ($P < 0.01$). Clinically significant moderate pain (defined as a Numeric Rating Scale pain score >4) was reported more frequently in the IV PCA group ($P < 0.05$) along with increased sedation ($P < 0.05$). Pruritus was reported more frequently in the PCEA group of patients compared to the IV PCA group ($P < 0.05$). Significant between-group differences were not found for the incidence of postoperative vomiting, the time at which patients began fluid intake, the time to initial ambulation, or the length of hospital stay. In conclusion, epidural analgesia provides better postoperative pain relief, less sedation, but more pruritus than IV PCA after live liver donation.

Received May 29, 2010; accepted November 4, 2010.

Live liver donation has become a viable option for liver transplantation.[1] Advances in surgical techniques and anesthesia safety have made live liver donation a safe procedure.[2,3] Early studies examining live liver donation revealed that appropriate patient selection was a critical factor in preventing postoperative complications.[4,5] Therefore, before donating a liver, the donor undergoes extensive preoperative screening to ensure patient safety.[5] Psychosocial predictors of donor outcomes, as well as the financial, vocational, and interpersonal impact of live liver donation have been recently reported.[6,7]

Opioid-based analgesia has been the modality of choice for perioperative analgesia after right live donor hepatectomy (RLDH) because opioids are useful in the treatment of moderate to severe pain.[8,9] Standard perioperative pain management practice often relies on opioids as the primary pain medication via the

Abbreviations: APS, acute pain service; AUPC, area under the pain score curve; IV, intravenous; NRS, numeric rating scale; PACU, postanesthetic care unit; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; POD, postoperative day; RLDH, right live donor hepatectomy; SD, standard deviation.

Address reprint requests to Hance Clarke, MSc, FRCPC, Department of Anesthesia and Pain Management, Toronto General Hospital, 200 Elizabeth Street, Eaton North 3 EB 317, Acute Pain Research Unit, Toronto, Ontario M5G 2C4, Canada. Telephone: 416-340-4800, ext. 6649; Fax: 416-340-3698; E-mail: hance.clarke@uhn.on.ca

TABLE 1. Baseline Characteristics Prior to the Initiation of Postoperative Pain Modality

Variable	Group: i.v. patient-controlled analgesia (N = 158)	Group: Patient-controlled epidural analgesia (N = 68)
Age (years)	36.4 ± 11.5	36.2 ± 11.1
Sex (M/F)	76 / 82	28 / 40
Body mass index (BMI)	25.2 ± 3.9	25.1 ± 3.8
Intraoperative fentanyl (μg)	478.9 ± 205.4*	311.32 ± 171.1*
Intraoperative morphine (mg)	9.6 ± 7.9*	2.1 ± 3.6*

Data are mean ± SD. Asterisk (*) represents significant difference between groups ($P < 0.001$).

administration of intravenous patient-controlled analgesia (IV PCA). However, opioids tend to be ineffective for pain that is associated with movement and have significant short-term side effects including nausea, vomiting, sedation, pruritus, constipation, urinary retention, and respiratory depression,[10] which are factors that often hinder a patient's recovery. Epidural analgesia has become an accepted alternative to IV PCA. Prospective randomized trials have found epidural analgesia to be superior to IV PCA in several surgical populations.[11-13]

The physiologic effects of thoracic epidural anesthesia on the cardiovascular, respiratory, and gastrointestinal systems have been well documented.[14-16] Epidural analgesia works by inhibiting afferent impulses, blunting neuronal transmission from the periphery to the central nervous system and by inhibiting sodium channels at the level of the spinal cord.[15,17] Two systematic reviews have demonstrated that epidural analgesia provides superior pain relief up to 72 hours after intra-abdominal surgery when compared to IV PCA.[18,19] Studies have demonstrated that epidural analgesia is associated with fewer postoperative pulmonary complications and lower postoperative opioid consumption.[15,16] The use of epidural analgesia has also been associated with early return of bowel function, a shorter length of stay in hospital,[15,16,20-22] enhanced functional exercise capacity, and better health-related quality of life.[23]

Although effective postoperative pain management is of great importance to patients, there have been few reports documenting postoperative pain intensity after live liver donation.[24-26] One study, which compared patients who underwent right lobe donor hepatectomy with patients who had undergone major hepatic resection for tumor, found that patients who underwent RLDH had significantly more intense pain and were 2.76 times more likely to report increased pain at all postoperative time points.[24] Studies have prospectively examined postdonation changes in health-related quality of life after liver donation surgery.[27-29] Of these prospective studies, only 1 addressed postoperative pain, and the authors reported that the patient's anticipation of their postoperative pain was far worse than their actual experience of it.[28] The authors recommended further study of postoperative pain after live liver donation surgery.

Despite the potential advantages of epidural analgesia, the risk of an extremely rare but significant complication such as an epidural hematoma has led several transplant centers to abandon the use of epidural analgesia.[1] However, there has been minimal published evidence with respect to epidural use in the live liver donor population. The abandonment of epidural use in this highly functioning population is a decision that should not be taken lightly. Detailed documentation of these patients' postoperative pain experiences and the effect of postoperative pain on their subsequent quality of life is an important outcome yet to be investigated.

The primary aim of this study was to examine difference in postoperative pain intensity and adverse effects between patients who received IV PCA or patient-controlled epidural analgesia (PCEA) for pain control after live liver donation surgery. A secondary aim was to determine whether postoperative complications and length of hospital stay differed significantly between patients that received IV PCA or PCEA.

PATIENTS AND METHODS

The study was reviewed and approved by the Research Ethics Board of the Toronto General Hospital, University Health Network, Toronto, Canada. We performed a retrospective analysis of pain intensity scores, analgesic consumption, and postoperative side effects after live liver donation. The Toronto General Hospital is a major liver transplant center, which performs more than 120-150 liver transplants annually. Live liver donation accounts for one-third of all organ transplants at our institution (150 of 490 transplants). Consecutive patients who had undergone elective RLDH surgery between April 2004 and January 2009 (n = 226) were identified using institutional electronic databases. A total of 158 patients received IV PCA, and the other 68 patients received PCEA devices for control of postoperative pain. Prior to attending the preoperative anesthesia consultation clinic

visit, patients were seen by their attending surgeon. Following that encounter, all patients were booked for a preoperative anesthesia consultation. At the anesthesia assessment visit, all risks/benefits of placing an epidural catheter (ie, infection, hypotension, postural dizziness, risk of epidural hematoma leading to paralysis) versus IV PCA (nausea, vomiting, urinary retention, and ileus and respiratory depression) perioperatively were discussed with each individual patient. Patients were not asked to choose between the postoperative pain modalities at that visit. Rather, they were asked to think about it and inform their anesthesiologist on the morning of surgery whether they wanted a PCEA or an IV PCA for postoperative pain control. Electronic documents of all identified patients were made available and reviewed.

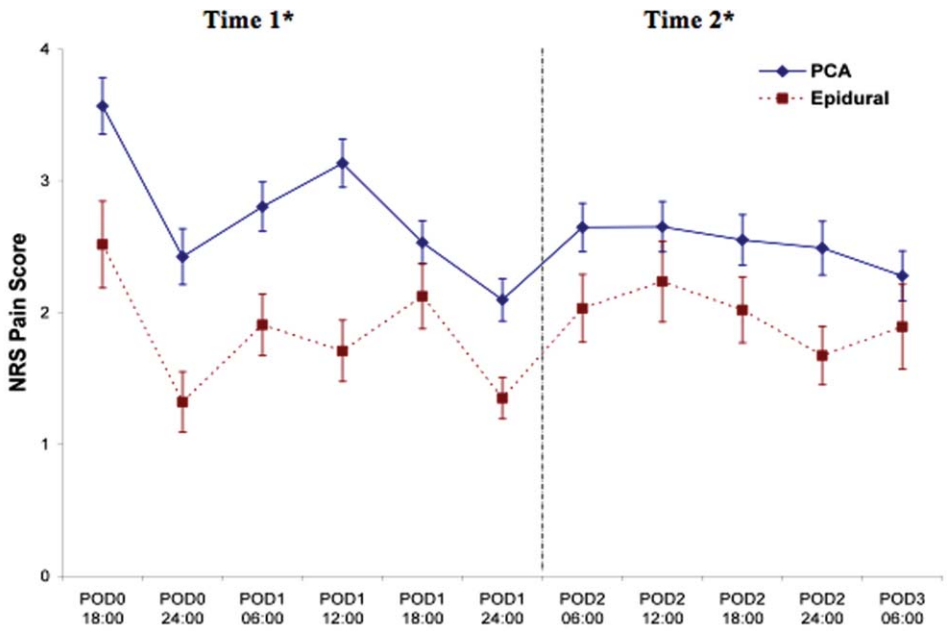
The perioperative pain management protocol for living donor hepatectomy is standardized. Patients who consented to receive a thoracic epidural had the catheter placed in the sitting position before induction of anesthesia. The standard site of epidural catheter placement is typically between thoracic levels T7 to T10. A standardized test dose of 3 mL of 2% lidocaine was injected to confirm appropriate epidural placement.

All patients had standard Canadian Anesthesiology Society monitors placed for surgery and were monitored using a radial arterial blood pressure transducer and internal jugular central venous pressure transducer. General anesthesia was induced using 1-2 mg/kg body weight of propofol, 1-2 μg/kg of fentanyl, and a nondepolarizing muscle relaxant to facilitate endotracheal intubation. The triple lumen central venous catheter was placed under ultrasound guidance (Sonosite; Bothell, WA). The central venous pressure was maintained between 2 and 6 mm Hg during liver resection. General anesthesia was maintained with a volatile anesthetic agent (isoflurane, sevoflurane, or desflurane). PCEA infusions were typically commenced within the first 2 hours after the start of surgery. For patients who were to receive IV PCA for postoperative pain control, intraoperative opioid boluses were given at the discretion of the attending anesthesiologist. For those patients who received epidural analgesia, epidural pumps were prepared by our postanesthetic care unit (PACU) on the morning of surgery and brought to the operating room. Typically, we do not receive the epidural pumps until patients are anesthetized and positioned for surgery. Other than the initial bolus of 3-5 mL of lidocaine into the epidural to confirm that the catheters were not intrathecal, boluses are kept to a minimum intraoperatively. The practice at our institution is to run the epidurals during the surgery because it also helps to decrease the central venous pressures, which helps to minimize blood loss. After surgery, all patients were extubated in the operating room or PACU. Shortly after arriving in the PACU, all patients were given a hand-held push-button that controlled the PCEA or IV PCA device, and recording of their analgesic consumption was begun. All patients were transferred to the surgical step-down ward upon discharge from the PACU.

The Acute Pain Service (APS) at the Toronto General Hospital has standardized algorithms for managing postoperative pain. Patients with thoracic epidurals placed below the T6 dermatome received a 0.1% bupivacaine solution with 0.015 mg/mL hydromorphone. The epidural infusion was delivered via an Abbott GemStar (Hospira, Lake Forest, IL) pump at a rate of 5 mL/hour (with a 3 mL bolus, 20-minute lockout period, and a 4-hour maximum of 50 mL). Patients in the PCEA group were not given IV opioids during the acute postoperative period. IV PCA was administered with an Abbott LifeCare PCA II (Hospira, Lake Forest, IL) pump using a hydromorphone concentration of 0.4 mg/mL boluses at a dose of 0.2-0.4 mg with a 5-minute lockout period and a 4-hour maximum of 10 mg or using a morphine concentration of 1 mg/mL boluses at a dose of 1.0-2.0 mg with a 5-minute lockout period and a 4-hour maximum of 40 mg. Patients received both hydromorphone and morphine IV PCA pumps. We converted opioid consumption use into morphine equivalents. The number of patients varies in Fig. 1 due to the inherent issues with retrospective reviews, because not all patients provided data at every time point. Acetaminophen is not prescribed to living related donors until the surgeons are comfortable with liver function. Nonsteroidal antiinflammatory drugs are also not routinely prescribed in the early postoperative period.

Pain intensity was measured with a numeric rating scale (NRS). The NRS consists of a series of numbers ranging from 0 to 10 with endpoints representing the most extreme pain experiences (0 = no pain and 10 = worst possible pain). The NRS has been shown to have good reliability and validity and is sensitive to change following pharmacological intervention.[30] Clinically significant moderate pain is defined as a score greater than 4 out of 10, with severe pain being reported as pain greater than 6 out of 10 on the NRS.[31,32] Pain intensity was measured using the NRS every 4 hours by the attending nursing staff following surgery until discharge from the APS. The APS reviewed each patient a minimum of 2 times per day while the epidural was in situ and once per day while the IV PCA was in use. If patients reported a pain score equal to or greater than 5 of 10 on 2 consecutive time points (after having been assessed by the ward nurse and deemed to be using the PCEA or IV PCA device adequately), the patient's attending nurse paged the APS physician, who then visited the patient and adjusted the epidural rate or the IV PCA settings as needed to ensure patient comfort.

Data from the postoperative period was manually obtained from the scanned version of the paper chart, including APS records (ie, postoperative analgesic mode [IV PCA versus PCEA], pain intensity scores, volume of epidural solution infused, opioid consumption, side effects [sedation, pruritus, nausea, and vomiting] and the duration of patient care by the APS), physiotherapy notes (day of ambulation),



PCA (*n*)	123	139	153	142	141	124	142	112	116	98	104
Interval morphine consumption (every 12 hours) (mg)	0.3 ± 2.2		20.3 ± 18.1		21.8 ± 15.2		15.7 ± 12.2		13.6± 14.2		10.3± 14.2
Epidural (*n*)	58	62	65	62	64	57	61	51	50	43	47
Interval Volume of Epidural Solution used (mL)			130.6 ± 16.3				143.4± 27.6				191.6 ± 32.7

Postoperative Day and Time

Figure 1. Effects of postoperative analgesic modality on postoperative pain. Data are expressed as mean ± standard error of the mean. Postoperative pain intensity was significantly lower in patients who received epidural analgesia. The AUPC was significantly lower in patients who received epidural analgesia versus those who received IV PCA throughout both Time 1 ($P = 0.00005$) and Time 2 ($P = 0.019$).

nursing documentation records (diet advancement), and drug administration record (supplemental analgesic use). Data were obtained at specific daily time points of 06:00, 12:00, 18:00, and 24:00 when under the care of the APS. Pain scores were collected from postoperative day (POD) 0 (day of surgery) until patients were discharged from the APS. Demographic information including sex, age, height, and weight were also recorded from the electronic records. All patients received an American Society of Anesthesiologists classification score of 1 or 2.

The presence or absence of sedation, nausea, vomiting, and pruritus was recorded from the electronic records. We also recorded the time to achieve initial ambulation, when oral fluid intake first occurred, and the date of hospital discharge.

Statistical Analysis

The primary outcome variable of interest was pain intensity scores across the first 3 days after surgery. For each patient, we computed 2 measures of area under the pain curve (AUPC): (1) Time 1: from POD0 18:00 to POD1 24:00 (total of 6 time points covering 30 hours) (2) Time 2: from POD1 24:00 to POD3 06:00 (total of 6 time points covering 30 hours). In computing the AUPC, patients were excluded if they (1) had more than 2 pain scores missing during the time period or (2) were missing pain scores for 2 or more consecutive time points. For the remaining patients, missing pain scores were imputed by calculating the mean of the pain scores of the adjacent time points.

For the comparison of AUPC values between the 2 treatment groups, the analysis was adjusted for potential confounding factors. This was particularly important because the study was not a randomized controlled trial and potential biases between the groups were therefore minimized by statistically controlling for age, sex, and surgeon via stratification using the nonparametric Aligned Rank test.[33] This test is known to be more powerful than the van Elteren test.[34] For the stratification according to age, the data were dichotomized based on the median age value. For the comparison of adverse events, the data were dichotomized representing presence or absence of sedation, nausea, vomiting, and pruritus.

Demographic and clinical variables were compared between the two groups using Wilcoxon test for continuous (or ordinal) variables and Fisher's exact test

for categorical variables. All calculations were performed using SAS statistical software package version 9.2 (SAS Institute, Inc., Cary, NC) and R software environment version 2.10 (The R Foundation for Statistical Computing, Vienna, Austria), under the Microsoft Windows XP Professional (version 2002, Service Pack 3; Microsoft Corp., Redmond, WA) operating system.[35]

RESULTS

The patients receiving postoperative epidural analgesia and those receiving IV PCA were similar with respect to age, sex, and body mass index. Patients who chose IV PCA for postoperative pain control received significantly more intraoperative opioids than patients who opted for a PCEA ($P < 0.001$; Table 1).

Pain Scores

Figure 1 shows the NRS pain scores across the 2 time periods as well as the IV PCA and PCEA groups' consumption of analgesics/epidural solution. Overall, postoperative pain was better controlled with the use of epidural analgesia. The AUPC was significantly smaller in patients who received PCEA versus IV PCA throughout both Time 1 ($P < 0.00005$) and Time 2 ($P = 0.019$). The analysis shows that postoperative pain was significantly less intense from POD0 to the morning of POD3 for patients who received epidural analgesia as their primary pain modality. In order to control for possible bias within this retrospective database, a secondary analysis of pain scores which were stratified for age, sex, and surgeon also demonstrated that the AUPC was significantly smaller in patients who received PCEA versus IV PCA for both Time 1 ($P < 0.0001$ all time points) and Time 2 ($P = 0.05$ all time points; Table 2).

TABLE 2. Stratified Analysis of Age, Sex, and Surgeon

	Stratifying Factors (*P* Values)		
AUPC	Age + Sex	Age + Surgeon	Sex + Surgeon
Time 1	<0.0001*	<0.0001*	<0.0001*
Time 2	0.0369*	0.0212*	0.0267*

*$P < 0.05$ at all time points, pain was significantly lower in patients that received PCEA vs. i.v. PCA across both Time 1 and Time 2 regardless of the variables tested.

Clinically Significant Moderate Pain

Clinically significant moderate pain, defined as an NRS score greater than 4,[31] was reported significantly less often in the epidural group than the IV PCA group at POD0 24:00 ($P < 0.01$), POD1 06:00 ($P < 0.05$), POD1 12:00 ($P < 0.05$), and POD1 24:00 ($P < 0.01$; Table 3)

Adverse Effects

Sedation was present more often in the IV PCA group when compared to patients who received PCEA at various time points until the morning of POD3 (Table 4). The reported incidence of pruritus was higher in the PCEA group (Table 5). Patients who received PCEA also demonstrated a higher incidence of nausea on the morning of POD3 (Table 6). Vomiting rarely occurred, and the incidence did not differ significantly between the groups.

Hospital-Based Outcomes

Table 7 demonstrates that significant intergroup differences were not found with respect to the time that oral fluid intake was initiated, the time to initial ambulation, or the length of hospital stay.

TABLE 3. Number of patients in the i.v. PCA and PCEA groups that reported numeric rating scale pain intensity scores > 4. Data were analyzed by Fisher's exact test

Postoperative Day and Time	i.v. PCA No./Total (%)	PCEA No./Total (%)	*P* Value*
POD0 18:00	42/123 (34)	14/58 (24)	0.23
POD0 24:00	29/139 (21)	3/62 (5)	0.003*
POD1 06:00	37/153 (24)	7/65 (11)	0.026*
POD1 12:00	36/142 (25)	4/62 (6)	0.002*
POD1 18:00	23/141 (16)	6/64 (9)	0.28
POD1 24:00	15/124 (12)	0/57 (0)	0.003*
POD2 06:00	29/142 (20)	8/61 (13)	0.24
POD2 12:00	19/112 (17)	6/51 (12)	0.49
POD2 18:00	19/116 (16)	5/50 (10)	0.34
POD2 24:00	16/98 (16)	3/43 (7)	0.18
POD3 06:00	13/104 (13)	4/47 (9)	0.59

Abbreviations: i.v. PCA, intravenous patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; POD, postoperative day.
*Indicates significant difference $p<0.05$.

TABLE 4. Incidence of Sedation

Postoperative Day and Time	i.v. PCA (%)	PCEA (%)	P Value
POD0 18:00	79.0	61.6	0.02*
POD0 24:00	80.6	61.9	0.004*
POD1 6:00	58.1	43.9	0.05
POD1 12:00	44.4	36.9	0.31
POD1 18:00	39.4	30.3	0.21
POD1 24:00	59.1	46.7	0.11
POD2 06:00	45.9	33.9	0.12
POD2 12:00	45.7	25.9	0.01*
POD2 18:00	36.1	18.9	0.03*
POD2 24:00	54.5	46.5	0.46
POD3 06:00	48.1	23.4	0.004*

POD = Postoperative Day.
*Indicates significant difference $P < 0.05$.

TABLE 5. Incidence of Pruritus

Postoperative Day and Time	i.v. PCA (%)	PCEA (%)	*P* Value
POD0 18:00	2.4	3.3	0.66
POD0 24:00	0.0	0.0	n/a
POD1 6:00	3.2	16.4	0.001*
POD1 12:00	4.9	13.6	0.04*
POD1 18:00	2.12	15.1	0.0008*
POD1 24:00	3.8	10.0	0.1
POD2 06:00	7.0	10.1	0.56
POD2 12:00	5.2	9.3	0.3
POD2 18:00	5.7	15.1	0.07
POD2 24:00	2.1	14.3	0.01*
POD3 06:00	2.9	4.3	0.7

POD = Postoperative Day.
*Indicates significant difference $P < 0.05$.

DISCUSSION

Given the excellent health status and high functional disposition of live liver donors, the pain experienced upon awakening from surgery is often the patient's first experience with significant pain. Throughout the early postoperative time period, patients using IV PCA devices reported significantly more intense pain compared to patients who received PCEA (Fig. 1). Although the mean pain scores depicted in Fig. 1 are by and large below an NRS score of 3, we further examined each time point with respect to the number of patients who reported moderate pain (ie, NRS > 4 out of 10).[36] The NRS cut-point corresponding to the transition from mild to moderate pain occurs when a patient reports a pain score greater than 4 out of 10; the cut-point for moderate to severe pain corresponds to an NRS pain score greater than 6 out of 10.[31,32,37] Table 3 demonstrates that until POD2, significantly more patients in the IV PCA group reported more clinically significant postoperative pain (ie, reported pain scores greater than 4 out of 10) than did patients in the PCEA group. Severe pain was a very rare occurrence in both groups. Given that the *P* value for Time 2 ($P = 0.019$) in Fig. 1 demonstrates less overall significance than the *P* value of Time 1 ($P < 0.00005$), we accept the criticism that the difference in postoperative pain demonstrated at Time 2 may or may not be of clinical significance. The significant between group difference in intraoperative opioid administration (Table 1) may have also contributed to the greater postoperative pain scores in the IV PCA group. Evidence shows that opioids, such as fentanyl, paradoxically activate pronociceptive systems associated with acute opioid tolerance and opioid-induced hyperalgesia.[38-41] Thus, it is possible that the more intense pain in the IV PCA group may be due, in part, to the greater systemic dose of intraoperative opioids, in particular fentanyl.

The limited literature evaluating the effect of different modes of postoperative analgesia among live liver donors is not surprising because this surgery has a relatively short history. Yong and colleagues found no difference in the intensity of postoperative pain between those receiving epidural analgesia when compared to those receiving IV PCA.[25] Cywinski and colleagues demonstrated that live liver donor patients had more significant pain as compared to patients with liver malignancies.[24] The authors attributed the lack of adequate pain control in the live donors to the increased surgical time and to the lack of appropriate nursing care/knowledge with respect to the PCEA devices.[24]

Millions of patients undergo surgery on an annual basis in North America to remedy diseased states.[42] However, surgery for living organ donation is different in many respects. Healthy patients subject themselves to an otherwise unnecessary surgery for an altruistic cause. Although every aspect of the donor surgery is important, the patient's postoperative pain experience should not be overlooked. Patients' experiences in the immediate postoperative period often shape their recovery trajectories, their ability to resume normal activities, and their willingness to recommend live liver donation to other healthy, highly functioning individuals. A painful experience could conceivably limit a patient's willingness to recommend this altruistic act to others who may be considering potential liver donation.[43] Given that previous studies have demonstrated a higher incidence of postoperative pain than patients had anticipated,[43-45] this aspect of the liver transplant experience demands future attention.

Epidural analgesia is extremely safe; however, the literature does report a very low risk of patients developing an epidural hematoma (ie, 1:150,000 patients).[46,47] Although epidural hematomas are extremely rare, the consequences can be catastrophic with paralysis as the result. Postoperative coagulopathy can occur in a subset of patients (manifested as a transient prolongation of international normalized ratio and prothrombin times),[48] which could potentially increase the risk of developing an epidural

hematoma, although to our knowledge, there have been no published reports of epidural hematomas after live liver donor surgeries. Unfortunately, the very rare incidence of an epidural hematoma precludes the study of this adverse event in a prospective trial. A report that reviewed the use of epidural analgesia for live liver donors found that although the coagulation profiles were abnormal in some patients, values returned to baseline by POD3 and there were no reports of epidural hematomas.[48]

At our institution, of the 226 live liver donor operations analyzed, only 68 patients received epidural analgesia as their primary analgesic modality. This general trend is not surprising given the reluctance of the perioperative team to expose such highly functioning patients to the risk of a catastrophic event. In recent years, epidural analgesia has become more popular with anesthesiologists for hepatic carcinoma resections.[24,49] Clearly, the safety of epidural analgesia after live liver donation requires further study.

Animal models have demonstrated that acute hepatic failure causes increased plasma levels of systemic opioids[50]; therefore, sedation following liver resection may be an early sign of liver insufficiency. Table 1 demonstrates that patients without PCEA received significantly more opioids intraoperatively, which most likely added to the increased sedation found at POD0 18:00 (Table 4). However, beyond that initial time point, the increased interval opioid usage by the IV PCA group is presented in Fig. 1 and is congruent with the increased sedation demonstrated by this group in Table 4. Our current results are supported by a previous study that also found that the use of PCEA for primary pain relief after liver resection has reduced the amount of systemic opioids administered to patients by more than 50%.[51] The increased incidence of pruritus (Table 5) reported by the PCEA group can be improved by removing the opioid from our epidural solutions. Furthermore, the use of an opioid-free epidural may not only offer excellent pain control, it may also reduce side effects and should not affect liver function or the ability of the transplant team to detect early liver insufficiency.

There are several limitations to our retrospective analysis. First, given the retrospective nature of the data collected, adequate standardization of postoperative care was unlikely. Second, coagulation profiles of our patients were not collected because it was not one of the aims of our study. Limited coagulation profile data, even if collected in our population, would likely be insignificant with respect to determining the risk of perioperative bleeding and the potential risks associated with the development of an epidural hematoma. Finally, pain data were not available after patients were discharged from the APS.

The results of this study demonstrate that the use of PCEA significantly reduces moderate pain in the early postoperative period among patients who had undergone living donor hepatectomy when compared to use of IV PCA. Significant pain relief was noted up to the morning of postoperative day 3. Ongoing research is being conducted by the Adult to Adult Living Donor Liver Transplantation (A2ALL) Consortium with respect to long-term health-related quality of life after live liver donation. It is imperative that the following aspects of live liver donation surgery be thoroughly investigated: pain experience, the potential risks/benefits of epidural analgesia relative to other analgesic modalities, and that the physical, psychological, and long-term effects on the functioning of these patients continue to be documented. The remote possibility of the occurrence of an epidural hematoma is not sufficient rationale to dismiss this modality of pain control for all patients undergoing live liver donation. Collecting data in a prospective manner would help to validate or refute the current results and improve patient preoperative awareness and informed consent for live liver donation.

TABLE 6. Incidence of Nausea

Postoperative Day and Time	i.v. PCA (%)	PCEA (%)	P Value
POD0 18:00	4.8	8.3	0.34
POD0 24:00	3.5	3.1	1.0
POD1 6:00	4.4	2.9	0.72
POD1 12:00	4.9	7.5	0.52
POD1 18:00	1.4	3.0	0.59
POD1 24:00	1.5	1.6	1.0
POD2 06:00	7.0	3.3	0.56
POD2 12:00	11.3	5.6	0.39
POD2 18:00	6.6	3.8	0.72
POD2 24:00	4.1	2.4	1.0
POD3 06:00	3.0	12.8	0.03*

POD = Postoperative Day.
*Indicates significant difference $P < 0.05$.

TABLE 7. Postoperative Milestones

Variable	N	i.v. PCA	N	PCEA	*P* Value
Commencing fluid sips (days)	125	1.6 ± 1.0	52	1.6 ± 0.9	0.9
Time to ambulation (days)	127	1.8 ± 1.0	56	1.9 ± 1.0	0.22
Length of hospital stay (days)	158	6.5 ± 1.7	68	6.6 ± 1.7	0.69

Data are mean ± SD. Significant differences were not found between groups.

REFERENCES

1. Hwang GS, McCluskey SA. Anesthesia and outcome after partial hepatectomy for adult-to-adult donor transplantation. Curr Opin Organ Transplant 2010;15:377-382.
2. Belghiti J. Will improved donor safety increase liver donations? Transplantation 2009;88:19-20.
3. Hashikura Y, Ichida T, Umeshita K, Kawasaki S, Mizokami M, Mochida S, et al. Donor complications associated with living donor liver transplantation in Japan. Transplantation 2009;88:110-114.
4. Basaran O, Karakayali H, Emiroglu R, Tezel E, Moray G, Haberal M. Donor safety and quality of life after left hepatic lobe donation in living-donor liver transplantation. Transplant Proc 2003;35:2768-2769.
5. Pascher A, Sauer IM, Walter M, Lopez-Haeninnen E, Theruvath T, Spinelli A, et al. Donor evaluation, donor risks, donor outcome, and donor quality of life in adult-to-adult living donor liver transplantation. Liver Transpl 2002;8:829-837.
6. DuBay DA, Holtzman S, Adcock L, Abbey S, Greenwood S, Macleod C, et al. Adult right-lobe living liver donors: quality of life, attitudes and predictors of donor outcomes. Am J Transplant 2009;9:1169-1178.
7. Holtzman S, Adcock L, DuBay DA, Therapondos G, Kashfi A, Greenwood S, et al. Financial, vocational, and interpersonal impact of living liver donation. Liver Transpl 2009;15:1435-1442.
8. Aubrun F, Monsel S, Langeron O, Coriat P, Riou B. Postoperative titration of intravenous morphine. Eur J Anaesthesiol 2001;18:159-165.
9. Aubrun F, Salvi N, Coriat P, Riou B. Sex- and age-related differences in morphine requirements for postoperative pain relief. Anesthesiology 2005;103:156-160.
10. Strassels SA, McNicol E, Suleman R. Postoperative pain management: a practical review, part 2. Am J Health Syst Pharm 2005;62:2019-2025.
11. Steinberg RB, Liu SS, Wu CL, Mackey DC, Grass JA, Ahlen K, Jeppsson L. Comparison of ropivacaine-fentanyl patient-controlled epidural analgesia with morphine intravenous patient-controlled analgesia for perioperative analgesia and recovery after open colon surgery. J Clin Anesth 2002;14:571-577.
12. Boylan JF, Katz J, Kavanagh BP, Klinck JR, Cheng DC, DeMajo WC, et al. Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery: analgesic, respiratory, and myocardial effects. Anesthesiology 1998;89:585-593.
13. Jayr C, Beaussier M, Gustafsson U, Leteurnier Y, Nathan N, Plaud B, et al. Continuous epidural infusion of ropivacaine for postoperative analgesia after major abdominal surgery: comparative study with i.v. PCA morphine. Br J Anaesth 1998;81:887-892.
14. Clemente A, Carli F. The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems. Minerva Anestesiol 2008;74:549-563.
15. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology 1995;82:1474-1506.
16. Liu SS, Wu CL. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. Anesth Analg 2007;104:689-702.
17. Richman JM, Wu CL. Epidural analgesia for postoperative pain. Anesthesiol Clin North America 2005;23: 125-140.
18. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database Syst Rev 2005;1:CD004088.
19. Nishimori M, Ballantyne JC, Low JH. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev 2006;3:CD005059.
20. Liu SS, Wu CL. The effect of analgesic technique on postoperative patient-reported outcomes including analgesia: a systematic review. Anesth Analg 2007;105:789-808.
21. Pöpping DM, Elia N, Marret E, Remy C, Tramer MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg 2008;143:990-999.
22. Pöpping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. Br J Anaesth 2008;101:832-840.
23. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. Anesthesiology 2002;97:540-549.
24. Cywinski JB, Parker BM, Xu M, Irefin SA. A comparison of postoperative pain control in patients after right lobe donor hepatectomy and major hepatic resection for tumor. Anesth Analg 2004;99:1747-1752.
25. Yong BH, Tsui SL, Leung CC, Lo CM, Liu CL, Fan ST, Young K. Management of postoperative analgesia in living liver donors. Transplant Proc 2000;32:2110.
26. Hsu HT, Hwang SL, Lee PH, Chen SC. Impact of liver donation on quality of life and physical and psychological distress. Transplant Proc 2006;38:2102-2105.
27. Erim Y, Beckmann M, Valentin-Gamazo C, Malago M, Frilling A, Schlaak JF, et al. Quality of life and psychiatric complications after adult living donor liver transplantation. Liver Transpl 2006;12:1782-1790.
28. Verbesey JE, Simpson MA, Pomposelli JJ, Richman E, Bracken AM, Garrigan K, et al. Living donor adult liver transplantation: a longitudinal study of the donor's quality of life. Am J Transplant 2005;5:2770-2777.
29. Walter M, Dammann G, Papachristou C, Pascher A, Neuhaus P, Danzer G, Klapp BF. Quality of life of living donors before and after living donor liver transplantation. Transplant Proc 2003;35:2961-2963.
30. Katz J, Melzack R. Measurement of pain. Surg Clin North Am 1999;79:231-252.
31. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain 1997;72:95-97.
32. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 2001;18:205-207.
33. Hodges JL, Lehman EL. Rank methods for combination of independent experiments in analysis of variance. Ann Math Stat 1962;33:482-497.
34. Mehrotra DV, Liu X, Li X. Rank-based analyses of stratified experiments: alternatives to the van Elteren test. Am Stat 2010;64:121-130.
35. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria; 2007. www.R-project.org. Accessed November 2010.
36. Mendoza TR, Chen C, Brugger A, Hubbard R, Snabes M, Palmer SN, et al. Lessons learned from a multiple-dose post-operative analgesic trial. Pain 2004;109:103-109.
37. Milojevic KG, Cantineau JP, Ruiz R, Coudert B, Bataille S, Boutot F, et al. Can severe acute pain escape visual analog scale screening in the ED? Am J Emerg Med 2004;22:238-241.
38. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain 1995;62:259-274.

39. Minville V, Fourcade O, Girolami JP, Tack I. Opioid-induced hyperalgesia in a mice model of orthopaedic pain: preventive effect of ketamine. Br J Anaesth 2010; 104:231-238.
40. Celerier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology 2000;92:465-472.
41. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. Best Pract Res Clin Anaesthesiol 2007;21:65-83.
42. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-1137.
43. Coelho JC, Parolin MB, Baretta GA, Pimentel SK, de Freitas AC, Colman D. Donor quality of life after living donor liver transplantation [in Portuguese]. Arq Gastroenterol 2005;42:83-88.
44. Diaz GC, Renz JF, Mudge C, Roberts JP, Ascher NL, Emond JC, Rosenthal P. Donor health assessment after living-donor liver transplantation. Ann Surg 2002;236:120-126.
45. Trotter JF, Talamantes M, McClure M, Wachs M, Bak T, Trouillot T, et al. Right hepatic lobe donation for living donor liver transplantation: impact on donor quality of life. Liver Transpl 2001;7:485-493.
46. Ruppen W, Derry S, McQuay H, Moore RA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. Anesthesiology 2006;105:394-399.
47. Wijeysundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. Lancet 2008;372:562-569.
48. Choi SJ, Gwak MS, Ko JS, Kim GS, Ahn HJ, Yang M, et al. The changes in coagulation profile and epidural catheter safety for living liver donors: a report on 6 years of our experience. Liver Transpl 2007;13:62-70.
49. Shontz R, Karuparthy V, Temple R, Brennan TJ. Prevalence and risk factors predisposing to coagulopathy in patients receiving epidural analgesia for hepatic surgery. Reg Anesth Pain Med 2009;34:308-311.
50. Kostopanagiotou G, Markantonis SL, Arkadopoulos N, Andreadou I, Charalambidis G, Chondroudaki J, et al. The effect of acutely induced hepatic failure on remifentanil and fentanyl blood levels in a pig model. Eur J Anaesthesiol 2006;23:598-604.
51. Mondor ME, Massicotte L, Beaulieu D, Roy JD, Lapointe R, Dagenais M, Roy A. Long-lasting analgesic effects of intraoperative thoracic epidural with bupivacaine for liver resection. Reg Anesth Pain Med 2010;35:51-56.