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Original Article / Özgün Araştırma

Donor Hepatectomy Surgery using Ketamine to Compliment Analgesia and Reduce Morbidity - a Retrospective Chart Review Investigation

Analjezi Sağlamak ve Morbiditeyi Azaltmak İçin Ketamin Kullanılan Donör Hepatektomi Ameliyatı - Retrospektif Bir Tıbbi Kayıt İncelemesi

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Abstract / Öz

Objective: Inferior and limited analgesic options/techniques during living donor hepatectomy surgery can result in pain and risks of morbidity, opioid-related adverse events (AEs), predisposition to the development of chronic pain and concerns of potential narcotic abuse. Traditional analgesia uses unimodal intravenous opioids that can cause significant side effects. Ketamine provides analgesia and may be opioid sparing, but use in living-donor hepatectomy has not been studied.

Methods: Following human investigation committee approval and informed written consent, 47 liver donor patients over a 5-year period scheduled for surgery were categorized into one of three groups: 24 patients received no ketamine (Group 1), 9 received only intraoperative ketamine (Group 2) and 14 patients received intraoperative plus postoperative ketamine (Group 3). Subjects had access to opioid patient-controlled analgesia (PCA). Chart reviews (including operating room and intensive care unit) were collected and analysed for morphine consumption, pain-intensity scores, opioid-sparing effects, AEs of analgesics and for evidence of ketamine side effects on donor hepatectomy patients.

Results: There were no differences in patient demographics. Living donor hepatectomy patients receiving intraoperative ketamine that was continued postoperatively consumed fewer morphine-equivalents and had lower median pain scores than subjects from the other two groups. Ileus occurred in those not receiving ketamine, pruritus was lowest in Group 3, and there was no evidence or reports of ketamine-associated AEs.

Conclusion: Perioperative ketamine for donor hepatectomy patients could safely provide improved analgesia and be opioid sparing when compared to PCA opioids alone, and there is no evidence of ketamine-related AEs at the dose and delivery methods described here during partial liver donation surgery.

Keywords: Living-donor liver transplantation, ketamine, perioperative analgesia

Amaç: Canlı donörlü hepatektomi ameliyatı sırasında uygulanan inferior ve sınırlı analjezi seçenekleri/teknikleri ağrıya ve morbidite riskine, opioide bağlı yan etkilere, kronik ağrı gelişimi eğilimine ve potansiyel narkotik bağımlılığına neden olabilirler. Geleneksel analjezi uygulamasında, önemli yan etkilere neden olabilen unimodal intravenöz opioidler kullanılmaktadır. Ketamin analjezi sağlar ve opioid tüketimini azaltabilir. Ancak canlı donörlü hepatektomide kullanımı hakkında henüz çalışma yapılmamıştır.

Yöntemler: İnsan araştırmaları etik kurulu onayı ve yazılı bilgilendirilmiş hasta onam formu alındıktan sonra, 5 yıllık bir süreçte ameliyat olması planlanan 47 canlı donör hastası 3 gruba ayrıldı. 24 hastaya hiç ketamin verilmedi (Grup 1); 9 hastaya sadece intraoperatif ketamin verildi (Grup 2); ve 14 hastaya intraoperatif ve postoperatif ketamine uygulandı (Grup 3). Denekler hasta kontrollü opioid analjezisi kullandılar. Hastaların tıbbi kayıtları toplandı (ameliyathane ve yoğun bakım ünitesinden) ve morfin kullanımı, ağrı-yoğunluk skorları, opioid tüketiminin azaltıcı etkisi, analjeziklerin yan etkileri ve ketaminin donör hepatektomi hastaları üzerindeki yan etkileri açısından analiz edildiler.

Bulgular: Hastaların demografik verilerinde herhangi bir fark izlenmedi. İntraoperatif ve postoperatif ketamin alan canlı donör hepatektomi hastalarında, diğer iki gruptaki hastalara kıyasla, daha az morfin ve dengi ilaçların tüketimi ve daha düşük medyan ağrı skorları gözlendi. Ketamin verilmeyen hastalarda ileus gelişti. Prurit gelişimi Grup 3'te en düşük düzeydeydi. Ketaminle ilişkili yan etkilere dair herhangi bir kanıt veya rapor bulunmadı.

Sonuç: Donör hepatektomi hastalarında perioperatif ketamin kullanımı, sadece hasta kontrollü opioid analjezisi ile kıyaslandığında, güvenli ve gelişmiş analjezi sağlayabilir ve opioid tüketimini azaltabilir. Bu çalışmada tanımlanan kısmi karaciğer nakli sırasında uygulanan ketamin dozuyla ve uygulama yöntemiyle ilişkili yan etkilere dair herhangi bir kanıt bulunmamaktadır.

Anahtar Kelimeler: Canlı donör karaciğer transplantasyonu, ketamin, perioperative analjezi

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Introduction

There has been little change in the number of deceased organ donors for liver transplant despite efforts targeting supply, and the numbers available from deceased donors remains below the need (1, 2). However, the number of patients awaiting transplant surgery continues to increase (3). In addition, with technical advances and improvements in management of immune-suppressants, liver transplantation continues to be a viable option for various end-stage liver diseases. Therefore, considering this deficiency of deceased donor organs, liver transplantation with living-donor liver transplantation (LDLT) at several centres in the US is increasing in frequency (4).

Living-donor liver transplantation procedures have proven to be a life-saving intervention for recipients; however, such surgery can introduce significant pain and morbidity for healthy living donors (5). Inadequate perioperative pain management can result in clinical, psychological and socioeconomic consequences that might lead to sub-optimal pain management, decreased patient satisfaction, delayed recovery, unanticipated readmissions, extended duration of opioid analgesia with potential for narcotic abuse, and might possibly lead to chronic and persistent postsurgical pain. One of the greatest disadvantages for live liver donors can be the pain induced by surgery because these patients receive no direct medical benefit but will experience exposure to severe surgical trauma and risk of persistent postoperative chronic pain (6) because there are limited analgesic and pain management options available.

There have been improvements in our understanding of the pain cascades coupled with interactions from independent mediators (i.e. ethnicity, prior pain exposure) that has resulted in increased awareness of the development of prolonged postoperative pain (7). The incidence of chronic pain is likely underestimated in the literature and is becoming more recognized secondary to evidence-based protocols identifying this syndrome (8, 9). However, effective analgesia in the treatment of surgical pain for live donor patients focuses only on intravenous opioids (10). These pain management strategies of unimodal opioid administration for donor hepatectomy patients might result in suboptimal analgesic effectiveness that can introduce compromising adverse effects (AEs) and further predispose these patients to the potential of prolonged postoperative pain. Therefore, analgesic alternatives and other supplemental pain management strategies need to be considered (11).

Table 1. Patient demographics and clinical characteristics stratified by ketamine administration status

	Ketamine Administration Status			
Variables	**No ketamine (Group 1; n=20)**	**Intraoperative only (Group 2; n=9)**	**Both intraoperative and postoperative (Group 3; n=14)**	**p**
Age (years)	36 (11)	35 (11)	36 (10)	0.96
Height (cm)	167.64 (5)	175.26 (3)	170.18 (4)	0.37
BMI (kg/m^2)	25 (4)	26 (4)	25 (3)	0.76
Gender				
Male	9 (45%)	8 (89%)	6 (43%)	0.053
Female	11 (55%)	1 (11%)	8 (57%)	
ASA				
I	13 (65%)	4 (44%)	10 (71%)	0.465
II	7 (35%)	5 (56%)	4 (29%)	
Ethnicity				
Black	1 (5%)	0 (0%)	0 (0%)	0.822
Other	2 (10%)	0 (0%)	2 (14%)	
Hispanic	5 (25%)	1 (11%)	2 (14%)	
Caucasian	12 (60%)	8 (89%)	10 (72%)	

BMI: body mass index; ASA: American Society of Anesthesiologist (physical status classification for assessing the fitness of patients before surgery); P-value: used in statistical hypothesis testing, specifically in null hypothesis significance testing; n: number of patients.
Data are presented as mean (SD: standard deviation) or percentage.

Table 2. Postoperative opioid administration (equivalents to morphine analgesics*)

Equivalent Dose (mg) of Opioid Agonist*	No ketamine administration Group 1 (n=20)**	Only intraoperative ketamine Group 2 (n=9)**	Both intraoperative & postoperative ketamine Group 3 (n=14)**	p
Total opioid consumption POD1 (mg)	106 (76-148)	66 (51-126)	66 (50-98)	0.041
Total opioid consumption POD2 (mg)	72 (35-115)	98 (51-159)	28 (20-49)	0.052
Total opioid consumption POD3 (mg)	29 (23-80)	21 (15-45)	15 (10-35)	0.24
Total of 3-day opioid consumption (mg)	221 (137-417)	189 (115-309)	92 (69-232)	0.036

n: number of patients/subjects in each group; POD: postoperative day.

*For purposes of this investigation, perioperative use of only morphine, fentanyl or hydromorphone were administered and converted to opioid equivalents to morphine.

**The opioid consumption (range; mg) from POD1 thru POD3 and identified as morphine equivalents.

Postoperative liver dysfunction and the potential for compromised coagulation effectiveness can be an outcome from liver resection surgery. This phenomenon has limited many other pain management alternatives such as the multi-modal use of many non-narcotic analgesics including non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, as well as an increased consideration for potential patient compromise from perioperative neuraxial blockade. Furthermore, dependence on opioids as the single analgesic agent for pain management can prove suboptimal due to opioid-related side-effects such that patients choose instead to select for suboptimal pain management rather than experience deleterious AEs from opioid analgesics (12). Therefore, adding ketamine as an analgesic adjunct might minimise the potential surgical issues mentioned above and could prove to be opioid sparing for liver donor patients.

The goals of this retrospective chart review were to examine perioperative ketamine use combined with traditional opioid patient-controlled analgesia (PCA) and to analyse 1) the influence of ketamine on total opioid consumption over a 3-day postoperative period; 2) the influence on pain intensity scoring; 3) analgesic side-effects; 4) the effects of perioperative ketamine use on morbidity for live liver donor hepatectomy patients; and 5) the effect(s) of perioperative opioid requirements.

Methods

This retrospective chart review examined perioperative ketamine administration along with traditional opioid PCA and was performed by measuring the effects of rescue opioid requirements (pain intensity scoring and opioid side effects) and analgesic influences on morbidity for live liver-donor hepatectomy patients. The Institutional Review Board of the Yale University School of Medicine (#1304011809) approved the study, and written informed consent was obtained from all participants. There were no exclusion criteria, and 47 patients aged 20-56 years scheduled for donor-hepatectomy surgery under general anaesthesia were included in the analysis. Chart reviews from these 47 consecutive LDLT patients were conducted in the hospital over a 5-year period from March 2008 until April 2013.

Patient data tabulation was performed with the institutions electronic medical record (EMR) systems from two different healthcare software companies (initially Sunrise Clinical Manager™--SCM and subsequently Epic Systems Corporation™--Epic). Group 1 patient's did not receive any supplemental ketamine; those in Group 2 received intraoperative low-dose ketamine that was discontinued in the operating suite following surgery; and Group 3 patients had low-dose intraoperative ketamine continued into the postoperative period (postoperative ketamine infusion rates were not changed throughout the entire duration of administration up to 72 h). Patients received postoperative opioid (morphine or hydromorphone) PCA analgesia as per standard practice. These donor patients had their EMR data captured and analysed, but data on four patients from Group 1 was excluded due to missing information from of either the intraoperative or postoperative medical records.

Preoperative assessments were performed on donor-hepatectomy patients, initially by the surgical services and then by the Preadmission Testing Centre (anaesthesia and nursing assessment). Consent for surgery was obtained, the risks and benefits of the anaesthesia care plan were discussed, and an anaesthesia informed consent was obtained. These patients were not randomised and incorporation of low-dose perioperative ketamine was based upon the discretion of the anaesthesiologist (three individuals) and intraoperative surgical care team (two surgeons). Standard American Society of Anesthe-

Table 3A. Summary of postoperative outcomes for patients stratified by ketamine administration status

	Ketamine Administration Status						
	Both intraoperative and postoperative (Group 3; n=14)		Intraoperative Only (Group 2; n=9)		No ketamine (Group 1; n=20)		
Variables	**n**	**Median (IQR) or (%)**	**n**	**Median (IQR) or (%)**	**n**	**Median (IQR) or (%)**	**p***
Day 1							
Pain score	14	2.86 (1.43-3.57)	9	4.17 (3.71-5)	20	4.23 (3.29-4.71)	0.04[a]
Opioids (mg)**	9	66 (50-98)	9	66 (51-125.5)	20	106 (76.4-148)	0.042
No PCA rescue requirements needed	5	35.7%	0	(0%)	0	(0%)	0.004
Day 2							
Pain score	14	3.18 (1.50-3.83)	9	3.83 (3-4.5)	20	2.67 (1.67-4.5)	0.24[b]
Opioids (mg)**	8	28 (20-49)	9	98 (51-159)	20	72 (35-115)	0.052
No PCA rescue requirements needed	6	42.9%	0	(0%)	0	(0%)	0.001
Day 3							
Pain score	14	1.45 (0.67-2.6)	9	4.25 (2.5-4.5)	20	2.5 (1.67-4.33)	0.01[c]
Opioids (mg)**	8	15.0 (10-35)	9	21.3 (15-45)	20	29.4 (23-80)	0.24
No PCA rescue requirements needed	2	42.9%	0	(0%)	0	(0%)	0.001
Secondary measurements							
Ambulation hours	14	51 (24-69.5)	9	65 (36-75)	20	56 (41-66)	0.58
ICU length of stay (days)	14	3 (3-3)	9	3(3-3)	20	3(3-3)	0.95
Hospital length of stay (days)	14	6 (6-8)	9	7.5 (7-9)	20	7 (6-8)	0.18
Adverse events							
Ileus							
Yes	0	(0%)	0	(0%)	3	(15%)	
No	14	(100%)	9	(100%)	17	(85%)	0.30
Pruritus							
Yes	5	(36%)	5	(56%)	10	(50%)	
No	9	(64%)	4	(44%)	10	(50%)	0.62
Sedation							
Yes	2	(14%)	1	(11%)	1	(5%)	
No	12	(86%)	8	(89%)	19	(95%)	0.13
PONV							
Yes	7	(50%)	3	(33%)	9	(45%)	
No	7	(50%)	6	(67%)	11	(55%)	0.85

n: number of patients; P-value: used in statistical hypothesis testing, specifically in null hypothesis significance testing; IQR: interquartile range; PCA: patient-controlled analgesia; ICU: intensive care unit; PONV: postoperative nausea and vomiting.

*P-value from nonparametric Kruskal-Wallis test for continuous variables or from Fisher's exact test for categorical variables; **opioid analgesics in mg calculated from morphine equivalents (see Table 1); a: The P-value (Group 1 versus Group 3)=0.02; b: The p-value (Group 1 versus Group 3)=0.05; c: The p-value (Group 1 versus Group 3)=0.03.

siologists (ASA) monitoring was implemented during surgery. Patients had a radial arterial-line placed and central venous catheter inserted. Patients were induced with 1-3 mg kg^{-1} of propofol and 1-3 mcg kg^{-1} of fentanyl. General anaesthesia was maintained with volatile inhalational agents (Sevoflurane, Desflurane or Isoflurane) mixed with oxygen. Intraoperative opioids (fentanyl, morphine and hydromorphone) were administered as required at the anaesthesiologist's discretion.

The donor-hepatectomy patients (Groups 2 and 3) received an intraoperative ketamine bolus (0.25 mg kg^{-1}) and were maintained on a ketamine infusion (100-150 mcg kg^{-1} h^{-1}) adjusted as needed at the anaesthesiologist's discretion.

Per protocol, patients were extubated in the operating room following surgery and then transported to the surgical intensive care unit (SICU). These patients received intravenous PCA opioids (morphine or hydromorphone) upon arrival to the unit provided by the SICU team. Only Group 3 patients had intraoperative ketamine continuing postoperatively and administered at 100-150 mcg kg^{-1} h^{-1} for up to 72 h. Nursing staff recorded the PCA requirements, opioid dosage amounts and the incidence/findings of specific AEs, including ileus, pruritus, postoperative nausea and vomiting (PONV) and sedation scores. Pain intensity was measured using the visual analogue scale (VAS; a psychometric response scale used in questionnaires as a measurement instrument for subjective characteristics or attitudes that cannot be directly measured) for pain scores ranging from 0 to 10 (0 being no pain and 10 being the worst possible pain). The recording of pain scores reported in the investigation represent a 'time-weighted average' for the previous 24 hours. For example, the postoperative day 1 VAS score represents the time-weighted average of the values collected in the first postoperative hours until the first postoperative morning.

Perioperative information was extracted, recorded and tallied from the institution's EMR. Each donor-hepatectomy patient was assigned a study number, and charts were analysed for events including date of surgery, sex, ethnicity, ASA classification, height and weight, intraoperative opioid consumption, intraoperative and postoperative ketamine dosing parameters, opioid consumption during 24, 48 and 72 h postoperative periods, VAS pain scores every 4 h for 72 h (grouped into days), number of postoperative hours until first ambulation, SICU length-of-stay (LOS) and hospital LOS. Opioid consumption was converted to morphine equivalents using the opioid equianalgesic chart.

Table 3B. Wilcoxon rank sum test p-value for pairwise comparisons of pain score and opioid consumption

Outcomes	Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
Pain score			
Day 1	0.67	0.019	0.85
Day 2	0.13	0.05	0.166
Day 3	0.03	0.005	0.19
Opioid consumption (mg)			
Day 1	0.112	0.047	0.18
Day 2	0.033	0.043	0.56
Day 3	0.15	0.091	0.389
Total (Day 1-3)	0.098	0.05	0.43

Group 1: No ketamine (n=20); Group 2: Intraoperative ketamine only (n=9); Group 3: Both intraoperative and postoperative ketamine (n=14)

Patients received pro-re-nata orders of odansetron for nausea and vomiting and diphenhydramine for pruritus. Daily EMR progress notes were analysed for evidence of opioid-associated AEs such as significant sedation [defined by the Richmond Agitation-Sedation Score-RASS (13)]; evidence of postoperative ileus; or ketamine-associated side effects, including visual changes, headache, hallucinations, convulsions or hyper-salivation, as well as any complications contributing to or adversely influencing the hospital course. Medications needed and/or medical management of AEs, including postoperative hematoma, pulmonary embolus, hepatic thrombus, postoperative biliary leak, deep vein thrombosis and urinary tract infection, were identified.

Statistical analysis

Patient demographics and clinical characteristics were summarised using mean (SD) or median (interquartile range: IQR) for continuous variables and N (percentage) for categorical variables. Differences between the groups in primary outcomes, including morphine-equivalent opioid consumption within the postoperative period and VAS pain scores from the beginning of recovery to 72 h post-surgery, along with secondary outcomes of duration (hours) from end of surgery to ambulation, SICU-LOS, and hospital-LOS were assessed using the nonparametric Kruskal-Wallis test (i.e. one-way ANOVA on ranks) for continuous variables. The comparisons of different AEs including postoperative ileus, pruritus, sedation and PONV were determined using Fisher's exact test. All statistical analyses were performed using SAS software, v9.4 (Cary, NC). A two-sided p-value of <0.05 was considered statistically significant.

Results

Demographics showed no statistical differences between the groups (Table 2). Group 3 patients reported less pain, and the VAS pain scores were 2.86 versus 4.17 in Group 2 and 4.23 in Group 1 on postoperative day (POD) 1 (p=0.04; Table 3; Figure 1). On POD3, Group 3 patients reported VAS pain scores of 1.45 versus 4.25 in in Group 2 and 2.5 in Group 1 (p=0.01; Table 3; Figure 1).

Total median morphine-equivalent consumption on POD1 (i.e. 20-24 h post-surgery) for patients from Groups 2 and 3 were both 66 mg compared to 106 mg in Group 1. The IQR was narrower in Group 3 patients when compared to those from Groups 1 and 2 (Table 1; Figure 1). Total rescue opioid consumption required by the patients for the first 3 postoperative days suggested that those from Group 3 consumed less overall morphine equivalents than those from Groups 1 and

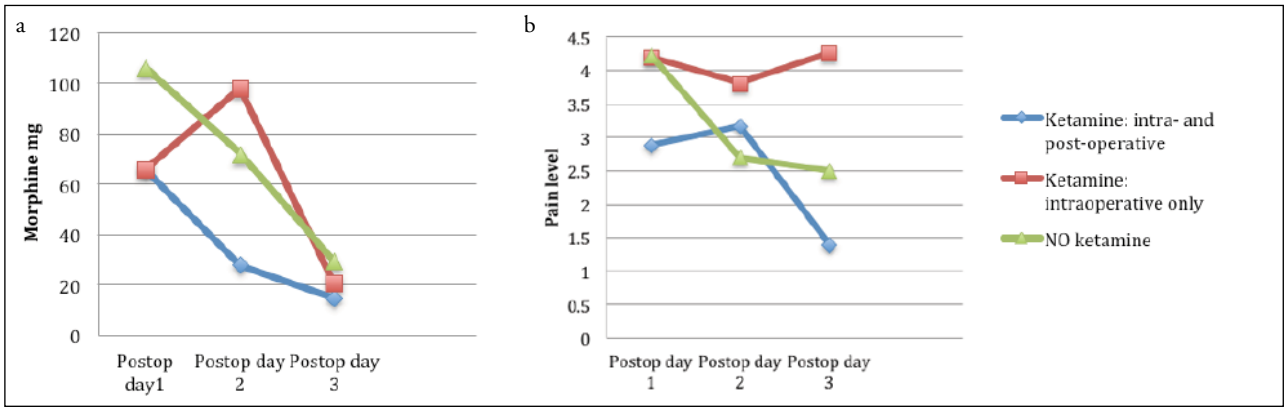

Figure 1. a, b. (a) Postoperative morphine consumption. (b) Median pain scores

2. The median morphine-equivalents were 66 mg for patients from Group 3 compared to 106 mg and 66 mg in Groups 1 and 2, respectively, on POD1 (i.e. 20-24 h post-surgery; P=0.04); the median morphine-equivalents were 28 mg for patients in Group 3 compared to 72 mg and 98 mg in Groups 1 and 2, respectively, on POD2 (i.e. 40-48 h post-surgery; p=0.052); and the median morphine-equivalents were 15 mg in Group 3 patients compared to 29.4 mg and 21.3 mg in Groups 1 and 2, respectively, on POD3 (i.e. 60-72 h post-surgery; p=0.24). The total median morphine-equivalent consumption over the entire 3-day study period for patients from Group 3 was 103 mg versus 199 mg and 221 mg in Groups 2 and 1, respectively (p=0.035) (Table 1; Figure 1).

It was anticipated that all donor-patients would require postoperative opioid analgesics; however, 36% of the patients from Group 3 required no rescue PCA opioids on POD1 compared to all patients from Groups 1 and 2 requiring rescue opioid analgesics (p=0.004). A similar trend continued onto POD2 and POD3 with 43% of patients from Group 3 not requiring opioids compared to all patients from Groups 1 and 2 requiring rescue opioid analgesics (Table 3).

Relative statistical comparisons were made between the two groups receiving ketamine, and 100% of patients from Group 2 required narcotic analgesics compared to those in Group 3 where only 64% (POD1) and 57% (POD2 and 3) of the patients required rescue postoperative opioid analgesics. This is in addition to higher VAS pain scores in patients from Group 2 when compared to those in Group 3 (4.17 versus 2.86, 3.83 versus 3.18 and 4.25 versus 1.45 on POD1, 2 and 3 respectively; Table 3).

No statistical differences were identified for hours until ambulation (p=0.58), ICU-LOS (p=0.95), hospital-LOS (p=0.18), postoperative ileus (p=0.30), pruritus (p=0.62), PONV (p=0.85) or sedation (p=0.13) among any of the groups (Table 3). However, 15% of Group 1 patients (3 out of 20) experienced an ileus versus 0% from Groups 2 and 3, and pruritus occurred in more patients from Group 1 (50%; 10 out of 20) compared to those in Group 3 (36%; 5 out of 14). Although not statistically significant, fewer subjects from Group 1 (5%) experienced mild-to-moderate sedation when compared to Groups 2 (11%) and 3 (14%) (Table 3). Patients were not found to have experienced any AEs attributed to perioperative ketamine such as visual changes, headache, hallucinations, convulsions or hyper-salivation.

Ileus (transient and not needing radiographic support) was described as decreased bowel propulsive ability and classified as caused by bowel obstruction, intestinal atony or paralysis. For the purposes of this investigation, ileus was diagnosed with symptoms and signs (absence of a mechanical obstruction) of a bowel obstruction as:

- Moderate, diffuse abdominal discomfort
- Abdominal distension
- Nausea and vomiting (especially following meals)
- Vomiting of bilious fluid
- Lack of bowel sounds and/or flatulence
- Excessive belching

The Richmond Agitation-Sedation Scale (RASS) ranging from +4 (combative or overly combative creating an immediate danger) to 0 (alert and calm) to -5 (no response to voice or physical simulation) is a medical classification used to measure the agitation or sedation level of a patient. For this investigation, any RASS score worse than or equal to –3 was recorded as an AE. The RASS score was obtained as a step toward performing a confusion assessment of the study subjects in the ICU (it is a tool to detect delirium in ICU patients).

Discussion

Perioperative ketamine targeting LDLT pain management has not been previously studied and should not be underestimated. It was hypothesized that perioperative low-dose ketamine for donor-liver patients lowers opioid analgesic requirements, decreases pain scores, influences perioperative surgical parameters leading to improved recovery and reduce opioid

AEs. Thus, the objectives of this chart review investigation evaluated perioperative ketamine combined with traditional opioid-based pain management and examined narcotic rescue requirements in LDLT patients. If perioperative ketamine can be shown to improve postoperative pain and positively influence donor-patient analgesic experiences, then given the deficiencies of current analgesic options for this type of surgery, ketamine use during partial hepatectomy might prove beneficial and might improve patient outcomes (14).

Although additional investigation is needed, this study has indicated that there was a reduction and trend toward decreased opioid consumption during LDLT surgery in those receiving continued perioperative ketamine into the postoperative period with a) fewer patients requiring supplemental opioids postoperatively, and b) decreased overall morphine-equivalent consumption postoperatively throughout the 3-day duration of the investigation. In addition to reduced rescue opioid analgesic requirement, intraoperative low-dose ketamine with continuation into the postoperative period was also associated with fewer reports of postoperative pain and decreased pain scores compared to patients managed with opioid analgesics alone.

There were 51.4 million surgical procedures performed in the United States in 2010 (15). However, unlike elective, urgent or emergency surgery, organ donation remains unique because donor-hepatectomy patients are healthy, without need of surgical intervention and are willing to expose themselves to unnecessary and traumatic surgery. Liver donor-hepatectomy patients are expected to experience full recovery and return to activities of daily living shortly following surgery. Unfortunately, concerns remain that negative and debilitating aspects of the operation can be intense along with protracted postoperative pain (16). Donor-hepatectomy patients endorse the 'living organ donation' philosophy, but it remains conceivable that apprehension, anxiety and fear of painful surgical experiences could limit a patient's willingness to proceed with such a life-altering decision. Therefore, providing more optimal and uninterrupted multimodal perioperative pain management remains important when considering LDLT surgery.

Perioperative pain needs along with the potential for postoperative liver dysfunction and altered coagulation are considerations of LDLT surgery (17). The role of some non-opioid analgesics and pain management options such as NSAIDs, acetaminophen and neuraxial blockade have been suggested, but these often introduce questionable perioperative value, concerns about patient safety and limited clinical utility. Clarke et al. (18) in a retrospective study suggested analgesic superiority when using epidurals for analgesia during LDLT surgery. However, there are inherent risks of neuraxial hematoma - despite the fact that liver donors have normal preoperative liver function (19) - due to unanticipated coagulation derangements from such surgery that could result in a catastrophic neuraxial hematoma making regional techniques controversial for these patients (20). In addition, certain non-narcotic analgesics (NSAIDs) used alone or in combination with neuraxial techniques can be impact modifiers of the coagulation system, and these carry risks that might result in adverse influences on coagulation and platelet-inhibition (increasing the risk of surgical bleeding) and should receive risk-to-benefit consideration in LDLT patients (21-23).

Other non-narcotic analgesic options such as cyclooxygenase inhibitors, aspirin and acetaminophen also carry inherent risks that might result in adverse influences for donor hepatectomy patients. Pharmacodynamic interactions from combination analgesic therapy that influences coagulation can undermine platelet function and clot formation (24, 25), and LDLT surgery can further influence liver dysfunction. Acetaminophen is the leading cause of acute liver failure (26), and susceptible liver-donor patients might experience compromised liver function from a single overdose ingestion or therapeutic misadventure causing toxicity. Other factors such as concomitant alcohol use/abuse, concurrent medications, genetic factors and nutritional status might also influence the susceptibility/severity of acetaminophen-induced hepatotoxicity (27).

Ketamine is a non-opioid N-methyl-D-aspartate receptor antagonist and effective adjunct to opioids for improving postoperative analgesia following moderate-to-severe pain-inducing surgery (14, 28). Ketamine is also associated with opioid tolerance reversal, and no medication interactions have been reported with its use (29). Zakine et al. (30) compared supplemental ketamine and found improved analgesia along with decreased morphine consumption and a lower incidence of nausea and other side effects when administered for 48 h postoperatively. Another study examined sub-anaesthetic ketamine administration and found that it was effective in reducing morphine requirements for 24 h after surgery along with reduced PONV and with AEs reported as mild or absent (31).

Low-dose ketamine has been shown to improve pain management and decrease opioid requirements during surgical procedures and in certain patient populations (i.e. chronic pain patients) (32). However, a complete understanding of the mechanisms of action and pharmacology are missing. A systematic review and meta-analysis concluded that intraoperative ketamine inhibits early inflammatory markers (i.e. interleukin-6) during major surgery (33). These authors concluded that additional studies were needed to a) determine the anti-inflammatory effects, b) determine whether such treatment alters functional outcomes and c) determine the mechanisms of action. Therefore, this investigation has been able to suggest that adding ketamine as an adjunct and continuing its

administration into the early postoperative period might 1) reduce perioperative opioid rescue requirements, 2) minimize opioid analgesic AEs, 3) improve upon patient postoperative pain management experiences and 4) reduce the severity of AEs in the LDLT patient population.

Study limitations

After dividing the limited number of LDLT patients into three study groups with relatively small sample sizes, the opioid consumption results showed a degree of statistical significance, but only within some of the postoperative periods (i.e. Groups 1 and 3 on POD1 and the total of all 3 PODs together). Furthermore, a sample size estimate (post hoc sample size estimation) from the results obtained in this study for future prospective, randomized control trials analysing the information for 'opioid (mg) consumption over a 3-day study period' using Wilcoxon rank sum test would require that the number of patients per group to have 80% power and to detect the effect assuming a type-I error of 0.05 would be substantial. Therefore, to more closely determine a patient sample size, a more precise number could be achieved if the effects were estimated from two patient groups-patients-receiving perioperative opioids alone (n=52)-compared to patients with perioperative opioids combined with ketamine continued into the postoperative period-(n=52). The data would then be assessed using the nonparametric Kruskal-Wallis test (i.e. one-way ANOVA on ranks) for continuous variables, and a two-sided P-value of <0.05 would be considered statistically significant.

Limitations of this retrospective observational investigation include lack of randomisation, a protocol preventing chart reviewers from being completely blinded, and other minor investigational flaws due to the retrospective nature of the study. The diversity of perioperative medicine practiced by healthcare providers during LDLT surgery limited attempts to strictly standardise both intraoperative and postoperative anaesthesia care along with intraoperative and postoperative pain management. Patient numbers enrolled into each group were based on perioperative team (inclusive of intraoperative anesthesiologist, surgeon and ICU physician providers) choice(s) of intraoperative care protocols. This study also permitted opioid use, anaesthesia selection, timing of medication administration, use of non-opioid adjuncts and ketamine infusion dosing range to be determined by individual anaesthesia care team providers.

Two surgeons were conducting LDLT surgery during the period of this trial, and there were no restrictions or intraoperative guidelines placed on surgical team members. There were no major or significant alterations in surgical techniques reported (i.e. 6-inch right upper costal incisions) by the surgical team personnel. Therefore, degrees of variability in surgical approach, technique, etc., that could have influenced patient intraoperative anaesthesia and analgesic needs were considered of minimal influence. In addition, communication with the surgeons revealed that the surgical techniques over the duration of the investigation were not altered, except for minor changes in intraoperative surgical times secondary to increased numbers of cases being performed leading to improved surgical efficiency and non-statistically significant shortening of surgical times.

VAS is a valid and reliable instrument and is recommended in clinical trials to assess quality of life with sensitivity to acute treatment interventions (34). However, the timing of pain score collections could not always be standardised and could possibly be complicated by transitions in patient care. Patients scheduled for LDLT surgery consented to the study and were enrolled, but the annual number of procedures being performed limited the power of the investigation. The relatively small sample size was due to the annual average of only 250 living liver-donor surgeries being performed nationwide between 2008 and 2013 (15).

Conclusion

Living-donor liver transplantation is a life-saving measure for recipients, but can produce significant pain and risk of morbidity for donors. Morbidity can be associated with inferior and limited analgesic options and opioid-related AEs that predispose patients to the development of chronic pain and/or narcotic abuse/addiction. However, combining evidence from the literature and results from this retrospective investigation has shown that donor-hepatectomy patients administered perioperative ketamine continued postoperatively might have less perioperative pain with lower early postoperative pain scores and fewer postoperative analgesic AEs. Traditional LDLT analgesia focuses on unimodal opioids that often require high doses, but this observational investigation showed that those administered perioperative ketamine consumed less morphine-equivalent analgesics.

Perioperative ketamine can provide added value compared to PCA opioids alone and can be opioid sparing. Ketamine analgesia has not been studied in LDLT surgery, but when combined with traditional opioid PCA it might positively influence pain management. Additional prospective investigations to strategize ketamine administration, to determine anti-inflammatory effects, to determine whether such treatment alters functional outcomes, to investigate the mechanisms of action, and to determine the most appropriate dosing/timing for perioperative pain management in LDLT patients is needed. However, this retrospective chart review has suggested that ketamine can reduce opioid rescue requirements and might provide improved pain management for liver-donor patients without evidence of AE and might complement the optimisation of surgical outcome when it is continued into the postoperative period.

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Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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