Multimodal Analgesia Decreases Postoperative Opioid Consumption in Living Liver Donation

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Abstract

Objective: To evaluate the effects of multimodal analgesia on postoperative opioid consumption and perioperative pain management in patients undergoing living liver donation.

Methods: A retrospective study was conducted of 129 patients who underwent living liver donation between 2006 and 2015. Patients were separated into 2 cohorts, pre–multimodal analgesia and multimodal analgesia, to allow intergroup analysis. All patients received an intrathecal opioid injection and underwent donor hepatectomy. Primary outcome data compared opioid consumption in oral morphine equivalents for postoperative days (PODs) 0 to 4 between the cohorts. Secondary outcomes compared yearly averaged cumulative opioid consumption on PODs 0 to 4 in oral morphine equivalents; yearly averaged numeric rating scale pain scores; hospital length of stay; and percentage of patients receiving intravenous ketorolac, ketamine, or transversus abdominis plane blocks.

Results: For PODs 0 to 4, a 50% reduction in overall opioids administered postoperatively (359 mg vs 179 mg; $P<.01$) was observed in the multimodal analgesia cohort, whereas no significant difference was found in year-to-year average postoperative pain scores (4.5 vs 3.6). The proportion of patients receiving ketorolac increased to more than 90% by 2013. More than 40% of all patients in the multimodal analgesia group received a perioperative regimen of acetaminophen, gabapentin, ketamine, and transverse abdominal plane blocks (0% in pre–multimodal analgesia). Mean hospital length of stay was reduced from 7.7 to 6.6 days ($P<.01$).

Conclusion: Implementation of multimodal analgesia to manage perioperative pain in living liver donation resulted in a 50% reduction of postoperative opioid consumption. Clinically satisfactory average pain scores were maintained for PODs 0 to 4.

Perioperative clinical pain pathways using opioid-sparing medications, regional anesthesia techniques, and provider education on methods to treat perioperative pain have had a dramatic impact on pain control and patient outcomes.[1,2] These improved outcomes are most notably observed in orthopedic, gynecologic, and colorectal surgery as these services were early adopters of these enhanced recovery pathways.[3-7] However, in the modern era of multimodal analgesia and associated improved outcomes, few data have been published on opioid consumption and postoperative pain control in living liver donation.

Pain management regimens for living liver donation have traditionally relied on large doses of opioid medications, particularly morphine, for perioperative analgesia.[8] However, in recent years, multimodal pain regimens, often highlighted by regional anesthesia techniques, have become more widespread.[9-14] These multimodal regimens are now being deployed to better treat postoperative pain, and it is hoped that they will continue to have an impact on improved perioperative outcomes.[15-19]

Given the paucity of information on pain control outcomes in this population of patients, a gap in knowledge exists for providers caring for living liver donors and up-to-date postoperative opioid reduction practices. The aim of this study was to determine the impact of multimodal analgesia on postoperative

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opioid consumption in patients undergoing living liver donation and to investigate the pain management techniques enacted at a single center.

METHODS

This study was approved by the International Review Board of Mayo Clinic, Rochester, Minnesota. We performed a retrospective data analysis of 129 patients who underwent living liver donation between 2006 and 2015 and met study inclusion and exclusion criteria. Patients were separated into 2 surgical cohorts, a pre—multimodal analgesia group (46 patients, 2006-2010) and a multimodal analgesia group (83 patients, 2011-2015), to allow an intergroup analysis. The multimodal analgesia group was retroactively defined by the year 2011, when intravenous ketorolac (>50% of patients receiving it) was consistently provided to patients perioperatively. Primary outcome data compared opioid consumption in oral morphine equivalents (OMEs) for each postoperative day (POD) 0 through 4 between cohorts. Secondary outcomes compared yearly averaged cumulative opioid consumption on PODs 0 to 4 in OMEs; yearly average numeric rating scale (NRS) pain scores during this same time period; hospital length of stay; and percentage of patients receiving intravenous ketorolac, ketamine, or transversus abdominis plane block (TAP).

All consecutive adult patients who underwent a living liver donation between the years of 2006 and 2015, received a preoperative intrathecal opioid injection (morphine or hydromorphone), and underwent a right or left hepatectomy by subcostal J-shaped incisions were included in patient data collection. Patients who did not receive intrathecal opioids were excluded. Patient selection criteria for liver donation are rigorous and include the following parameters: 18 to 60 years old; body mass index of less than 35 kg/m^2; absent of heart, kidney, or liver disease; free from substance abuse; and no ongoing malignant disease.[20,21] There was no formalized standard clinical pathway for postoperative analgesia during these time periods. Of note, in 2013, patients intermittently started receiving intraoperative ultrasound-guided TAP blocks at the conclusion of surgery. If TAP blocks were administered, the block placement entailed a multi-injection technique in the bilateral subcostal regions and right lateral TAP plane with a total of 20 to 30 mL of 0.25% plain bupivacaine mixed with 20 mL (266 mg) of liposomal bupivacaine.[15] Standard postoperative care of living liver donors includes extubation in the operating room at the conclusion of surgery, followed by immediate postoperative recovery in the postanesthesia care unit. The patient is then transferred to the intensive care unit for initial monitoring and then discharged to the ward thereafter for further care.

Baseline demographic characteristics and perioperative medication administration were extracted from a unified electronic record. Data collection occurred through manual chart review and electronic query of the medical and anesthesia records. Data were reported by mean and standard deviation for continuous variables and frequency (percentages) for categorical variables and evaluated at both the yearly and cohort levels to assess for statistical change. A Wilcoxon rank sum test for continuous variables and a 2-tailed Fisher exact test for categorical variables were used to compare cohort demographic characteristics and outcomes. Calculation of yearly pain scores included first averaging each patient's daily available pain scores on each POD, then averaging across all patients in a given year. Opioid use was converted to mean OMEs,[22] which were then averaged across patients for a given year or cohort. A P value of less than .05 was set for statistical significance. JMP Pro version 14.3.0 (SAS Institute) was used for analysis.

RESULTS

All patients undergoing living liver donation were assigned to American Society of Anesthesiologists class I and class II as presented in Table 1. No statistically significant differences in baseline characteristics were appreciated between the groups. Intrathecal opioid dosing for hydromorphone (range, 50 to 200 μg; median, 100 μg) did not differ between groups, but 19 patients (41%) in the pre—multimodal analgesia group received spinal morphine (range, 0.5 to 0.8 mg; median, 0.6 mg) rather than hydromorphone. All PODs 0 through 4 demonstrated a significant reduction in oral morphine consumption in the multimodal analgesia group (Table 2). The reduction in

TABLE 1. Preoperative Demographic Characteristics of Patients for Each Cohort[a,b]		
	Pre—multimodal analgesia, 2006-2010	Multimodal analgesia, 2011-2015
Total No. of patients	46	83
Sex		
Male	24 (52)	43 (52)
Female	22 (48)	40 (48)
Age (y)	37.5 (9.1)	37.6 (10.3)
ASA class		
I	25 (54)	60 (72)
II	21 (46)	23 (28)
BMI (kg/m^2)	25.5 (3)	25.7 (3)
Surgery type		
Left hepatectomy	3 (7)	11 (13)
Right hepatectomy	43 (93)	72 (87)
Surgery duration (min)	205 (30)	194 (33)

[a]ASA, American Society of Anesthesiologists; BMI, body mass index.
[b]Categorical variables are presented as number (percentage). Continuous variables are presented as mean (standard deviation). No statistically significant difference was found between groups.

oral morphine consumption was relatively equal between PODs 0 and 4, and there was no identified significant reduction between days investigated. Cumulative PODs 0 through 4 also had a reduction in OMEs in the multimodal analgesia group (179 mg vs 359 mg; P<.01). Despite the decrease in opioid use between the start and close of the study, there was no clinically significant difference between average pain scores between time periods of high opioid administration and lower dose use. Average pain scores categorized by each day and grouped by each year were less than or equal to 4, and between the 2 cohorts, although not clinically relevant, only 1 statistically significant average pain data point on POD 2 was observed favoring the pre—multimodal analgesia group (3.5, 4.0; P=.04).

Ketorolac was first introduced into this institution's living liver donation surgical practice in 2008 and reached more than 90% utilization in 2013 and beyond (Figure). More than 40% of all patients in the multimodal analgesia group received acetaminophen, gabapentin, ketamine, and TAP blocks (Table 2). The addition of TAP blocks with a liposomal bupivacaine mixture began in 2013; 20% of patients received a TAP block in 2013, which increased to 100% in 2015 (Figure). Patients' cumulative average NRS pain scores for each year between the groups on PODs 0 to 4 during this 10-year period averaged 2.9 to 4.0. On analysis of each year from 2006 to 2015 (Table 2), average NRS pain scores ranged from 3.2 (2007) to 4.5 (2006). Average hospital length of stay also decreased from 7.7 days in the pre—multimodal analgesia group to 6.6 days in the multimodal analgesia group (P<.01; Table 2). The number of liver donation operations performed each year ranged from 2 (2006) to 19 (2014). During the study period, 14 patients (11%) underwent left hepatectomy, whereas 115 patients (89%) underwent right hepatectomy. There was no temporal difference in technique during this time. Pain scores and OME requirements were not noted to be statistically different on the basis of surgical technique.

DISCUSSION

The addition of multimodal analgesia to perioperative pain management of living liver donation operations performed at a large academic medical center resulted in a 50% reduction in opioid consumption between the cohorts while clinically satisfactory average pain scores (NRS pain score ≤4.5) were maintained for PODs 0 to 4. This finding demonstrates that the addition of subcostal TAP blocks and medications such as intravenous ketorolac and ketamine provided to patients for living liver donation have an opioid-

TABLE 2. Differences Between Cohort Groups for Opioid Use and Pain Scores With Additional Details on Multimodal Prescribing Practice[a,b]

	Pre—multimodal analgesia, 2006-2010 (N=46)	Multimodal analgesia, 2011-2015 (N=83)	P value[c]
Opioid use (mg OME)			
POD 0	39 (34)	17 (19)	<.01
POD 1	120 (85)	63 (67)	<.01
POD 2	96 (69)	42 (45)	<.01
POD 3	59 (50)	32 (41)	<.01
POD 4	46 (31)	25 (41)	<.01
Total PODs 0-4	359 (211)	179 (170)	<.01
Average daily pain score			
POD 0	3.6 (2)	3.2 (1.7)	.25
POD 1	3.4 (1.3)	3.8 (1.6)	.1
POD 2	3.5 (1.2)	4.0 (1.4)	.04
POD 3	3.4 (1.2)	3.9 (1.5)	.07
POD 4	3.6 (1.4)	3.8 (1.7)	.59
Overall average on PODs 0-4	3.5 (1.0)	3.8 (1.2)	.11
Preoperative multimodal			
Acetaminophen	0 (0)	4 (5)	
Gabapentin	0 (0)	38 (46)	
Postoperative multimodal			
Acetaminophen	7 (15)	36 (44)	
Ketamine	3 (7)	34 (41)	
Ketorolac	10 (22)	70 (85)	
Liposomal bupivacaine TAP block	0 (0)	35 (42)	
Hospital duration (d)	7.7 (2.3)	6.6 (1.8)	<.01

[a]OME, oral morphine equivalent; POD, postoperative day; TAP, transversus abdominis plane.
[b]Categorical variables are presented as number (percentage). Continuous variables are presented as mean (standard deviation).
[c]Between-group comparison was done by Wilcoxon rank sum test for mean of nonparametric parameters.

sparing effect without negatively affecting postoperative pain control.

Despite the overall opioid reduction observed from the beginning of 2006 to the end of 2015, in the pre—multimodal analgesia group, a dramatic initial decrease was seen in overall OMEs from 2006 to 2008, which is likely to be the result of the small sample size in 2006. Other potential reasons may reflect an early cultural shift in surgical opioid prescribing practices, provider education in practices to reduce opioid consumption, or the beginning of ketorolac use (in 2008, 33% of patients received it). However, a rise in 2009 is not consistent with this message and may be more reflective of the variability in opioid administration. In analysis of other variables that may have contributed to the decline in opioid consumption in the multimodal analgesia group, as shown in Table 2

and the Figure, there was also increased utilization of acetaminophen (15% vs 44%), gabapentin (0% vs 46%), and ketamine (7% vs 41%) in the multimodal analgesia group. Last, we previously performed an investigation to evaluate the perioperative pain outcomes of subcostal liposomal bupivacaine TAP blocks performed on living liver donors in 2018.[15] Our results showed lower NRS pain scores and opioid consumption in the immediate postoperative period (POD 0); however, beyond that time frame, no statistical or clinical significance was observed. This helps explain the rationale that the medications that compose multimodal analgesia have a layered benefit to treating perioperative pain, and together as a whole they have added benefit. However, when 1 individual component is removed for study, it is difficult to show statistically and clinically significant
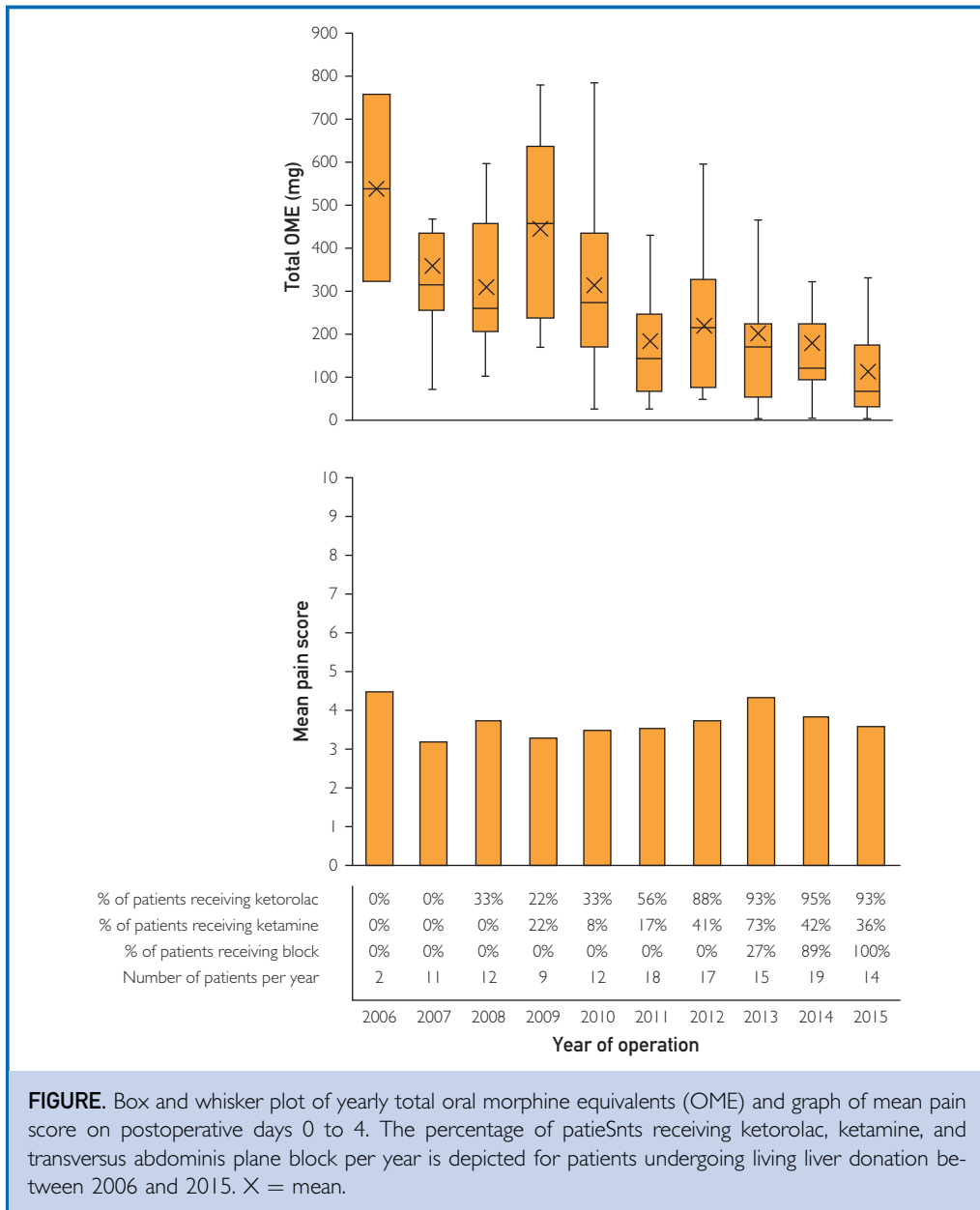
FIGURE. Box and whisker plot of yearly total oral morphine equivalents (OME) and graph of mean pain score on postoperative days 0 to 4. The percentage of patieSnts receiving ketorolac, ketamine, and transversus abdominis plane block per year is depicted for patients undergoing living liver donation between 2006 and 2015. X = mean.

pain score reductions without drastically increasing the sample size.

Strengths of the study include a homogeneous study population, a well-defined surgical procedure, and pain outcomes past the immediate postoperative period. Furthermore, this study reflects practice trends of opioid prescribing and tracks the slow introduction of new medications and procedures into a previously well defined perioperative anesthetic. Another unique point of the study is the variability observed in multimodal analgesia prescribing as not a single nonopioid medication reached 100% administration during the study period. This variability in practice is the rationale for the establishment of a well-defined enhanced recovery after surgery best practice protocol. A common pathway provides consistency for providers caring for the patients and allows nursing staff to anticipate pain control needs on the basis of routine practice and experience.

The main limitations of this study are the retrospective study design and lack of a defined time period when all elements of multimodal analgesia were implemented into a standardized enhanced recovery after surgery protocol. As an example, this allowed study group allocation of limited numbers of patients who received some component of multimodal analgesia (eg, ketorolac or ketamine) to be included in the pre—multimodal analgesia group, whereas not all in the multimodal analgesia group received a standardized regimen. Furthermore, although the intrathecal dose of hydromorphone used across this study was consistent, some patients in the pre—multimodal analgesia group received intrathecal morphine, albeit in similar dosing potency, limiting the comparison between groups. Despite this variability, we believe the story between the 2 groups is unchanged and strongly promotes the overall opioid-sparing effects of these medications. An appropriately powered prospective trial is needed to truly investigate the effects of the individual components of multimodal analgesia and the regional techniques deployed to treat postoperative pain in this subspecialty group of patients.

CONCLUSION

Inadequately treated acute postoperative pain can result in increased morbidity, patient dissatisfaction, functional limitations, longer hospital stays, impaired quality of life, increased medical costs, and increased potential for long-term opioid use.[23-29] Because of these myriad negative consequences related to poorly controlled acute postoperative pain, it is paramount for clinicians caring for this essential donor population to be aware of the wide range of opioid-sparing multimodal analgesia strategies, several highlighted in this study, that are available to properly treat acute pain in the perioperative period.[24] Implementation of multimodal analgesia to manage perioperative pain in living liver donation resulted in a reduction of postoperative opioid consumption while clinically satisfactory average pain scores were maintained for PODs 0 to 4 and hospital length of stay was reduced.

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