

Comparison of the analgesic effect of intrathecal morphine between laparoscopic and open living donor hepatectomy

Propensity score matching analysis

Ji-Hye Kwon, MD, PhD^a, Justin Sangwook Ko, MD, PhD^a, Hyo Jin Kim, MD^b, Sangbin Han, MD, PhD^a, Mi Sook Gwak, MD, PhD^a, Gaab Soo Kim, MD, PhD^a, Seung Young Lee, MD^c, Wongook Wi, MD^{b,*} 

Abstract

Laparoscopic donor hepatectomy is being increasingly adopted in transplant programs due to its numerous advantages. However, the role of intrathecal morphine (ITM) in laparoscopic donor hepatectomy has not been thoroughly investigated. This study aimed to compare the analgesic effects and safety of ITM between laparoscopic and open donor hepatectomy. This retrospective study included 742 donors who underwent hepatectomy with ITM between April 2007 and June 2019. Among them, 168 and 574 donors underwent laparoscopic hepatectomy (LH) and open hepatectomy (OH), respectively. Propensity score matching yielded two comparable groups of 168 donors each. The primary endpoint was the incidence of moderate-to-severe pain (maximum numerical rating scale [NRS] pain score ≥ 4) within 24 postoperative hours. The LH group had a significantly lower incidence of moderate-to-severe pain within 24 postoperative hours than the OH group (16.1% vs 64.3%, $P < .001$). Moreover, the cumulative rescue intravenous opioids (in morphine-equivalent dose) on postoperative day (POD) 1 was lower in the LH group than in the OH group (3.3 [0–8.3] mg vs 10 [3.3–17.3] mg; $P < .001$). There were no significant between-group differences in the incidence of respiratory depression (2.4% vs 0.6%; $P = .371$) and prescriptions for pruritus (14.3% vs 15.5%; $P = .878$). However, the prescriptions for postoperative nausea and vomiting (PONV) was significantly higher in the LH group than in the OH group (64.9% vs 41.7%; $P < .001$). The predictors of antiemetic agent prescription included the use of laparoscopic procedure (adjusted odds ratio [OR], 2.05; 95% confidence interval [CI], 1.11–3.79; $P = .021$) and female sex (adjusted OR, 5.63; 95% CI, 3.19–9.92; $P < .001$). Preoperative ITM administration resulted in a significantly lower incidence of moderate-to-severe pain within 24 postoperative hours after laparoscopic donor hepatectomy than after open donor hepatectomy.

Abbreviations: BIS = bispectral index, CI = confidence interval, ESPB = erector spinae plane block, ITM = intrathecal morphine, IV PCA = intravenous patient-controlled analgesia, LH = laparoscopic hepatectomy, NRS = numerical rating scale, OH = open hepatectomy, OR = odds ratio, PACU = postanesthesia care unit, POD = postoperative day, PONV = postoperative nausea and vomiting, SMD = standard mean difference

Keywords: hepatectomy, laparoscopy, liver transplantation, morphine, respiratory depression, spinal injection.

1. Introduction

Liver transplantation is a crucial treatment for end-stage disease, with living donor liver transplantation being an effective

option. However, liver donation carries significant burden of postoperative pain, with a survey indicating that 63% of donors experience higher than anticipated pain severity.^[1] Moreover, since most donors are opioid-naïve, perioperative opioid use

JHK and JSK contributed equally to this work.

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The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2020-03-215-001). Patient consent was waived due to retrospective nature of the study design.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

^a Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, ^b Department of Anesthesiology and Pain Medicine, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong, Korea, ^c Department of Anesthesiology and Pain Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea.

*Correspondence: Wongook Wi, Department of Anesthesiology and Pain Medicine, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gyeonggi-do, Korea, 110 Deokan-ro, Gwangmyeong-si, Gyeonggi-do 14353, Korea (e-mail: hestia.w@gmail.com).

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increases the risk of chronic opioid use.^[2] Our institute has adopted a standard protocol of intrathecal morphine (ITM) for donor hepatectomy since April 2007, to reduce postoperative pain and opioid consumption. Although ITM administration before abdominal surgery is considered safe and effective, potential side effects such as postoperative nausea and vomiting (PONV), pruritus, and respiratory depression, make it difficult for donors to use.^[3–5]

There has been increasing popularity of laparoscopic donor hepatectomy due to its numerous benefits, including less blood loss, decreased postoperative opioid consumption, shortened hospital stay, and few complications.^[6–8] In our institution, laparoscopic donor hepatectomy began being performed in May 2013. Generally, laparoscopic donor hepatectomy is associated with decreased opioid consumption.^[6] However, no studies have compared the analgesic effects of ITM between laparoscopic and open donor hepatectomy; moreover, the safety of ITM administration before laparoscopic donor hepatectomy remains unclear. Accordingly, this study aimed to compare the analgesic effects and safety of ITM between laparoscopic and open donor hepatectomy.

2. Materials and methods

2.1. Study participants

This retrospective study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2020-03-215-001), which waived the requirement for informed consent. We collected data, including postoperative numerical rating scale (NRS) pain scores and prescriptions, from a consecutive series of donors who underwent hepatectomy in Samsung Medical Center between April 2007 and June 2019. All data were retrieved from the clinical data warehouse of Samsung Medical Center. During the study period, 1087 donors underwent hepatectomy and received postoperative analgesia through a combination of intravenous patient-controlled analgesia (IV PCA), ITM injection, wound PCA, and erector spinae plane block (ESPB). The exclusion criteria were as follows: donors who received wound PCA, donors who received ESPB, donors who did not receive ITM, donors with conversion to open procedure, donors with less than 2 measurements of pain scores on each 24-hour intervals as the study endpoint needs at least 2 measurements of pain scores.

2.2. Study endpoints

The primary study endpoint was the incidence of moderate-to-severe pain (maximum NRS pain score ≥ 4) within 24 postoperative hours. The secondary study endpoints included the incidence of moderate-to-severe pain within 24 to 48 hours and 48 to 72 hours; the maximum NRS pain scores within 24 postoperative hours, 24 to 48 hours, and 48 to 72 hours; cumulative rescue intravenous opioids in morphine-equivalent dose in the postanesthesia care unit (PACU) as well as postoperative day (POD) 1, 2, and 3; incidence of pulse oximeter value $\leq 93\%$ within 24 postoperative hours; incidence of prescriptions for pruritus (chlorpheniramine) and PONV (serotonin antagonists, metoclopramide) in POD 3; length of hospital stay; and 30-day readmission rate. Finally, we collected operative findings, including operation time, crystalloid infusion, estimated blood loss, and urine output.

2.3. ITM injection

ITM injection was performed prior to anesthesia induction. Preoperative standard monitoring was performed. The donor was placed in the right lateral decubitus position. After intravenous administration of 1 to 2 mg of midazolam, the skin

was infiltrated using 1% lidocaine. Dura puncture was performed using a 27-gauge Whitacre spinal needle in the lumbar 3 to 4 or 4 to 5 intervertebral space with a midline approach. Subsequently, the attending anesthesiologist collected 1.6 mL of free-flowing cerebrospinal fluid and mixed it with 0.4 mL (400 μ g) of morphine sulfate to yield a 2 mL solution. This mixture was injected into the intrathecal space and the donor was placed in a supine position for anesthesia induction.

2.4. Anesthetic protocol

Standard monitoring equipment was used to monitor patients during the surgery, including measures for oxygen saturation (SpO_2), electrocardiography, noninvasive blood pressure, neuromuscular monitoring, and bispectral index. Anesthesia was induced by administering 5 mg/kg of thiopental sodium along with sevoflurane or desflurane, and remifentanyl. Once the patient lost consciousness, an intravenous dose of 0.6 to 0.8 mg/kg of rocuronium was given, followed by intubation. Anesthetic maintenance was carried out using isoflurane or desflurane. Supplementary monitors were utilized to measure end-tidal carbon dioxide ($EtCO_2$), esophageal temperature, and invasive arterial blood pressure through a radial artery catheter. Central venous catheterization was not performed, but an additional peripheral venous line was used at the discretion of the anesthesiologist. A fluid restriction policy was implemented, with a crystalloid solution administered at a rate of 200 mL/h during the operation. An additional 200 mL of crystalloid solution was given when there was an increase in hematocrit or a urine output below 0.3 mL/kg/h. Following heparin administration, a colloid solution of 500 mL was infused. Hypotension was managed with a 5 mg dose of ephedrine, while bradycardia was treated with atropine. Neostigmine or pyridostigmine was used to reverse the neuromuscular block.

2.5. Postoperative analgesia

At the end stage of the operation, all patients received 25 mg of intravenous pethidine. After discharge to the PACU, IV PCA (100 mL solution containing 1500 μ g of fentanyl) was started. For patients aged > 65 years, the fentanyl dose was adjusted to 1200 μ g. Further titration of the fentanyl dose was considered if the donor had a reduced glomerular filtration rate or extremely low body weight. The delivery rate was 1 mL/h with a 1 mL bolus volume and a 15-minutes lockout time. The attending anesthesiologist in the PACU prescribed a rescue intravenous opioid if the patients had an NRS pain score ≥ 4 . After the patient was transferred to a general ward, the attending general surgery staff prescribed rescue intravenous opioids based on the aforementioned NRS pain score criteria.

2.6. Surgical procedures

In our institution, the first case of laparoscopic donor hepatectomy was performed in May 2013. A review describing the surgical techniques for laparoscopic^[9] as well as open^[10] donor hepatectomy have been previously published from our institution. Prior to laparoscopic hepatectomy (LH), all laparotomy was performed through the Mercedes incision or extended right subcostal incision and labeled as open hepatectomy (OH) regardless of the incision type. During the procedure of pure laparoscopic donor right hepatectomy, trocar ports were inserted according to the following specifications: a 12 mm port was positioned at the umbilicus, accommodating a 30-degree optical device; two 12 mm operative trocars were placed, one at the subcostal margin in the right midaxillary line and another in the midline between the umbilicus and xiphoid process; and two 5 mm trocars were utilized for instrumental assistance, positioned along the subcostal margin in the left midclavicular line

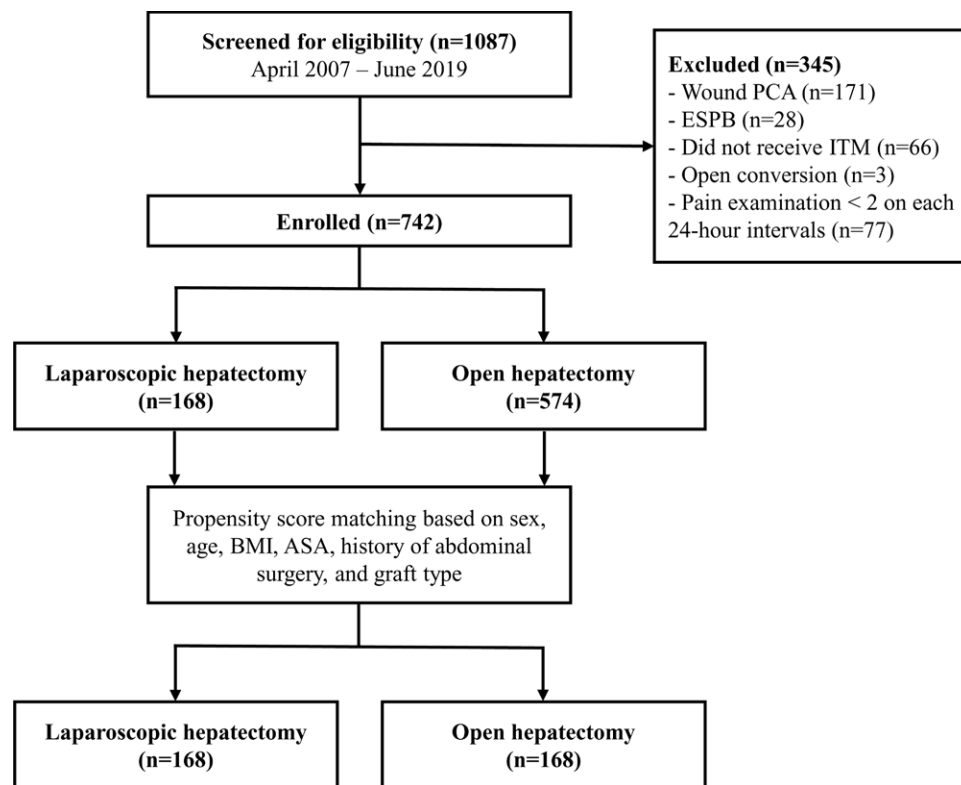


Figure 1. Study flow diagram of patient selection and allocation.

and in the subxiphoid region. The hepatic graft was extracted through a 12 to 14 cm Pfannenstiel incision located in the suprapubic area. Surgeon did not perform local wound anesthetic infiltration in any of the surgical incisions. Eligibility for liver donation was determined based on our institution standard criteria: age ≤ 65 years; body mass index < 35 kg/m²; macrosteatosis $\leq 30\%$; and residual liver volume $\geq 30\%$.

2.7. Statistical analyses

The normality of data distribution was examined using the Shapiro–Wilk test. Continuous variables are presented as mean $\pm$ standard deviation or median with interquartile range, as appropriate, with between-group comparisons using Student *t* test or Mann–Whitney test, as appropriate. Categorical variables are presented as numbers with percentages, with between-group comparisons using the chi-squared test or Fisher exact test. To minimize selection bias, we performed 1:1 propensity score matching using the nearest-neighbor method without replacement. In the multiple logistic regression analyses, we adjusted for the following covariates: sex, age, body mass index, American Society of Anesthesiologists, history of abdominal surgery, and graft type. After propensity matching, a standard mean difference (SMD) < 0.2 suggested an appropriate between-group balance of preoperative variables. Unadjusted simple and multivariate logistic regression analyses were used to evaluate the influence of each variable on the prescriptions for PONV. The odds ratio (OR) was reported with a 95% confidence interval (CI) and *P* value. All statistical analyses were performed using R Statistical Software 3.6.1 (Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a 2-tailed *P* value of .05.

3. Results

Among 1087 living liver donors who underwent hepatectomy during the study period, we excluded 171 donors with wound

PCA, 28 donors with ESPB, and 66 donors who did not receive ITM injections. Three donors with open conversion of laparoscopic surgery and 77 donors with less than 2 measurements of pain scores on each 24-hour intervals were excluded. Among the remaining 742 patients for analysis, 168 underwent LH group and 574 underwent OH group. Propensity score matching yielded two comparable groups of 168 donors each. A flow diagram of patient selection and allocation is presented in Figure 1. Table 1 summarizes the baseline characteristics of both groups before and after matching.

3.1. Operative findings

After matching, the LH group had a significantly shorter operation time than the OH group (268.8 ± 58.3 minutes vs 349.7 ± 61.8 minutes; $P < .001$). Moreover, the LH group had significantly lower crystalloid infusion (1500 [1300–1850] mL vs 2000 [1700–2400] mL; $P < .001$) and estimated blood loss (200 [150–300] mL vs 400 [287.5–420] mL; $P < .001$) than the OH group. Table 1 summarizes the operative findings of both groups before and after matching.

3.2. Postoperative outcomes

After matching, the LH group had a significantly lower incidence of moderate-to-severe pain within 24 postoperative hours (16.1% vs 64.3% ; $P < .001$), 24 to 48 hours (50.6% vs 69.0% ; $P = .001$), and 48 to 72 hours (32.1% vs 70.2% ; $P < .001$) than the OH group. Figure 2 depicts bar plots presenting the distribution of the maximum NRS pain score for each 24-hour intervals. Moreover, the LH group had significantly lower cumulative rescue intravenous opioids morphine-equivalent dose in the PACU (0 [0–3.3] mg vs 3.3 [2–6.7] mg; $P < .001$), POD 1 (3.3 [0–8.3] mg vs 10 [3.3–17.3] mg; $P < .001$), POD 2 (10 [3.3–23.3] mg vs 18 [6.7–30.2] mg; $P < .001$), and POD 3 (10 [3.3–30] mg vs 24 [10–43.5] mg, $P < .001$) than the OH group. There were no

Table 1**Baseline characteristics and operative findings of the two groups before and after propensity score matching.**

	Entire population				1:1 Propensity-score matched population			
	LH (N = 168)	OH (N = 574)	P	SMD	LH (N = 168)	OH (N = 168)	P	SMD
Female, n (%)	72 (42.9)	199 (34.7)	.065	0.169	72 (42.9)	64 (38.1)	.437	0.097
Age, yr	30.5 [24.0, 42.0]	31.0 [25.0, 40.0]	.838	0.046	30.5 [24.0, 42.0]	31.0 [25.0, 40.3]	.89	0.03
BMI, kg/m ²	23.4 ± 2.9	23.4 ± 2.9	.839	0.018	23.4 ± 2.9	23.7 ± 3.1	.433	0.086
ASA grade II, n (%)	32 (19.0)	43 (7.5)	<.001	0.346	32 (19.0)	35 (20.8)	.785	0.045
History of previous abdominal surgery, n (%)	24 (14.3)	93 (16.2)	.632	0.053	24 (14.3)	22 (13.1)	.874	0.035
Graft, n (%)			.592	0.094			.461	0.155
Right hemi & extended hepatectomy	157 (93.5)	523 (91.1)			157 (93.5)	154 (91.7)		
Left hemi & extended hepatectomy	5 (3.0)	20 (3.5)			5 (3.0)	3 (1.8)		
Left lateral sectionectomy	6 (3.6)	31 (5.4)			6 (3.6)	11 (6.5)		
Operation time, min	268.8 ± 58.3	346.9 ± 60.2	<.001	1.317	268.8 ± 58.3	349.7 ± 61.8	<.001	1.346
Crystalloids, mL	1500.0 [1300.0, 1850.0]	2000.0 [1700.0, 2400.0]	<.001	0.938	1500.0 [1300.0, 1850.0]	2000.0 [1700.0, 2400.0]	<.001	0.907
Estimated blood loss, mL	200.0 [150.0, 300.0]	400.0 [300.0, 450.0]	<.001	0.921	200.0 [150.0, 300.0]	400.0 [287.5, 420.0]	<.001	0.958
Urine output, mL	280.0 [210.0, 370.0]	300.0 [205.0, 420.0]	.457	0.185	280.0 [210.0, 370.0]	295.0 [205.0, 421.3]	.489	0.198

Data are presented as means ± SDs, medians with IQRs in brackets, or numbers with percentages in parentheses.

ASA = American Society of anesthesiologists, BMI = body mass index, LH = laparoscopic hepatectomy, OH = open hepatectomy, SMD = standardized mean difference.

significant between-group differences in the incidence of pulse oximeter value $\leq 93\%$ (2.4% vs 0.6%; $P = .371$) and prescriptions for pruritus (14.3% vs 15.5%; $P = .878$). However, the incidence of prescriptions for PONV was significantly higher in the LH group than in the OH group (64.9% vs 41.7%; $P < .001$). Table 2 summarizes the postoperative outcomes of both groups after matching. Simple and multivariate logistic regression analyses were performed to evaluate the influence of each variable on the prescriptions for PONV (Table 3). The predictors of prescriptions for PONV included the use of laparoscopic procedure (adjusted OR, 2.05; 95% CI, 1.11–3.79; $P = .021$) and female sex (adjusted OR, 5.63; 95% CI, 3.19–9.92; $P < .001$).

4. Discussion

Our findings indicated that ITM was more effective in postoperative pain management in the LH group than in the OH group, as indicated by the lower incidence of moderate-to-severe pain (maximum NRS score ≥ 4) within 24 postoperative hours. Generally, the laparoscopic procedure is related to lower postoperative pain severity than the open procedure in numerous abdominal surgeries.^[11–13] Therefore, the superior analgesic results in the LH group could be attributed, at least in part, to the less invasiveness of the laparoscopic surgery compared to the open surgery. Reflecting that, the lower incidence of moderate-to-severe pain in the LH group was observed throughout the entire pain assessment period (72 postoperative hours). However, the effect size (SMD = 1.129) of the incidence of moderate-to-severe pain between the two groups was unexpectedly large within 24 postoperative hours, which is the duration of ITM,^[14] suggesting an additional analgesic benefit when the laparoscopic surgery was performed with ITM. It is presumed that the additional benefit comes from the low-lying location of the Pfannenstiel incision. The pharmacokinetics of intrathecal opioids are complex, and the distribution is mainly determined by the lipophilicity of the opioids.^[15] As the morphine is one of the most hydrophilic opioids, diffusion into the white matter of the spinal cord or the epidural space is limited, and rostral

spread within the cerebrospinal fluid is most extensive among intrathecally injected opioids.^[16] The resulting wide band of analgesia from the site of injection allows the use of ITM in various types of surgeries including open heart and thoracic surgery.^[13] However, our study result indicates that there are segmental analgesic properties according to the level of the afferent pain pathway into the spinal cord. Intrathecal administration of 0.4 mg morphine appears to have additional analgesic benefit in the low-lying Pfannenstiel incision below T10 than in the vertical incision above.

Due to the large effect size of the primary endpoint, we have conducted a literature survey. Moderate-to-severe pain is commonly used as a threshold for initiating pain treatment,^[17] or allowing patients to engage in activities such as ambulation.^[18] Most studies determined moderate-to-severe pain as a maximum NRS pain score ≥ 4 .^[17–21] According to the literature, the incidence of moderate-to-severe pain during the first 24 hours after abdominal surgery ranges from 30% to 55%.^[19] The selected analgesic modality influences the incidence of moderate-to-severe pain, with reported incidence rates of 67% for intramuscular opioid injection, 36% for IV PCA, and 21% for epidural catheter analgesia within 24 hours after major surgery.^[20] In specific, liver donors managed with epidural PCA or IV PCA experience 42% and 74% incidence of moderate-to-severe pain during rest and movement, respectively, on the first POD.^[21] The study results of 16.1% incidence of moderate-to-severe pain in the LH group is among the lowest incidence of the literature findings and less than one third of the incidence in the OH group (64.3%). The results of this study strongly suggest that the ITM has a profound analgesic effect for the Pfannenstiel incision, establishing additional benefit of ITM for liver donors undergoing LH. Attaining additional analgesic benefit in acute postoperative period is highly valuable since it is related to an increased risk of chronic persistent postoperative pain.^[22,23] Among liver donors, the incidence of persistent postoperative pain is 30.9% and 26.9% at 6 months and 12 months, respectively.^[21] Furthermore, since opioid use among opioid-naïve donors increases the risk of chronic opioid use,^[2] it is crucial that the use of ITM in laparoscopic donor hepatectomy

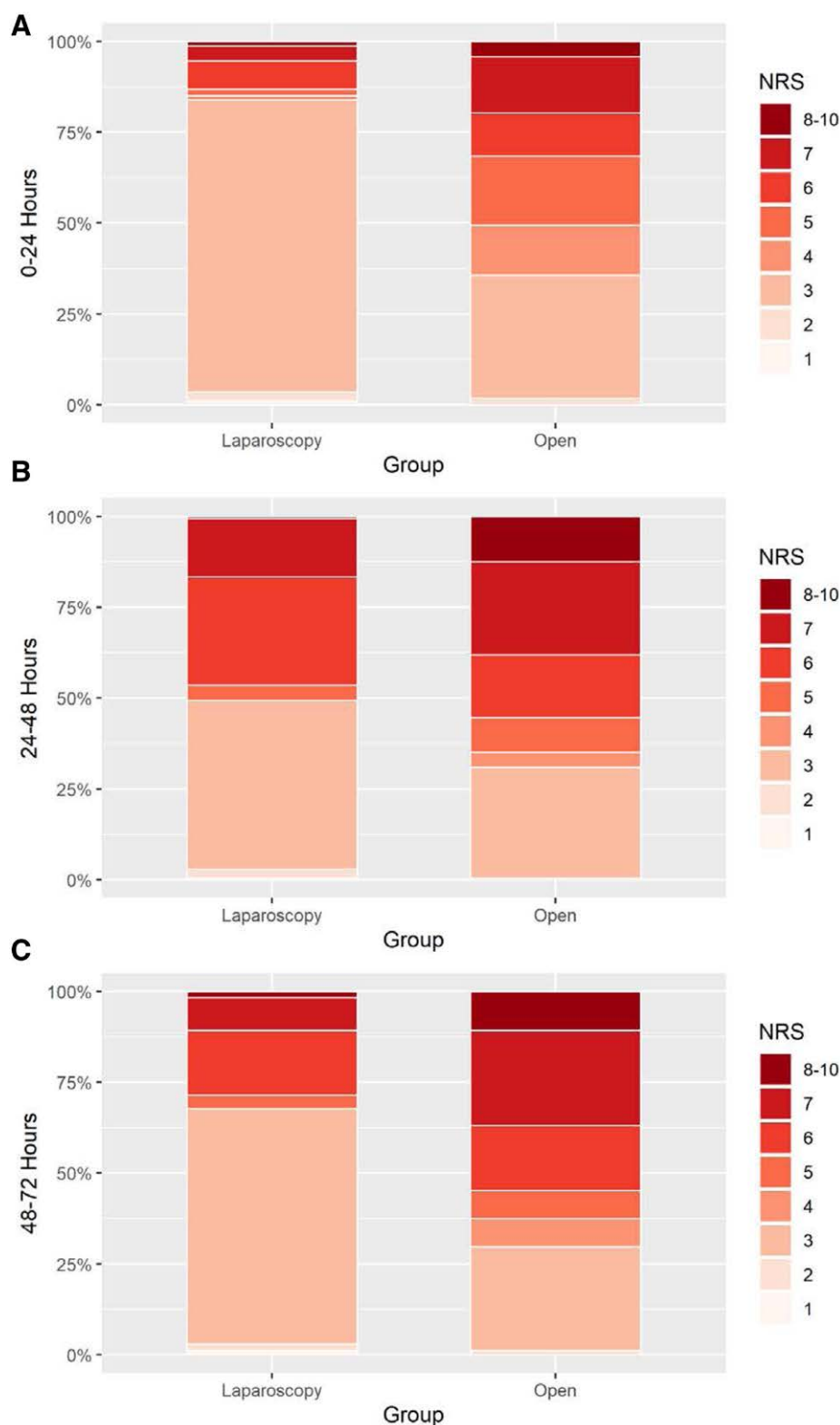


Figure 2. Bar plots presenting the distribution of the maximum NRS pain score for each 24-h intervals. NRS = numerical rating scale.

also decreased the cumulative rescue opioid dose than in open donor hepatectomy in this study.

As was noted above, the LH group continued to have a lower incidence of moderate-to-severe pain than the OH group, after 24 hours. However, the decreased effect size ($SMD = 0.383$) and increased incidence rate of 50.6% indicates the need for further research on the optimal analgesia protocol for liver donors after

24 hours, even for laparoscopic surgery. Given the relatively short-acting duration of ITM, we have compared ITM with other analgesic strategies such as continuous wound infusion with ropivacaine,^[24] bilateral single-injection ESPB,^[25] quadratus lumborum block,^[26] and bilateral continuous ESPB using a programmed intermittent bolus regimen.^[27] However, none of these protocols showed superior analgesic effects compared

Table 2
Postoperative outcomes of the two groups after propensity score matching.

	LH (N = 168)	OH (N = 168)	P	SMD
Maximum NRS ≥ 4 for 0–24 h, n (%)	27 (16.1)	108 (64.3)	<.001	1.129
Maximum NRS ≥ 4 for 24–48 h, n (%)	85 (50.6)	116 (69.0)	.001	0.383
Maximum NRS ≥ 4 for 48–72 h, n (%)	54 (32.1)	118 (70.2)	<.001	0.824
Maximum NRS for 0–24 h	3.0 [3.0, 3.0]	5.0 [3.0, 6.0]	<.001	0.837
Maximum NRS for 24–48 h	5.0 [3.0, 6.0]	6.0 [3.0, 7.0]	<.001	0.443
Maximum NRS for 48–72 h	3.0 [3.0, 6.0]	6.0 [3.0, 7.0]	<.001	0.762
Rescue IV opioids MED at PACU, mg	0.0 [0.0, 3.3]	3.3 [2.0, 6.7]	<.001	0.761
Rescue IV opioids MED at POD 1, mg	3.3 [0.0, 8.3]	10.0 [3.3, 17.3]	<.001	0.661
Rescue IV opioids MED at POD 2, mg	10.0 [3.3, 23.3]	18.0 [6.7, 30.2]	<.001	0.417
Rescue IV opioids MED at POD 3, mg	10.0 [3.3, 30.0]	24.0 [10.0, 43.5]	<.001	0.537
Pulse oximeter ≤ 93 , n (%)	4 (2.4)	1 (0.6)	.371	0.148
Prescriptions for pruritus, n (%)	24 (14.3)	26 (15.5)	.878	0.033
Prescriptions for PONV, n (%)	109 (64.9)	70 (41.7)	<.001	0.478
Length of stay, d	10.0 [9.0, 11.0]	14.0 [11.0, 18.0]	<.001	0.999
Readmission within 30 d, n (%)	1 (0.6)	5 (3.0)	.215	0.181

Data are presented as means $\pm$ SDs, medians with IQRs in brackets, or numbers with percentages in parentheses.

LH = laparoscopic hepatectomy, MED = morphine equivalent dose, NRS = numerical rating scale, PACU = post-anesthesia care unit, POD = postoperative days, PONV = postoperative nausea and vomiting, OH = open hepatectomy, SMD = standardized mean difference, IV = intravenous.

Table 3
Simple and multivariate logistic regression of factors associated with the probability of antiemetic agent prescription.

	Crude Odds Ratio (95% CI)	Crude P	Adjusted Odds Ratio (95% CI)	Adjusted P
Group: Laparo vs Open	2.59 (1.66,4.02)	<.001	2.05 (1.11,3.79)	.021
Sex: Female vs Male	4.79 (2.96,7.76)	<.001	5.63 (3.19,9.92)	<.001
Age	1.01 (0.99,1.03)	.311	0.99 (0.96,1.01)	.364
BMI	1 (0.93,1.08)	.939	1.08 (0.99,1.17)	.1
ASA grade II	0.7 (0.41,1.2)	.2	0.7 (0.36,1.39)	.311
History of previous abdominal surgery	1.43 (0.76,2.7)	.268	1 (0.47,2.12)	.994
Graft: ref.=Right hemi & extended hepatectomy				
Left hemi & extended hepatectomy	0.88 (0.22,3.6)	.864	0.86 (0.18,4.17)	.855
Left lateral sectionectomy	1.26 (0.47,3.41)	.643	0.8 (0.25,2.55)	.71
Operation time	0.99 (0.99,1)	<.001	1 (0.99,1)	.496
Crystalloids	1 (1,1)	.004	1 (1,1)	.843
Estimated blood loss	1 (1,1)	<.001	1 (1,1)	.131
Urine output	1 (1,1)	.848	1 (1,1)	.996

ASA = American Society of Anesthesiologists, BMI = body mass index, CI = confidence interval.

with ITM. Nonetheless, bilateral continuous ESPB was associated with a statistically non-significant lower pain score at 24 postoperative hours and significantly lower pain score at 48 and 72 hours, while resting.^[27] A combined use of ITM and bilateral continuous ESPB may overcome the relatively short duration of ITM. A recent liver donor study on the ERAS protocol^[28] and a review on liver donor management^[29] also recommend a multimodal analgesia strategy for liver donors that comprises neuraxial techniques, truncal nerve blocks, and intravenous agents other than opioids.

Among the major complications associated with ITM administration in donors, the most feared one is respiratory depression, which can occur up to 31 hours after injection despite the elimination half-life of ITM being ≈ 3.2 hours.^[16,30] However, the incidence of respiratory depression in patients receiving ITM remains unclear given the differences in the diagnostic criteria across studies. A Cochrane review reported that the incidence of respiratory depression among patients receiving IV PCA was 2.3% based on 3 criteria: pulse oximeter value $\leq 90\%$, respiratory rate $<10/\text{min}$, and/or intervention (naloxone) requirement.^[31] Since our study was retrospective, we could not determine the respiratory frequency. Instead, respiratory depression was indicated by pulse oximeter value $\leq 93\%$, which indicates an intervention requirement. We observed no significant between-group difference in the incidence of respiratory depression, which may be attributed to our institutional safety

standards for monitoring oxygen saturation overnight and nasal cannula oxygenation at 2 L/min. A meta-analysis that used the respiratory frequency criterion reported that the incidence of respiratory depression was 2%, 1%, and 9% in the placebo, morphine < 0.3 mg, and morphine ≥ 0.3 mg groups, respectively, which indicates that a morphine dose > 0.3 mg increases the risk of respiratory depression.^[4] Another recent meta-analysis that used the intervention criterion reported that the incidence of respiratory depression was $< 0.5\%$ and 0.5% in the control and morphine < 0.5 mg groups, respectively, and thus recommended a morphine dose of < 0.5 mg for clinical use.^[5] We observed no additional risk of respiratory depression with intrathecal administration of 0.4 mg morphine in the LH group. Notably, our finding should be cautiously interpreted given the differences in the diagnostic criteria for respiratory depression across studies; moreover, our study may have insufficient power to detect an increased risk given the rare incidence of respiratory depression.

In our study, the incidence of pruritus and PONV was determined based on the prescriptions for chlorpheniramine and antiemetic agents, respectively. There was no between-group difference in the incidence of prescriptions for pruritus; however, the incidence of prescriptions for PONV was higher in the LH group than in the OH group. Moreover, the use of the laparoscopic procedure and female sex were risk factors for prescriptions for PONV. This is consistent with previous reports of a higher incidence of PONV following laparoscopic

procedures.^[32,33] This could be attributed to stretching of the pneumoperitoneum during laparoscopy, which irritates the peritoneum and results in apparent vagal input to the nucleus tractus solitarius, a key center for PONV.^[34] We recently reported a lower incidence of PONV in the 0.3 mg morphine group than in the 0.4 mg morphine group, with a non-inferior analgesic effect.^[35] Further studies on optimal dosing and administration strategies of ITM are warranted.

This study has several limitations. First, this was a single-center retrospective observational study, which may limit the generalizability of the findings. Nonetheless, we attempted to minimize selection bias through 1:1 propensity score matching to adjust for covariates. Second, the timing and frequency of NRS pain examination varied across patients. To address this issue, we selected the maximum pain score on each 24-hour intervals and analyzed the incidence of moderate-to-severe pain rather than the pain score at a specific time point. Third, the use of intraoperative use of remifentanyl and postoperative IV PCA was not controlled between the two groups. Although there was no patient without remifentanyl or IV PCA, the amount of remifentanyl and IV PCA consumption may differ between the two groups. Fourth, the occurrence of respiratory depression was determined based on a pulse oximeter value $\leq 93\%$, which differs from the criteria used in other studies. However, our criterion is a faithful setting to detect the respiratory depression without clinical symptoms, given the nature of ITM-related respiratory depression (reduced compensation to hypoxia). Fifth, we could not differentiate the nature of postoperative pain (visceral or somatic pain). Nonetheless, this study has several strengths, including the adoption of clinically meaningful endpoints and analysis of data collected at 24-hour intervals for comprehensive examination of the burden of acute postoperative pain.

5. Conclusion

Our findings suggest that preoperative ITM administration can significantly reduce the incidence of moderate-to-severe pain among donors within 24 postoperative hours following LH than following OH. Further studies are warranted to validate our findings and to identify the optimal dosing and administration strategies.

Author contributions

Conceptualization: Justin Sangwook Ko, Mi Sook Gwak, Wongook Wi.

Data curation: Ji-Hye Kwon, Justin Sangwook Ko, Gaab Soo Kim, Wongook Wi.

Formal analysis: Hyo Jin Kim, Sangbin Han, Wongook Wi.

Methodology: Ji-Hye Kwon, Sangbin Han.

Project administration: Justin Sangwook Ko, Mi Sook Gwak, Gaab Soo Kim.

Visualization: Ji-Hye Kwon, Hyo Jin Kim, Seung Young Lee.

Writing – review & editing: Ji-Hye Kwon, Justin Sangwook Ko, Wongook Wi.

Writing – original draft: Justin Sangwook Ko, Wongook Wi.

References

- [1] Barr ML, Belgithi J, Villamil FG, et al. A report of the Vancouver forum on the care of the live organ donor: lung, liver, pancreas, and intestine data and medical guidelines. *Transplantation*. 2006;81:1373–85.
- [2] Stark N, Kerr S, Stevens J. Prevalence and predictors of persistent post-surgical opioid use: a prospective observational cohort study. *Anaesth Intensive Care*. 2017;45:700–6.
- [3] Meylan N, Elia N, Lysakowski C, et al. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth*. 2009;102:156–67.

- [4] Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia*. 2009;64:643–51.
- [5] Koning MV, Klimek M, Rijs K, et al. Intrathecal hydrophilic opioids for abdominal surgery: a meta-analysis, meta-regression, and trial sequential analysis. *Br J Anaesth*. 2020;125:358–72.
- [6] Bekheit M, Khafagy PA, Bucur P, et al. Donor safety in live donor laparoscopic liver procurement: systematic review and meta-analysis. *Surg Endosc*. 2015;29:3047–64.
- [7] Xu J, Hu C, Cao HL, et al. Meta-analysis of laparoscopic versus open hepatectomy for live liver donors. *PLoS One*. 2016;11:e0165319.
- [8] Gao Y, Wu W, Liu C, et al. Comparison of laparoscopic and open living donor hepatectomy: a meta-analysis. *Medicine (Baltim)*. 2021;100:e26708.
- [9] Kwon CHD, Joh J-W. Totally laparoscopic right hepatectomy for living donors. In: Aseni P, Grande AM, De Carlis L, eds. *Multiorgan Procurement for Transplantation*. Cham: Springer International Publishing; 2016:239–245.
- [10] Shin M, Song S, Kim JM, et al. Donor morbidity including biliary complications in living-donor liver transplantation: single-center analysis of 827 cases. *Transplantation*. 2012;93:942–8.
- [11] Nguyen NT, Lee SL, Goldman C, et al. Comparison of pulmonary function and postoperative pain after laparoscopic versus open gastric bypass: a randomized trial. *J Am Coll Surg*. 2001;192:469–76; discussion 476–467.
- [12] Reza MM, Blasco JA, Andradas E, et al. Systematic review of laparoscopic versus open surgery for colorectal cancer. *Br J Surg*. 2006;93:921–8.
- [13] Holzer A, Jirecek ST, Illievich UM, et al. Laparoscopic versus open myomectomy: a double-blind study to evaluate postoperative pain. *Anesth Analg*. 2006;102:1480–4.
- [14] Ko JS, Choi SJ, Gwak MS, et al. Intrathecal morphine combined with intravenous patient-controlled analgesia is an effective and safe method for immediate postoperative pain control in live liver donors. *Liver Transpl*. 2009;15:381–9.
- [15] Hindle A. Intrathecal opioids in the management of acute postoperative pain. *Cont Educ Anaesth Crit Care Pain*. 2008;8:81–5.
- [16] Nordberg G, Hedner T, Mellstrand T, et al. Pharmacokinetic aspects of intrathecal morphine analgesia. *Anesthesiology*. 1984;60:448–54.
- [17] Gerbershagen HJ, Rothaug J, Kalkman CJ, et al. Determination of moderate-to-severe postoperative pain on the numeric rating scale: a cut-off point analysis applying four different methods. *Br J Anaesth*. 2011;107:619–26.
- [18] van Boekel RL, Vissers KC, van der Sande R, et al. Moving beyond pain scores: multidimensional pain assessment is essential for adequate pain management after surgery. *PLoS One*. 2017;12:e0177345.
- [19] Sommer M, de Rijke JM, van Kleef M, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur J Anaesthesiol*. 2008;25:267–74.
- [20] Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth*. 2002;89:409–23.
- [21] Holtzman S, Clarke HA, McCluskey SA, et al. Acute and chronic post-surgical pain after living liver donation: incidence and predictors. *Liver Transpl*. 2014;20:1336–46.
- [22] Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiol Clin North Am*. 2005;23:21–36.
- [23] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618–25.
- [24] Lee SH, Gwak MS, Choi SJ, et al. Prospective, randomized study of ropivacaine wound infusion versus intrathecal morphine with intravenous fentanyl for analgesia in living donors for liver transplantation. *Liver Transpl*. 2013;19:1036–45.
- [25] Kang R, Chin KJ, Gwak MS, et al. Bilateral single-injection erector spinae plane block versus intrathecal morphine for postoperative analgesia in living donor laparoscopic hepatectomy: a randomized non-inferiority trial. *Reg Anesth Pain Med*. 2019;44:1059–65.
- [26] Lee S, Kang RA, Kim GS, et al. Comparison of postoperative analgesic effects of posterior quadratus lumborum block and intrathecal morphine in laparoscopic donor hepatectomy: a prospective randomized non-inferiority clinical trial. *Reg Anesth Pain Med*. 2022;47:527–33.
- [27] Kang R, Chin KJ, Kim GS, et al. Bilateral continuous erector spinae plane block using a programmed intermittent bolus regimen versus intrathecal morphine for postoperative analgesia in living donor laparoscopic hepatectomy: a randomized controlled trial. *J Clin Anesth*. 2021;75:110479.

- [28] Khalil A, Ganesh S, Hughes C, et al. Evaluation of the enhanced recovery after surgery protocol in living liver donors. *Clin Transplant*. 2018;32:e13342.
- [29] Sakai T, Ko JS, Crouch CE, et al. Perioperative management of living donor liver transplantation: part 2 - donors. *Clin Transplant*. 2022;36:e14690.
- [30] Shapiro A, Zohar E, Zaslansky R, et al. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth*. 2005;17:537–42.
- [31] McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev*. 2015;2015:CD003348.
- [32] Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth*. 2012;109:742–53.
- [33] Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118:85–113.
- [34] Andrews PL, Naylor RJ, Joss RA. Neuropharmacology of emesis and its relevance to anti-emetic therapy. Consensus and controversies. *Support Care Cancer*. 1998;6:197–203.
- [35] Lee S, Kang R, Choi GS, et al. Comparison of two doses of intrathecal morphine in laparoscopic donor hepatectomy: a randomized double-blinded non-inferiority trial. *Clin Transplant*. 2023:e14996.