UMSHA Press

AJPR
Avicenna Journal of Pharmaceutical Research
Avicenna J Pharm Res, 2022; 3(2):63-68. doi:10.34172/ajpr.1079
http://ajpr.umsha.ac.ir

Original Article

Intrathecal Morphine for Colorectal Cancer Surgery: Immediate Postoperative and Post-Discharge Outcomes

Nathan Strugnell[1*], Jamie Young[2,3], Elizabeth Williams[4], Bernhard Riedel[3,5]

[1]Melbourne Medical School, The University of Melbourne, Melbourne, Australia
[2]Department of Anaesthesia, Perioperative and Pain Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia
[3]Department of Critical Care, University of Melbourne, Melbourne, Australia
[4]Department of Pharmacy, Peter MacCallum Cancer Centre, Melbourne, Australia
[5]The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia

Article history:
Received: February 16, 2023
Revised: May 21, 2023
Accepted: May 30, 2023
ePublished: September 1, 2023

***Corresponding author:**
Nathan Strugnell,
Email: nathanstrugnell1@gmail.com

Abstract

Background: Colorectal cancer is a major cause of morbidity and mortality in Australia. Following colorectal cancer surgery, although systemic opioids are often first-line analgesia, they may be associated with various adverse effects. Intrathecal morphine (ITM) has been shown to provide good analgesia with a safe side effect profile. This study assessed whether ITM alongside patient-controlled analgesia (PCA) reduces the incidence of immediate postoperative adverse effects and post-discharge outcomes compared to PCA alone following colorectal cancer surgery.

Methods: In this retrospective cohort study, data from 260 patients undergoing colorectal cancer surgery during 2014-2018 at Peter MacCallum Cancer Centre was extracted from a clinical database and medical records. Immediate postoperative outcomes included pruritus, postoperative ileus, and time to mobilisation. Post-discharge outcomes encompassed chronic postoperative pain and long-term opioid consumption. Cancer recurrence was an exploratory endpoint. Comparative analysis was undertaken for ITM with PCA (the ITM group) compared to PCA alone (the PCA group), overall and after stratification into laparoscopy versus laparotomy procedures.

Results: In total, 260 patients were included in this study (160 in the ITM group and 100 in the PCA group). The ITM group trended toward a lower incidence of postoperative ileus, lower incidence of chronic pain, and opioid use at three and six months but not at twelve months.

Conclusion: Based on the findings, the ITM group trended toward reductions in postoperative ileus, chronic pain, and opioid use at three and six months.

Keywords: Morphine, Patient-controlled analgesia, Anesthesia, Ileus, Colorectal surgery, Colorectal neoplasms

Please cite this article as follows: Strugnell N, Young J, Williams E, Riedel B. Intrathecal morphine for colorectal cancer surgery: immediate postoperative and post-discharge outcomes. Avicenna J Pharm Res. 2022; 3(2):63-68. doi:10.34172/ajpr.1079

Introduction

In Australia, colorectal cancer is the fourth most commonly diagnosed cancer and the cause of the second most cancer-related deaths (1). Surgery is at the forefront of the management of colorectal cancer, and optimal analgesia is required to reduce postoperative complications, enable earlier hospital discharge, and facilitate timely return to adjuvant therapy (2). Following colorectal cancer surgery, systemic opioids are commonly used for postoperative analgesia. However, the postoperative use of opioids may be associated with adverse effects such as nausea and vomiting, respiratory depression, and postoperative ileus, which may slow postoperative recovery and prolong hospital length of stay (3).

Intrathecal morphine (ITM) is of interest because it may have extended opioid-sparing effects, providing an alternative to systemic opioids with the provision of adequate postoperative analgesia and the potential for reduced side effects. The proposed mechanism of action of ITM is through direct access to G-protein linked pre- and post-synaptic opioid receptors in the dorsal horn, binding and reducing nociceptive transmission (4). ITM is also thought to increase adenosine concentration in the cerebrospinal fluid, reducing both neural activity and release of gamma-aminobutyric acid, and thereby reducing nociceptive transmission (5). ITM provides effective analgesia with a favourable side effect profile. This is demonstrated by a randomised control trial which recommended intrathecal analgesia as the mode of choice in laparoscopic surgery compared to epidural and patient-

controlled analgesia (PCA) (6).

In a retrospective study investigating the efficacy of ITM analgesia in patients who underwent laparoscopy or laparotomy procedures for colorectal cancer, a reduction in oral morphine equivalent dose was reported after 24 hours and reduced sedation after 48 hours for those who received ITM (7). However, acute postoperative outcomes such as postoperative ileus, time to mobilisation, and postoperative pruritus were not explored in that study nor were longer term post-discharge outcomes.

There is increasing interest in the longer-term effects of neuraxial techniques, including ITM, for the prevention of chronic postsurgical pain and cancer recurrence. ITM has been associated with the reduced incidence of chronic postsurgical pain after open abdominal surgeries through blocking afferent pain fibre transmission and thereby preventing the induction of central sensitisation (8,9). A meta-analysis study suggested an association between neuraxial techniques, including ITM, and the reduced recurrence of various cancers, including colorectal cancer (10). Proposed direct and indirect mechanisms include the reduction of immunosuppression and angiogenesis through reduced exposure to systemic opioid administration and the attenuation of the surgical stress response through the suppression of the hypothalamic-pituitary-adrenal axis and the reduction of the suppression of natural killer (NK) cells (10-16).

The aim of this study was to focus on the immediate postoperative outcomes of pruritus, postoperative ileus, time to mobilisation, post-discharge outcomes of chronic postoperative pain, and long-term opioid consumption. Cancer recurrence was analysed as an exploratory endpoint. We considered the hypothesis that ITM may reduce the time to mobilisation, the incidence of postoperative ileus, chronic pain, and long-term opioid use.

Materials and Methods

This retrospective study reviewed a single institution experience (July 2014 – June 2018) in adult patients who had colorectal cancer surgery with an inpatient stay, were administered either ITM with PCA or PCA alone, and were followed up postoperatively by the Acute and Persistent Pain Service at Peter MacCallum Cancer Centre. Data were gathered retrospectively from both hospital's paper-based and electronic medical records.

Outcome Measures

The outcomes of this study included immediate postoperative and post-discharge outcome measures. Immediate postoperative outcomes included pruritus, time to mobilisation, and postoperative ileus. Time to mobilisation (standing or ambulating) was recorded as the number of days from the operation (day 0) until documented in the medical, nursing, or physiotherapy records.

Post-discharge outcomes included the incidence of chronic pain and long-term opioid use. Chronic postoperative pain was recorded as positive if ongoing pain was identified in outpatient clinic notes three, six, and twelve months after the surgery. Long-term opioid consumption was calculated based on doses of opioid medications recorded in outpatient clinic notes and pharmacy records, accounting for medications being administered before the operation. Chronic pain and opioid use data were not recorded beyond the time of any subsequent surgeries that patients underwent. For the exploratory endpoint of cancer recurrence, outpatient clinic notes and/or medical records from subsequent admissions were extracted for a period with data collected during three years post-operative. Cancer recurrence was not recorded following surgeries with non-curative intent.

Statistical Analysis

Data on patient demographics were presented descriptively. The IBM Statistical Package for Social Sciences (SPSS) was used for statistical analysis. Differences between ITM and PCA groups were assessed using the Mann-Whitney U Test with statistical significance at $P < 0.05$.

Results

Overall, 260 patients that met the inclusion criteria and were selected for analysis, including 160 patients in the ITM group and 100 patients in the PCA group. Patient demographics were similar between the two cohorts where the median age was 64 for both groups, and 55.6% and 55.0% were males in the ITM and PCA groups, respectively. In both cohorts, 52% and 48% of patients underwent open laparotomy and laparoscopy procedures, respectively. The most common colorectal procedure was anterior resection performed on 64 patients (26%), while colectomy was performed on 49 patients (19%), and 27 patients (10%) underwent hyperthermic intraperitoneal chemotherapy (HIPEC)/pelvic exenteration. A summary of patient demographics is reported in Table 1.

Immediate Postoperative Outcomes

The ITM group had increased pruritus, a similar time to mobilisation, and a similar incidence of postoperative ileus (ITM 20.0% vs. PCA 23.0%, $P = 0.57$) compared to the PCA group. Table 2 lists a summary of immediate postoperative outcomes The trend was similar in both laparoscopy and laparotomy subgroups (Appendix 1 and 2).

Post-discharge Outcomes

In the ITM group, 3.5% and 3.1% of patients had chronic pain at three months and six months, respectively. In contrast, 7.0% and 5.0% of patients had chronic pain at three and six months, respectively, in the PCA group. Similarly, 7.7% and 9.9% of the ITM group were on long-term opioids at three and six months, respectively, compared to 10.5% and 12.5% of the PCA group. At twelve months, 4.9% in the ITM group and 4.4% in the PCA group

Table 1. Demographics, Surgery Technique, and Performed Surgery

Demographics	Overall (n = 260)		ITM + PCA (n = 160)		PCA (n = 100)	
	No. of Patients	(%)	No. of Patients	(%)	No. of Patients	(%)
Male	144	(55.4%)	89	(55.6%)	55	(55.0%)
Median age (range)	64	(22-99)	64	(34-99)	64	(22-93)
Surgery technique						
Laparotomy	135	(51.9%)	83	(61.5%)	52	(38.5%)
Laparoscopy	125	(48.1%)	77	(61.6%)	48	(38.4%)
Surgery performed						
Anterior resection	64	(24.6%)	45	(70.3%)	19	(29.7%)
Colectomy	49	(18.8%)	29	(59.2%)	20	(40.8%)
HIPEC/pelvic exenteration	27	(10.4%)	20	(74.1%)	7	(25.9%)
Other	102	(39.2%)	52	(51.0%)	50	(49.0%)
Minor	18	(6.9%)	14	(77.8%)	4	(22.2%)

Note. ITM: Intrathecal morphine; PCA: Patient-controlled analgesia; HIPEC: Hyperthermic intraperitoneal chemotherapy.

Table 2. Immediate Postoperative Outcomes: Incidence of Ileus, Pruritus, and Time to Mobilisation

	Overall (n = 260)		ITM + PCA (n = 160)		PCA (n = 100)		*P* value
	No. of Patients	(%)	No. of Patients	(%)	No. of Patients	(%)	
Ileus							
No	205	(78.8%)	128	(80.0%)	77	(77.0%)	
Yes	55	(21.2%)	32	(20.0%)	23	(23.0%)	0.565
Pruritus							
No	246	(95.0%)	149	(93.7%)	97	(97.0%)	
Yes	13	(5.0%)	10	(6.3%)	3	(3.0%)	0.239
Time to mobilisation	1.39 days		1.38 days		1.39 days		0.452

Note. ITM: Intrathecal morphine; PCA: Patient-controlled analgesia.

reported ongoing pain, and 11.4% of the ITM group and 7.2% of the PCA group were on long-term opioids. There were no statistically significant differences between the groups. These outcomes are summarized in Table 3. In the laparoscopy subgroup, there were no consistent trends, with a similar incidence of chronic pain and opioid use at three and six months between the ITM and PCA groups (Appendix 1). In the laparotomy subgroup, there was a trend towards less chronic pain at three and six months in the ITM group, however the opioid use was not consistent with this (Appendix 2). Cancer recurrence was 37.8% for the ITM group compared to 36.0% for the PCA group (Supplementary file 1).

Discussion

In this retrospective study, ITM with PCA did not demonstrate statistically significant benefits compared to PCA alone in reducing the incidence of postoperative ileus, chronic pain, and opioid use at three and six months. There was no difference noted in time to mobilisation, and pruritus was more common in the ITM group. For the exploratory endpoint of cancer recurrence, the ITM group had a similar recurrence in comparison to PCA.

Postoperative ileus is a common complication of colorectal surgery and can have a significant impact on a patient's recovery and often impacts the length of hospital stay (17). Opioids are known to perpetuate postoperative ileus through the activation of central, and predominantly, peripheral mu-opioid receptors, leading to the inhibition of gut motility (18). Therefore, ITM may reduce the incidence of postoperative ileus through the reduction of exposure to systemic opioids and blocking sympathetic neural pathways which, when overstimulated, inhibit bowel motility (18). This is supported in the literature, with one randomised control trial, showing an improvement in bowel function with ITM compared with both PCA and epidural analgesia (6). However, other studies comparing ITM with PCA have not reported an improvement in the incidence of ileus in colorectal surgery, and this may be due to the complex and multifactorial causes of ileus, including reduced mobilisation and bowel handling during surgery (19,20). Our study findings suggested that

Table 3. Post-discharge Outcomes: Incidence of Chronic Pain and Opioid Use at 3, 6, and 12 Months

	Overall (n = 260)	ITM + PCA (n = 160)	PCA (n = 100)	*P* Value
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	
3 Months				
No chronic pain	218 (95.2)	138 (96.5)	80 (93.0)	0.235
Chronic pain	11 (4.8)	5 (3.5)	6 (7.0)	
No opioid use	209 (91.3)	132 (92.3)	77 (89.5)	0.474
Opioid use	20 (8.7)	11 (7.7)	9 (10.5)	
6 Months	202 (96.2)	126 (96.9)	76 (95.0)	
No chronic pain	8 (3.8)	4 (3.1)	4 (5.0)	0.483
Chronic pain	190 (89.6)	120 (90.1)	70 (87.5)	
No opioid use	22 (10.4)	12 (9.9)	10 (12.5)	0.433
Opioid use				
12 Months	181 (95.3)	116 (95.1)	65 (95.6)	
No chronic pain	9 (4.7)	6 (4.9)	3 (4.4)	0.875
Chronic pain	173 (90.1)	109 (88.6)	64 (92.8)	
No opioid use	19 (9.9)	14 (11.4)	5 (7.2)	0.360
Opioid use				

Note. ITM: Intrathecal morphine; PCA: Patient-controlled analgesia.

ITM represented no statistically significant reduction in postoperative ileus compared to PCA. The trend toward reduction may, however, warrant further investigation within an adequately powered prospective study.

Some studies indicated that ITM may reduce the risk of chronic pain in open abdominal surgeries (8,9). Peripheral and central sensitisation caused by prolonged afferent nociceptive input is considered a key mechanism in the development of chronic post-surgical pain (21,22). The prolonged firing of nociceptive afferents may lead to long-term structural changes in the dorsal horn, reducing pain thresholds and amplifying pain responses (21,22). Chronic post-surgical pain may therefore be reduced by adequately controlling acute postoperative pain. In this study, chronic pain trended towards being was lower in the ITM group at three (ITM 3.5% vs. PCA 7.0%) and six (ITM 3.1% vs. PCA 5.0%) months but not at twelve months (ITM 4.9% vs. PCA 4.4%). In patients who underwent laparotomies, 5.8% and 5.1% of the ITM group had chronic pain at three and six months, respectively, whereas 11.1% and 9.8% of the PCA group had chronic pain over the same timeframes. Overall, the trend was similar for long-term opioid use with a trend towards a small benefit at three (ITM 7.7% vs. PCA 10.5%) and six (ITM 9.9% vs. PCA 12.5%) months but not at twelve months (ITM 11.4% vs. PCA 7.2%). Chronic pain and opioid use at twelve months may have been influenced by the development of pain conditions not related to surgery, including the advanced cancer stage.The association between intrathecal analgesia and cancer recurrence is increasingly being investigated in the literature (23). Two in vivo studies have demonstrated a reduction in cancer recurrence with ITM alongside general anaesthesia in comparison to general anaesthesia alone (24,25). One proposed mechanism is through reducing total systemic opioid administration since high-dose opiates have been shown *in vitro* to exhibit the pro-angiogenic characteristics of tumours through the transactivation of vascular endothelial growth factor and promote metastatic progression (13-15). Another proposed mechanism is that ITM may reduce the surgical stress response and suppress the hypothalamic-pituitary-adrenal axis to reduce immunosuppressive cortisol release and preserve the activity of NK cells (16). In this study, cancer recurrence at three years was 37.8% in the ITM group compared to 36.0% in the PCA group.

Being a retrospective study at a single institution, this research had inherent limitations. Different surgical techniques, length of follow-ups, neoadjuvant therapy, cancer type, grade, and staging were unable to be controlled in this study. Other confounding factors included patient and anaesthetist preferences for analgesia, limitations on the consistency of data collection, and difficulty in distinguishing between postoperative pain and other pain syndromes. On the other hand, this study adds to the literature surrounding the safety and efficacy of ITM in the colorectal cancer setting. The moderate sample size with the presence of a control group and years of follow-up documentation through hospital medical records allowed the research team to understand the trends of postoperative and post-discharge outcomes in this setting. This study finding represented no statistically significant associations for these outcomes, thus prospective research is warranted to further elucidate the impact of ITM.

Conclusion

There is growing interest in ITM based on its good quality postoperative analgesia, reduced systemic opioid

requirements, and its potential to improve immediate postoperative and post-discharge outcomes. In the current study, in the colorectal setting, the ITM group suggested a reduction in postoperative ileus, chronic pain, and opioid use at three and six months that warrants further study with larger, adequately powered prospective studies.

Authors' Contribution

Conceptualization: Jamie Young, Bernhard Riedel, Elizabeth Williams.
Data analysis: Nathan Strugnell, Jamie Young.
Data handling: Nathan Strugnell, Elizabeth Williams.
Data presentation: Nathan Strugnell.
Experiments design: Jamie Young, Elizabeth Williams.
Project administration: Jamie Young, Elizabeth Williams.
Supervision: Jamie Young, Bernhard Riedel, Elizabeth Williams.
Writing–original draft: Nathan Strugnell, Jamie Young.
Writing–review & editing: Nathan Strugnell, Jamie Young, Prof Bernhard Riedel.

Competing Interests

The authors declare that they have no conflicts of interests.

Funding

Nil.

Supplementary Files

Supplementary file 1. Cancer Recurrence

References

1. Australian Institute of Health and Welfare (AIHW). Cancer Data in Australia [Internet]. Canberra: AIHW; 2021. Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia. Accessed April 10, 2022.
2. Garimella V, Cellini C. Postoperative pain control. Clin Colon Rectal Surg. 2013;26(3):191-6. doi: 10.1055/s-0033-1351138.
3. Kehlet H. Postoperative opioid sparing to hasten recovery: what are the issues? Anesthesiology. 2005;102(6):1083-5. doi: 10.1097/00000542-200506000-00004.
4. Chahl LA. Opioids-mechanisms of action. Aust Prescr. 1996;19(3):63-5. doi: 10.18773/austprescr.1996.063.
5. Hindle A. Intrathecal opioids in the management of acute postoperative pain. Continuing Education in Anaesthesia Critical Care & Pain. 2008;8(3):81-5. doi: 10.1093/bjaceaccp/mkn016.
6. Levy BF, Scott MJ, Fawcett W, Fry C, Rockall TA. Randomized clinical trial of epidural, spinal or patient-controlled analgesia for patients undergoing laparoscopic colorectal surgery. Br J Surg. 2011;98(8):1068-78. doi: 10.1002/bjs.7545.
7. Young J, Macpherson A, Thakerar A, Alexander M. Intrathecal morphine in postoperative analgesia for colorectal cancer surgery: a retrospective study. Pain Med. 2021;22(2):402-6. doi: 10.1093/pm/pnaa319.
8. Lavand'homme P, De Kock M. The use of intraoperative epidural or spinal analgesia modulates postoperative hyperalgesia and reduces residual pain after major abdominal surgery. Acta Anaesthesiol Belg. 2006;57(4):373-9.
9. Moriyama K, Ohashi Y, Motoyasu A, Ando T, Moriyama K, Yorozu T. Intrathecal administration of morphine decreases persistent pain after cesarean section: a prospective observational study. PLoS One. 2016;11(5):e0155114. doi: 10.1371/journal.pone.0155114.
10. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. Oncotarget. 2016;7(12):15262-73. doi: 10.18632/oncotarget.7683.
11. Hiller JG, Hacking MB, Link EK, Wessels KL, Riedel BJ. Perioperative epidural analgesia reduces cancer recurrence after gastro-oesophageal surgery. Acta Anaesthesiol Scand. 2014;58(3):281-90. doi: 10.1111/aas.12255.
12. Ismail H, Ho KM, Narayan K, Kondalsamy-Chennakesavan S. Effect of neuraxial anaesthesia on tumour progression in cervical cancer patients treated with brachytherapy: a retrospective cohort study. Br J Anaesth. 2010;105(2):145-9. doi: 10.1093/bja/aeq156.
13. Afsharimani B, Doornebal CW, Cabot PJ, Hollmann MW, Parat MO. Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. Br J Pharmacol. 2015;172(2):251-9. doi: 10.1111/bph.12589.
14. Page GG. Immunologic effects of opioids in the presence or absence of pain. J Pain Symptom Manage. 2005;29(5 Suppl):S25-31. doi: 10.1016/j.jpainsymman.2005.01.006.
15. Yeager MP, Colacchio TA, Yu CT, Hildebrandt L, Howell AL, Weiss J, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology. 1995;83(3):500-8. doi: 10.1097/00000542-199509000-00008.
16. Juneja R. Opioids and cancer recurrence. Curr Opin Support Palliat Care. 2014;8(2):91-101. doi: 10.1097/spc.0000000000000056.
17. Venara A, Neunlist M, Slim K, Barbieux J, Colas PA, Hamy A, et al. Postoperative ileus: pathophysiology, incidence, and prevention. J Visc Surg. 2016;153(6):439-46. doi: 10.1016/j.jviscsurg.2016.08.010.
18. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs. 2003;63(7):649-71. doi: 10.2165/00003495-200363070-00003.
19. Beaussier M, Weickmans H, Parc Y, Delpierre E, Camus Y, Funck-Brentano C, et al. Postoperative analgesia and recovery course after major colorectal surgery in elderly patients: a randomized comparison between intrathecal morphine and intravenous PCA morphine. Reg Anesth Pain Med. 2006;31(6):531-8. doi: 10.1016/j.rapm.2006.06.250.
20. Wongyingsinn M, Baldini G, Stein B, Charlebois P, Liberman S, Carli F. Spinal analgesia for laparoscopic colonic resection using an enhanced recovery after surgery programme: better analgesia, but no benefits on postoperative recovery: a randomized controlled trial. Br J Anaesth. 2012;108(5):850-6. doi: 10.1093/bja/aes028.
21. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003;26(12):696-705. doi: 10.1016/j.tins.2003.09.017.
22. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-S15. doi: 10.1016/j.pain.2010.09.030.
23. Heaney A, Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth. 2012;109 Suppl 1:i17-i28. doi: 10.1093/bja/aes421.
24. Wada H, Seki S, Takahashi T, Kawarabayashi N, Higuchi H, Habu Y, et al. Combined spinal and general anesthesia attenuates liver metastasis by preserving TH1/TH2 cytokine balance. Anesthesiology. 2007;106(3):499-506. doi: 10.1097/00000542-200703000-00014.
25. Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiology. 2001;94(6):1066-73. doi: 10.1097/00000542-200106000-00022.

Appendix 1. Incidence of Ileus, Pruritus, and Chronic Pain at 3 and 6 Months for Laparoscopy Surgeries

	Overall (n = 126)	ITM + PCA (n = 78)	PCA (n = 48)	*P*-value
Ileus	**No. pts (%)**	**No. pts (%)**	**No. pts (%)**	
No	109 (86.5)	68 (87.2)	41 (85.4)	
Yes	17 (13.5)	10 (12.8)	7 (14.6)	0.783
Pruritus				
No	117 (92.9)	70 (89.7)	47 (97.9)	
Yes	9 (7.1)	8 (10.3)	1 (2.1)	0.086
Three months	73 (97.3)	73 (98.6)	40 (97.6)	0.680
No chronic pain	2 (2.7)	1 (1.4)	1 (2.4)	
Chronic pain	108 (93.9)	71 (95.9)	37 (90.2)	0.225
No opioid use	7 (6.1)	3 (4.1)	4 (9.8)	
Opioid use				
Six months	109(99.1)	70 (98.6)	39 (100)	0.470
No chronic pain	1 (0.9)	1 (1.4)	0 (0.0)	
Chronic pain	101 (91.8)	66 (93.0)	35 (89.7)	0.563
No opioid use	9 (8.2)	5 (7.0)	4 (10.3)	
Opioid use				

Note. ITM: Intrathecal morphine; PCA: Patient-controlled analgesia.

Appendix 2. Incidence of Ileus, Pruritus, and Chronic Pain at 3 and 6 Months for Laparotomy Surgeries

	Overall (n = 134)	ITM + PCA (n = 82)	PCA (n = 52)	*P*-value
Ileus	**No. pts (%)**	**No. pts (%)**	**No. pts (%)**	
No	96 (71.6)	60 (73.2)	36 (69.2)	0.625
Yes	38 (28.4)	22 (26.8)	16 (30.8)	
Pruritus				
No	130 (97.0)	80 (97.6)	50 (96.2)	0.648
Yes	4 (3.0)	2 (2.4)	2 (3.8)	
Three months				
No chronic pain	105 (92.1)	65 (94.2)	40 (88.9)	0.309
Chronic pain	9 (7.9)	4 (5.8)	5 (11.1)	
No opioid use	101 (88.6)	61 (88.4)	40 (88.9)	0.941
Opioid use	13 (11.4)	8 (11.6)	5 (11.1)	
Six months				
No chronic pain	93 (93.0)	56 (94.9)	37 (90.2)	0.375
Chronic pain	7 (7.0)	3 (5.1)	4 (9.8)	
No opioid use	89 (87.3)	54 (88.5)	35 (85.4)	0.645
Opioid use	13 (12.7)	7 (11.5)	6 (14.6)	

Note. ITM: Intrathecal morphine; PCA: Patient-controlled analgesia.