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Intrathecal Morphine and Effect on Opioid Consumption and Functional Recovery after Pancreaticoduodenectomy

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BACKGROUND: Single-shot intrathecal morphine (ITM) is an effective strategy for postoperative analgesia, but there are limited data on its safety, efficacy, and relationship with functional recovery among patients undergoing pancreaticoduodenectomy.

STUDY DESIGN: This was a retrospective review of patients undergoing pancreaticoduodenectomy from 2014 to 2020 as identified by the institutional NSQIP Hepato-pancreato-biliary database. Patients were categorized by having received no spinal analgesia, ITM, or ITM with transversus abdominus plane block (ITM+TAP). The primary outcomes were average daily pain scores from postoperative days (POD) 0 to 3, total morphine equivalents (MEQ) consumed over POD 0 to 3, and average daily inpatient MEQ from POD 4 to discharge. Secondary outcomes included the incidence of opioid related complications, length of stay, and functional recovery.

RESULTS: A total of 233 patients with a median age of 67 years were included. Of these, 36.5% received no spinal analgesia, 49.3% received ITM, and 14.2% received ITM+TAP. Average pain scores in POD 0 to 3 were similar by mode of spinal analgesia (none [2.8], ITM [2.6], ITM+TAP [2.3]). Total MEQ consumed from POD 0 to 3 were lower for patients who received ITM (121 mg) and ITM+TAP (132 mg), compared with no spinal analgesia (232 mg) ($p < 0.0001$). Average daily MEQ consumption from POD 4 to discharge was lower for ITM (18 mg) and ITM+TAP (13.1 mg) cohorts compared with no spinal analgesia (32.9 mg) ($p = 0.0016$). Days to functional recovery and length of stay were significantly reduced for ITM and ITM+TAP compared with no spinal analgesia. These findings remained consistent through multivariate analysis, and there were no differences in opioid-related complications among cohorts.

CONCLUSIONS: ITM was associated with reduced early postoperative and total inpatient opioid utilization, days to functional recovery, and length of stay among patients undergoing pancreaticoduodenectomy. ITM is a safe and effective form of perioperative analgesia that may benefit patients undergoing pancreaticoduodenectomy. (J Am Coll Surg 2022;235:392–400. © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American College of Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 [CCBY-NC-ND], where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.)

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Abbreviations and Acronyms

ITM	=	intrathecal morphine
LOS	=	length of stay
MEQ	=	morphine equivalents
POD	=	postoperative day
TAP	=	transversus abdominus plane

Single-shot intrathecal morphine (ITM) is an emerging strategy for postoperative analgesia following major abdominal surgery. Traditional spinal analgesia protocols often rely on continuous thoracic epidural anesthesia due to its ability to provide adequate analgesia with few cardiopulmonary complications.[1-3] However, epidural anesthesia is also associated with more frequent perioperative hypotension, technical failure, increased fluid administration, and greater length of stay (LOS). Therefore, ITM is an appealing alternative because it offers easier administration, strong efficacy at low doses, and reduced postoperative complications, and provides an alternative form of spinal analgesia for patients where an epidural catheter is contraindicated.[4-10]

The analgesic properties of ITM have recently been demonstrated in cardiac,[11] gynecologic,[9,12] spinal,[13-15] orthopedic,[16] urologic,[17] colorectal,[18] hepatopancreatic-obiliary,[10,19-23] and major abdominal surgery.[7,24,25] With an estimated duration of action up to 24 hours,[26] these studies have focused on the initial postoperative recovery period and often identified lower pain scores and, in some cases, decreased initial postoperative opioid requirements. However, data regarding the use of ITM among a large cohort of patients undergoing pancreaticoduodenectomy are limited.

In 2016, our institution started the use of ITM for patients undergoing pancreaticoduodenectomy. In this study, we sought to evaluate the effect of ITM with and without transversus abdominus plane (TAP) blocks on postoperative pain scores, opioid utilization, and functional recovery during the postoperative recovery period for patients undergoing pancreaticoduodenectomy.

METHODS

Patient selection

All patients who underwent pancreaticoduodenectomy by the Division of Surgical Oncology from January 2014 to September 2020 were reviewed. Patients who received epidural anesthesia or TAP blocks alone were excluded due to limited sample size. All patients who were extubated after the case and survived the index hospitalization were eligible. At our institution, all patients recovered in the postanesthesia care unit until meeting appropriate milestones for transfer. After transfer, those who received ITM were initially monitored with a "step-down" level of care on a general surgery floor, unless their clinical status required the intensive care unit. For patients without spinal analgesia, postoperative recovery location was determined by clinical status alone.

Demographic (age, sex, ethnicity), clinical (BMI, comorbidities, method of analgesia), operative (indication, duration, approach [open vs minimally invasive], vascular reconstruction), and outcomes (patient-reported pain scores [0 = none to 10 = severe], morphine equivalents [MEQ] consumed, functional recovery, LOS) were abstracted from the NSQIP Hepato-pancreato-biliary collaborative database. This study was approved by the institutional review board.

Method of analgesia

Patients were categorized by the type of spinal analgesia administered preoperatively as follows: none, ITM alone, and ITM with TAP block (ITM+TAP). ITM was administered at a dose of 0.15–0.3 mg before induction, per the attending anesthesiologist discretion. Bilateral TAP blocks were administered with bupivacaine at the conclusion of the case by the operating surgeon under direct visualization or the attending anesthesiologist via ultrasound guidance. Multimodal analgesia and patient-controlled analgesia were routinely used, and patients were transitioned to oral analgesics per protocol or surgeon preference.

Definitions and equations

Patients with a history of chronic opioid use or an active opioid prescription (including buprenorphine/naloxone) within 6 months of their operation were considered chronic opioid users. Substance use disorder was defined as any recreational drug use disorder history. MEQ were calculated using published conversion factors as follows: MEQ = (strength per unit × quantity × morphine milligram equivalent conversion factor).[27] MEQ were assessed daily from postoperative day (POD) 0 to 3 and subsequently averaged from POD 4 to discharge by dividing the cumulative POD 4 to discharge MEQ by postoperative LOS. Operative duration included time from surgical incision to abdominal wall closure. Functional recovery was defined by the number of days until ambulation beyond 100 feet. Discharge was defined as the release of the patient from hospitalization to either home or rehabilitation facility.

Outcomes

The primary outcomes were average daily pain scores from POD 0 to 3, total MEQ consumed over POD 0 to 3, and average daily inpatient MEQ from POD 4 to discharge. Secondary outcomes of interest included the incidence of opioid related complications, LOS, and days to functional recovery. Any of the following were considered possible opioid-related complications: naloxone administration, postoperative respiratory failure, ileus, or delayed gastric emptying within 30 days of surgery.

Statistical analysis

The features of the cohorts were compared using the chi-square test for categorical variables and Kruskal–Wallis chi-square test where applicable. Bivariate associations among features of the cohorts with postoperative outcomes were evaluated using the Kruskal–Wallis test. Post hoc pairwise comparisons were carried out using Dunn's test[28] with the Benjamini–Hochberg[29] adjustment for multiple comparisons. Multivariable regression models were used to estimate the independent, adjusted association of patient and disease characteristics with continuous outcomes, while minimizing the impact of response outliers and high leverage points.[30] Model predictors included indicators for spinal analgesia plus any factor with a significant bivariate association ($p < 0.10$) with the outcome. Statistical analyses were conducted using SAS (v14.2) except for the post hoc pairwise tests, which used the R package, Dunn.test (v1.3.5).

RESULTS

A total of 233 patients were eligible (**Supplemental Digital Content 1**, http://links.lww.com/JACS/A92). The median age was 67 years, the majority (51.5%) were male, and 24.9% were considered chronic opioid users (Table 1). Most (81.6%) underwent open pancreaticoduodenectomy, the median operative duration was 378 minutes, and 84.3% of cases were performed for malignant pathology. The median LOS for the cohort was 7 days, and the median time to functional recovery (days to ambulation beyond 100 feet) was POD 2.

Overall, 36.5% of patients received no spinal analgesia, 49.3% received ITM, and 14.2% received ITM+TAP (Table 1). The distribution of chronic opioid users was similar across all cohorts ($p = 0.65$). Patients

Table 1. Demographics and Operative Characteristics

		Method of spinal analgesia			
Characteristic	**Total n = 233**	**None n = 85**	**ITM n = 115**	**ITM+TAP n = 33**	**p Value***
Age, y, median (IQR)	67 (59, 73)	66 (57, 72)	67 (59, 73)	68 (59, 74)	0.7478
Sex, m, n (%)	120 (51.5)	41 (48.2)	62 (53.9)	17 (51.5)	0.7294
White, n (%)	211 (90.6)	80 (94.1)	98 (85.2)	33 (100)	0.0140†
BMI, kg/m^2, median (IQR)	27 (23, 31)	27 (24, 30)	27 (23, 32)	26 (26, 32)	0.5757
COPD, n (%)	12 (5.2)	3 (3.5)	6 (5.2)	3 (9.1)	0.5151
Anxiety, n (%)	31 (13.3)	9 (10.6)	19 (16.5)	3 (9.1)	0.3528
Depression, n (%)	64 (27.5)	26 (30.6)	30 (26.1)	8 (24.0)	0.7055
Substance use disorder, n (%)	11 (4.7)	4 (4.7)	5 (4.4)	2 (6.1)	>0.999
Alcohol use disorder, n (%)	32 (13.7)	16 (18.8)	15 (13.0)	1 (3.0)	0.0782
Chronic opioid use, n (%)	58 (24.9)	24 (28.2)	27 (23.5)	7 (21.2)	0.6472
Malignant pathology, n (%)	193 (84.3)	68 (81.9)	95 (83.3)	30 (93.8)	0.2739
Operative duration, min, median (IQR)	378 (286, 475)	349 (269, 446)	397 (292, 495)	381 (349, 461)	0.0471†
Open approach, n (%)	190 (81.6)	69 (81.2)	91 (79.1)	30 (90.9)	0.3048
Year of operation, n (%)					<0.0001†
2014	34 (14.6)	34 (40.0)	0	0	
2015	18 (7.7)	18 (21.2)	0	0	
2016	44 (18.9)	20 (23.5)	22 (19.1)	2 (6.1)	
2017	38 (16.3)	4 (4.7)	24 (20.9)	10 (30.3)	
2018	32 (13.7)	3 (3.5)	20 (17.4)	9 (27.3)	
2019	39 (16.7)	2 (2.4)	28 (24.4)	9 (27.3)	
2020	28 (12.0)	4 (4.7)	21 (18.3)	3 (9.1)	

*Analgesia cohorts are compared using chi-square test for categorical characteristics or Wilcoxon rank sum test for continuous characteristics.
†Statistically significant.
IQR, interquartile range; ITM, intrathecal morphine; TAP, transversus abdominus plane block.

who received ITM and ITM+TAP had longer operative duration compared with those who did not receive spinal anesthesia ($p = 0.047$). The majority (73%) of TAP blocks were performed by the operating surgeon (data not shown).

Postoperative outcomes bivariate analysis

In bivariate analysis, average pain scores on POD 0 to 3 were similar by method of analgesia (no spinal [2.8], ITM [2.6], ITM+TAP [2.3]) (Table 2). Despite similar pain scores, the total MEQ consumed over POD 0 to 3 varied significantly by the mode of spinal analgesia (none [232 mg], ITM [121 mg], ITM+TAP [132 mg], $p < 0.0001$) (Table 2, Fig. 1A). Similarly, the average daily MEQ consumed from POD 4 to discharge varied by the type of spinal anesthesia (none [32.9 mg], ITM [18 mg], ITM+TAP [13.1 mg], $p = 0.0016$) (Table 2, Fig. 1B). After POD 3, no additional opioids were required in 23.5% of ITM and 24.2% of ITM+TAP patients, compared with just 2.3% of those with no spinal analgesia (**Supplemental Digital Content 2**, http://links.lww.com/JACS/A93). Patients younger than 60 years and those with a history of depression, substance or alcohol use disorder, or chronic opioid use had higher average pain scores throughout POD 0 to 3, greater MEQ consumption on POD 0 to 3, and higher average daily MEQ consumption from POD 4 to discharge (Table 2).

Increased days to functional recovery was more common among females and varied significantly among modes of spinal analgesia (none [2], ITM [1], ITM+TAP [1], $p = 0.0001$) (Table 2, Fig. 2A). LOS varied significantly by mode of spinal analgesia (none [9], ITM [7], ITM+TAP [6], $p < 0.0001$) (Table 2, Fig. 2B), and was increased for chronic opioid users and operative duration greater than 385 minutes.

Postoperative outcomes multivariable regression

Total MEQ consumed from POD 0 to 3 was significantly lower for the patients who received ITM (mean difference –81.4, $p < 0.0001$) or ITM+TAP (mean difference –91.2, $p = 0.0002$) compared with no spinal analgesia (Table 3). Additionally, the average daily MEQ consumption from POD 4 to discharge was lower for ITM (mean difference –12.0, $p = 0.0006$) and ITM+TAP (mean difference –8.8, $p = 0.072$) cohorts compared with no spinal analgesia (Table 3). Patients who received either ITM or ITM+TAP had similar total MEQ from POD 0 to 3 ($p = 0.67$) and daily MEQ from POD 4 to discharge ($p = 0.50$).

Young age, depression, and chronic opioid use were independent predictors of higher average pain scores POD 0 to 3, total MEQ POD 0 to 3, and average daily MEQ from POD 4 to discharge. Additionally, male sex and substance use disorder predicted increased total MEQ POD 0 to 3, while alcohol use disorder predicted higher average daily MEQ from POD 4 to discharge (Table 3).

Days to functional recovery were significantly reduced for patients receiving ITM (mean difference –0.57, $p = 0.0018$) or ITM+TAP (mean difference –0.9, $p = 0.0003$) compared with no spinal analgesia (Table 3). Similarly, LOS was significantly reduced for ITM (mean difference –1.97, $p < 0.0001$) and ITM+TAP (mean difference –2.25, $p = 0.0001$) cohorts compared with no spinal analgesia (Table 3). Patients who received either ITM or ITM+TAP had similar days to functional recovery ($p = 0.16$) and LOS ($p = 0.61$).

The only independent predictor of longer days to functional recovery was female sex. The only independent predictors of increased LOS were chronic opioid use and longer operative duration.

Opioid-related complications

Overall, there were 5 incidents of naloxone administration (none with underlying COPD) and 9 cases of postoperative respiratory failure requiring reintubation (3 with underlying COPD). Among the 3 patients with COPD who developed postoperative respiratory failure, 1 had no spinal analgesia, 1 had ITM, and 1 had ITM+TAP. The rate of each complication was similar among the no spinal anesthesia, ITM, and ITM+TAP groups (all $p > 0.45$). The incidence of ileus (26.6%) and delayed gastric emptying (15.5%) was similar regardless of spinal anesthetics (Table 4).

DISCUSSION

In this study, we evaluated the effect of ITM on postoperative pain scores and opioid utilization after pancreaticoduodenectomy. In the early postoperative period from days 0 to 3, there was no difference in average daily pain scores, yet patients who received ITM or ITM+TAP consumed significantly fewer opioids compared with those without spinal analgesia. This pattern persisted throughout the rest of hospitalization. Patients who received ITM or ITM+TAP also had significantly faster functional recovery and reduced LOS compared with those who did not receive spinal analgesia. The addition of TAP blocks to patients who received ITM did not appear to confer an additional analgesic or functional benefit to patients who received ITM alone. Overall, the rate of opioid-related or potentially related complications was low, but the distribution of these adverse events was similar across all modes of

Table 2. Unadjusted Associations with Postoperative Outcomes

		Average pain score POD 0 to 3		MEQ consumed POD 0 to 3		MEQ consumed/d POD 4 to discharge		Functional recovery (POD)		LOS, d	
Baseline factor	**n**	**Median (IQR)**	**p Value**	**Median (IQR)**	**p Value**	**Median (IQR)**	**p Value**	**Median (IQR)**	**p Value**	**Median (IQR)**	**p Value**
Overall	233	2.7 (1.6, 4.3)		166 (90, 283)		21.7 (3.8, 50.3)		2 (1, 3)		7 (6, 11)	
Spinal analgesia			0.19		<0.0001*		0.0016*		0.0001*		<0.0001*
None	85	2.8 (2.0, 4.5)		232 (149, 353)		32.9 (10.7, 59.9)		2 (1, 4)		9 (7, 14)	
ITM	115	2.6 (1.6, 4.1)		121 (62, 250)		18.0 (0.4, 38.7)		1 (1, 3)		7 (5, 10)	
ITM+TAP	33	2.3 (1.3, 3.4)		132 (61, 212)		13.1 (2.7, 35.8)		1 (1, 2)		6 (5, 9)	
Age at operation			<0.0001*		<0.0001*		<0.0001*		0.9419		0.9142
<59 y	67	4.2 (2.5, 5.4)		268 (164, 505)		46.8 (19.5, 67.5)		2 (1, 4)		7 (5, 12)	
60–70 y	80	2.6 (1.7, 3.8)		166 (104, 256)		21.1 (2.9, 45.8)		2 (1, 3)		7 (6, 10)	
≥70 y	86	2.2 (1.3, 3.0)		104 (55, 197)		12.0 (1.3, 28.2)		2 (1, 3)		7 (6, 13)	
Sex			0.38		0.0060*		0.93		<0.0001*		0.9477
Male	120	2.8 (1.6, 4.6)		202 (104, 356)		22.3 (3.8, 46.1)		1 (1, 2)		7 (6, 11)	
Female	113	2.5 (1.6, 4.0)		137 (85, 234)		20.7 (3.3, 53.6)		2 (1, 4)		7 (6, 11)	
Ethnicity			0.052		0.93		0.018*		0.9258		0.4625
White	211	2.6 (1.6, 4.2)		168 (89, 290)		20.2 (2.7, 46.8)		2 (1, 3)		7 (6, 11)	
Other	22	4.0 (2.2, 5.2)		165 (105, 247)		36.4 (18.8, 67.1)		2 (1, 3)		7.5 (7, 11)	
Anxiety			0.19		0.29		0.63		0.6305		0.4802
Yes	31	3.3 (2.0, 4.9)		208 (98, 306)		19.5 (12.5, 50.3)		2 (1, 3)		8 (6, 11)	
No	202	2.6 (1.6, 4.2)		165 (85, 280)		22.3 (2.7, 50.5)		2 (1, 4)		7 (6, 11)	
Depression			0.0056*		0.022*		0.0075*		0.4191		0.5612
Yes	64	3.2 (2.1, 5.1)		224 (111, 341)		27.4 (12.6, 60.0)		2 (1, 3)		8 (6, 11)	
No	169	2.5 (1.5, 3.9)		152 (84, 250)		18.6 (2.7, 38.6)		2 (1, 3)		7 (6, 12)	
Substance use disorder			0.022*		0.0014*		0.0018*		0.6646		0.1278
Yes	11	4.8 (3.2, 5.6)		507 (166, 662)		60.0 (30.1, 75.9)		2 (1, 2)		6 (5, 8)	
No	222	2.6 (1.6, 4.1)		156 (89, 279)		20.6 (2.7, 46.1)		2 (1, 3)		7 (6, 11)	
Alcohol use disorder			0.34		0.012*		0.0009*		0.6608		0.6594
Yes	32	2.8 (1.6, 5.2)		248 (119, 457)		51.9 (18.8, 71.7)		2 (1, 3)		7 (6, 10)	
No	201	2.7 (1.6, 4.1)		160 (89, 276)		18.9 (2.7, 41.9)		2 (1, 3)		7 (6, 11)	
Chronic opioid use			<0.0001*		<0.0001*		<0.0001*		0.3498		0.0421*
Yes	58	3.8 (2.5, 5.6)		246 (165, 499)		46.1 (19.5, 85.4)		2 (1, 4)		9 (6, 12)	
No	175	2.4 (1.5, 3.8)		137 (81, 246)		16.1 (2.0, 37.7)		2 (1, 3)		7 (5, 10)	
Approach			0.11		0.53		0.80		0.0610		0.3251
Open	190	2.7 (1.7, 4.4)		166 (86, 276)		22.5 (3.8, 50.3)		2 (1,4)		7 (6, 11)	
MIS	43	2.3 (1.3, 3.6)		168 (105, 323)		20.2 (2.4, 52.2)		1 (1, 2)		7 (5, 10.5)	
Operative duration			0.3078		0.0467*		0.031*		0.1275		0.0487*
<293 min	—	2.8 (1.8, 4.3)		151 (61, 242)		12.7 (0.1, 38.7)		1 (1, 3)		7 (5, 10)	
293–385 min	—	3.1 (1.4, 5.0)		191 (107, 412)		29.0 (3.8, 62.6)		2 (1, 3)		7 (5, 10)	
385–480 min	—	2.4 (1.6, 3.4)		132 (86, 237)		18.0 (5.6, 37.5)		2 (1, 4)		8 (6, 12)	
>480 min	—	2.8 (1.6, 4.2)		192 (106, 280)		25.4 (12.7, 42.7)		2 (1, 4)		8 (6, 14)	

Differences in continuous outcomes, described with median (IQR), were assessed with the Kruskal–Wallis chi-square test (p value].

*Statistically significant.

IQR, interquartile range; ITM, intrathecal morphine; LOS, length of stay; MEQ, morphine equivalents; MIS, minimally invasive surgery; POD, postoperative day; TAP, transversus abdominus plane block.

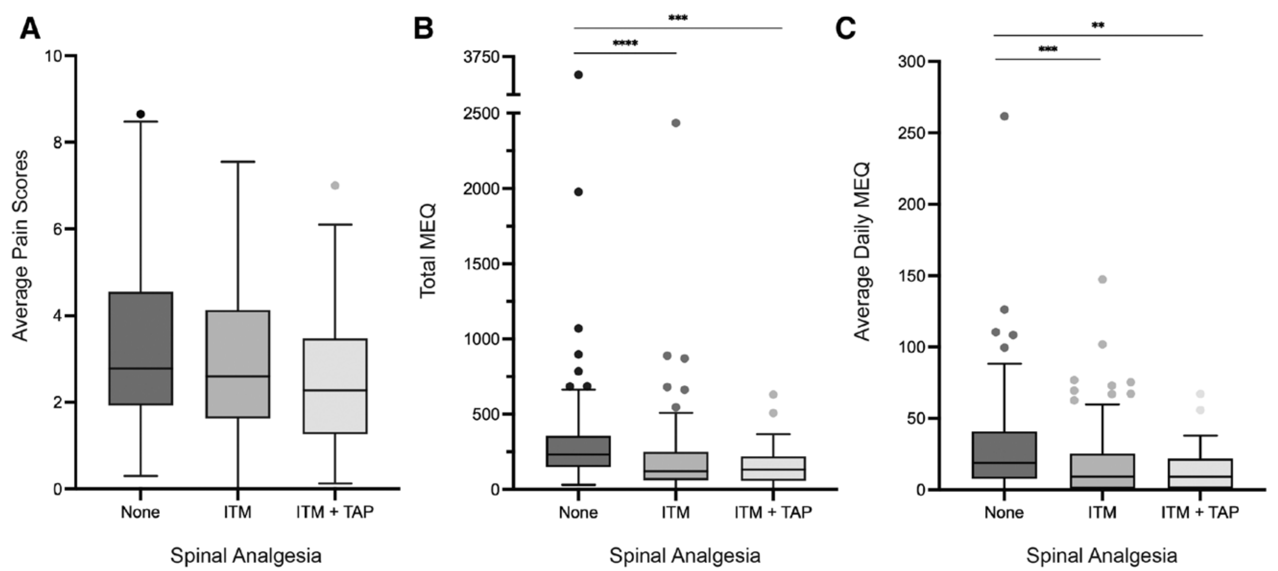

Figure 1. Tukey plots of median and interquartile range for (A) average pain score from postoperative day 0 to 3, (B) total morphine equivalents (MEQ) consumed from postoperative day 0 to 3, and (C) average daily MEQ from postoperative day 4 to discharge. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. ITM, intrathecal morphine; TAP, transversus abdominus plane block.

analgesia. In summary, these data demonstrated that spinal analgesia was safe and associated with less opioid consumption, similar pain scores, faster functional recovery (days to ambulation beyond 100 feet), and decreased LOS among patients undergoing pancreaticoduodenectomy.

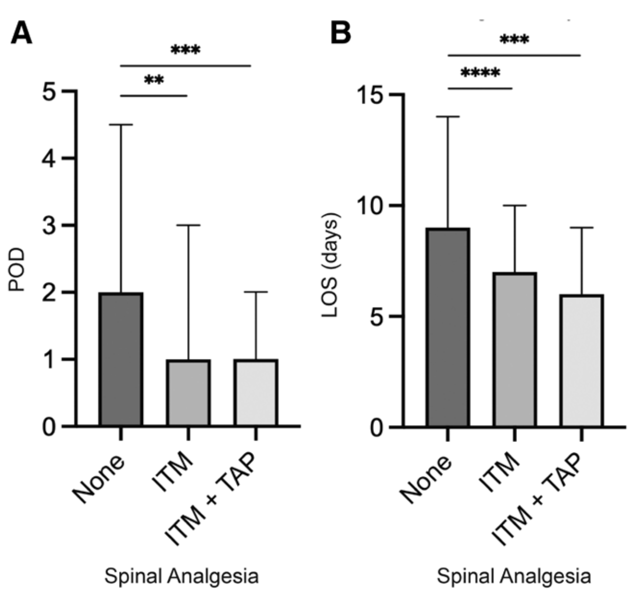

Figure 2. Bar graphs of median and interquartile range for (A) postoperative day (POD) of functional recovery, and (B) length of stay (LOS) by type of spinal analgesia. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. ITM, intrathecal morphine; TAP, transversus abdominus plane block.

While studies have evaluated the effect of ITM on postoperative pain control and opioid utilization, few have focused on pancreatic surgery and those undergoing pancreaticoduodenectomy, an operation in which inadequate analgesia can influence functional recovery and hospital LOS. Elsewhere, a retrospective review with 197 patients undergoing pancreaticoduodenectomy also showed lower opioid consumption on POD 0 with no difference in postoperative pain scores among pancreaticoduodenectomy patients who received ITM compared with those who received TAP or quadratus lumborum nerve blocks.[19] This is consistent with our findings that pancreaticoduodenectomy patients who receive ITM require less opioids to achieve adequate pain control, which reflects findings across multiple surgical disciplines[11,12,15,23] and demonstrates translation of this effect to pancreaticoduodenectomy. Compared to the previous studies of ITM in pancreaticoduodenectomy patients, we have additionally identified reduced days to functional recovery and LOS with the addition of ITM or ITM+TAP. This has potential economic implications through reduced inpatient hospital costs and warrants further investigation. We found no difference in potential side effects (delayed gastric emptying and ileus) and adverse events (naloxone administration and postoperative respiratory failure) after ITM administration, supporting the safety of this intervention.

Most previous studies of ITM have emphasized the first 24 to 72 hours postoperatively, given an estimated duration of action of 18 to 24 hours.[26] This is the first study to

Table 3. Robust Regression Estimation of Adjusted Association with Outcomes of Interest

Independent predictor*	Average pain score POD 0 to 3		MEQ total POD 0 to 3		Average daily MEQ POD 4 to discharge		Functional recovery (POD)		LOS	
	Estimate (SE)	p Value	Estimate (SE)	p Value	Estimate (SE)	p Value	Estimate (SE)	p Value	Estimate (SE)	p Value
Age, y†	−0.05 (0.01)	<0.0001‡	−4.5 (0.8)	<0.0001‡	−0.7 (0.2)	<0.0001‡	—	—	0.03 (0.02)	0.1303
Male vs female	—	—	56.4 (15.9)	0.0004‡	—	—	−0.77 (0.17)	<0.0001‡	—	—
White vs non-White	−0.46 (0.39)	0.24	—	—	−11.2 (5.6)	0.044‡	—	—	—	—
Depression, yes vs no	0.63 (0.25)	0.012‡	43.9 (17.9)	0.014‡	10.5 (3.6)	0.0032‡	—	—	—	—
Substance use disorder, yes vs no	0.76 (0.53)	0.16	107.2 (45.2)	0.018‡	11.6 (7.8)	0.14	—	—	—	—
Alcohol use disorder, yes vs no	—	—	−21.6 (24.8)	0.38	12.6 (4.7)	0.0079‡	—	—	—	—
Chronic opioid use, yes vs no	0.76 (0.28)	0.0059‡	61.7 (19.3)	0.0014‡	11.8 (4.0)	0.0030‡	—	—	1.20 (0.45)	0.0072‡
Open vs robotic approach	0.47 (0.29)	0.010	—	—	—	—	0.28 (0.21)	0.1780	—	—
Operative duration§, min	—	—	0.07 (0.07)	0.28	0.02 (0.01)	0.17	—	—	0.004 (0.002)	0.0285‡
ITM vs none (reference group)	−0.07 (0.24)	0.77	−81.4 (17.4)	<0.0001‡	−12.0 (3.5)	0.0006‡	−0.57 (0.18)	0.0018‡	−1.90 (0.41)	<0.0001‡
ITM+TAP vs none	−0.27 (0.34)	0.43	−91.2 (24.5)	0.0002‡	−8.8 (4.9)	0.072	−0.90 (0.25)	0.0003‡	−2.18 (0.58)	0.0002‡
ITM+TAP vs ITM‖	−0.20 (0.33)	0.55	−9.9 (23.0)	0.67	3.1 (4.7)	0.50	−0.33 (0.24)	0.1591	−0.09 (0.55)	0.8698

*Regression model for each outcome includes all factors significant in univariate analysis, and otherwise shown as —.
†Continuous factor age is centered at the overall mean (66 y).
‡Statistically significant.
§Continuous factor surgical duration is centered at the overall mean (387 min).
‖Additional test is a linear contrast of model parameters.
ITM, intrathecal morphine; LOS, length of stay; MEQ, morphine equivalents; POD, postoperative day; TAP, transversus abdominus plane block.

Table 4. Opioid-Related Complications

Characteristic	Total n = 233	None n = 85	ITM N = 115	ITM+TAP n = 33
Naloxone administration	5 (2.2)	3 (3.5)	1 (0.9)	1 (3.0)
Respiratory failure	9 (3.9)	3 (3.5)	4 (3.5)	2 (6.1)
Ileus	62 (26.6)	21 (24.7)	33 (28.7)	8 (24.2)
Delayed gastric emptying	36 (15.5)	12 (14.1)	19 (16.5)	5 (15.2)

Data presented as n (%).
Analgesia cohorts are compared using chi-square test. An exact test is used when any expected cell size is <5.
ITM, intrathecal morphine; TAP, transversus abdominus plane block.

extend the evaluation of MEQ consumed beyond the very early postoperative period. This was performed due to the observation that ITM in combination with thoracic epidurals had lasting effects for patients after hepatectomy.[6] The mechanism behind these prolonged analgesic effects is not fully understood but may reflect preemptive analgesia on central nociceptive sensitization,[31] tolerance to earlier mobilization, and/or transition to oral multimodal analgesia. These findings may also represent selection bias because patients are preoperatively counseled on the benefits of ITM, which can change expectation of perioperative pain management and affect opioid utilization postoperatively. Regardless, we observed significantly decreased average daily MEQ from POD 4 to discharge for patients receiving ITM and ITM+TAP compared with no spinal analgesia. This suggests that ITM can have lasting effects on postoperative opioid utilization in patients undergoing pancreaticoduodenectomy, even after the ITM effect has worn off. This was supported by the observation that nearly 25% of ITM patients did not require any additional opioids beyond POD 3 compared with just 2.3% of those without spinal analgesia. These data suggest that early postoperative regional analgesia sets the course for subsequent need of systemic opioids.

Similar to studies on cesarean deliveries, we observed comparable benefits with respect to postoperative pain scores and MEQ among all ITM patients with or without TAP.[32-34] Costello and colleagues conducted a randomized controlled trial of ITM with or without ultrasound-guided ropivacaine TAP blocks after cesarean delivery and found no difference in pain scores or opioid consumption.[32] Further supporting these findings, Singh and colleagues performed a randomized controlled trial of ITM in combination with high- or low-dose ropivacaine TAP blocks or placebo after cesarean delivery. Despite reduced pain scores at 12 hours postoperatively with high-dose ropivacaine, this effect did not last, and scores were no different at 24, 36, and 48 hours or at 6 and 12 weeks.[34] This may be due to a reliable visceral analgesic effect of

ITM compared with variable somatic analgesia of TAP blocks.[19,35] Singh and colleagues also found no difference in postoperative opioid consumption, adverse events, quality of recovery, or satisfaction among cohorts. This is an important discovery because patients may not require the additional procedural time and sedation required to conduct TAP blocks after ITM administration. However, our small sample size of patients with ITM+TAP may limit our ability to detect clinically important differences after pancreaticoduodenectomy.

Our study has strengths and limitations that should be acknowledged. This is the largest study to evaluate the effect of ITM on postoperative pain scores and opioid utilization in patients undergoing pancreaticoduodenectomy. Additionally, this is the first study in this population to show an association between ITM and earlier functional recovery and reduced LOS. Finally, these patients with benign and malignant pathology have representative rates of substance use and mental health diagnoses, which increases its external validity. Due to its retrospective nature, certain selection biases cannot be overcome. For example, all ITM patients underwent pancreaticoduodenectomy from 2016 to 2020 compared with just 16.3% (n = 13) of patients without spinal analgesia. This coincides with the implementation of the divisional enhanced recovery after surgery program, which included ITM as an adjunctive measure for pain control. This enhanced recovery pathway has reduced LOS among patients undergoing pancreaticoduodenectomy, which is why this was not chosen as a primary outcome measure. Instead, we focused on pain control and MEQ used since all patients routinely received multimodal and patient-controlled analgesia throughout the study period. Finally, due to limited sample size, we were unable to compare ITM with alternative forms of spinal analgesia, which may be routinely used at some institutions. Regardless, recent data suggest that ITM may be equally effective, safer, and better tolerated than other analgesic techniques across a variety of surgical disciplines.[4-9] Future studies should prospectively study ITM in combination with analgesic regimens for pancreatic surgery to provide further insight on outcomes such as operative duration, LOS, and hospital costs.

CONCLUSIONS

Compared with no spinal analgesia, ITM was associated with decreased early postoperative and total inpatient opioid utilization in patients undergoing pancreaticoduodenectomy, with no difference in patient-reported pain scores. Additionally, ITM and ITM+TAP were associated with decreased days to functional recovery and LOS, suggesting functional recovery benefit among patients undergoing pancreaticoduodenectomy. In this population, TAP blocks did not appear to confer additional benefits to ITM for postoperative pain control or opioid utilization. Opioid-related complications such as rates of ileus, delayed gastric emptying, postoperative respiratory failure, and naloxone administration were unchanged with the addition of ITM. ITM is therefore a safe and effective form of perioperative analgesia that may benefit patients undergoing pancreaticoduodenectomy.

Author Contributions

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