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ORIGINAL INVESTIGATION

Regional analgesia and surgical site infections after colorectal surgery: a retrospective cohort analysis

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Abstract
Background: The effect of regional analgesia on perioperative infectious complications remains unknown. We therefore tested the hypothesis that a composite of serious infections after colorectal surgery is less common in patients with regional analgesia than in those given Intravenous Patient-Controlled Analgesia (IV-PCA) with opiates.
Methods: Patients undergoing elective colorectal surgery lasting one hour or more under general anesthesia at the Cleveland Clinic Main Campus between 2009 and 2015 were included in this retrospective analysis. Exposures were defined as regional postoperative analgesia with epidurals or Transversus Abdominis Plane blocks (TAP); or IV-PCA with opiates only. The outcome was defined as a composite of in-hospital serious infections, including intraabdominal abscess, pelvic abscess, deep or organ-space Surgical Site Infection (SSI), clostridium difficile, pneumonia, or sepsis. Logistic regression model adjusted for the imbalanced potential confounding factors among the subset of matched surgeries was used to report the odds ratios along with 95% confidence limits. The significance criterion was $p < 0.05$.
Results: A total of 7811 patients met inclusion and exclusion criteria of which we successfully matched 681 regional anesthesia patients to 2862 IV-PCA only patients based on propensity scores derived from potential confounding factors. There were 82 (12%) in-hospital postoperative serious infections in the regional analgesia group vs. 285 (10%) in IV-PCA patients. Regional analgesia was not significantly associated with serious infection (odds ratio: 1.14; 95%

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Confidence Interval 0.87–1.49; *p*-value = 0.339) after adjusting for surgical duration and volume of intraoperative crystalloids.
Conclusion: Regional analgesia should not be selected as postoperative analgesic technique to reduce infections.

Introduction

Serious infections are a major source of morbidity and increased healthcare costs, especially deep surgical site infections, intra-abdominal and pelvic abscesses, pulmonary infections, and sepsis. These infections are common after colorectal surgery.[1-5] In 2017, more than one-third of deep or organ space infections in patients undergoing surgeries in acute care hospitals occurred after colorectal surgery.[6]

Low tissue perfusion is an important risk factor for post-surgical infections. Regional blocks have been shown to improve tissue perfusion by enhancing peripheral blood flow,[7-11] thereby enhancing delivery of essential nutrients to healing wounds and deprived tissues. Increased tissue perfusion with epidural anesthesia even extended beyond the dermatomal levels of the block.[12] Additionally, regional blocks have shown to reduce inflammation as well as plasma norepinephrine levels which may influence wound repair by affecting microcirculation.[13-17] Regional blocks could also indirectly reduce infections by sparing opioids which appear to promote infections in both surgical and non-surgical patients.[18-23] There is conflicting evidence regarding protective effects of regional analgesia on infectious complications. A meta-analysis of fifty-eight trials[24] showed that epidural analgesia reduced the odds of pneumonia after abdominal and thoracic surgery. However, this association was weak in patients using intravenous patient-controlled analgesia and in larger studies. Further studies[25-27] were unable to show association of regional analgesia with post-operative infectious complications like pneumonia, sepsis, and wound complications in abdominal surgeries.

We therefore tested the primary hypothesis that a composite of serious infections after colorectal surgery is less common in patients who received post-operative regional analgesia compared to patient-controlled intravenous analgesia with opioids. Secondarily, we tested the hypothesis that the overall postoperative opioid consumption during the initial 72 postoperative hours is associated with a composite of serious infections.

Methods

Use of de-identified registry data with waived consent was approved by the Cleveland Clinic Institutional Review Board, Cleveland, Ohio. Our retrospective cohort study included patients who had elective open or laparoscopic colorectal surgery lasting longer than one hour with general anesthesia at the Cleveland Clinic Main Campus between 2009 and 2015.

We excluded patients with pre-existing infections, a history of chronic pain conditions, or who were on long-term opioid therapy. We also excluded patients with missing data regarding exposure and confounding factors.

Postoperative analgesic technique

We compared patients who received regional analgesia, including epidurals or Transversus Abdominis Plane (TAP) blocks (regional analgesia group), to the patients who received only Intravenous Patient-Controlled Analgesia (IV-PCA group). Epidural catheters were inserted preoperatively, but infusions were initiated postoperatively, typically in the postanesthesia care unit (PACU). Epidural solutions typically contained a mixture of local anesthetics and opioids, usually bupivacaine 0.1% and fentanyl 2 μg.mL^{-1}. TAP blocks were performed with injection of long-acting local anesthetics, either as a single injection or by continuous infusion. Patients who received regional analgesia, but then had IV-PCA started within 4 hours after surgery and lasting at least 4 hours were assumed to have had failed blocks and were included into the IV-PCA group. Exposure analysis was restricted to the initial 72 postoperative hours.

Outcomes

Data were obtained from the Cleveland Clinic Perioperative Health Documentation System, EPIC electronic medical records, and the Colorectal Registry. Serious infections were defined as at least one of the following postoperative complications: intra-abdominal abscess, pelvic abscess, deep or organ-space Surgical Site Infection (SSI), clostridium difficile, pneumonia, or sepsis within 30 days after surgery.

Statistical analysis

To account for potential confounding due to systematic differences between study groups, we matched each patient with regional analgesia to five patients with IV-PCA-only on baseline demographic, morphometric, and the pre-surgical and intraoperative variables listed in Table 1. For analysis purposes, types of surgeries derived from Current Procedural Terminology (CPT) codes were collapsed into four main categories: 1) Colostomy or colorectal resection; 2) Ileostomy, small bowel resection and other enterostomy; 3) Lysis of adhesions; and 4) Other procedures.

Matching was implemented on the basis of the propensity score (i.e., the estimated probability of regional analgesia, as a function of the potential confounding variables) using a greedy distance-based matching algorithm. Propensity score was estimated with a multivariable logistic regression. We required an exact match on surgical category and propensity scores within 0.2 standard deviations of the propensity score logits. Balance between the two study groups on baseline and

Table 1 Patient characteristics.

Factor	Before Matching			After Matching		
	Regional (n = 684)	PCA (n = 7127)	ASD	Regional (n = 681)	PCA (n = 2862)	ASD
Age (years)	51 ± 16	53 ± 17	0.15	51 ± 16	51 ± 17	-0.00
Female (%)	354 (52)	3609 (51)	0.02	353 (52)	1479 (52)	0.00
BMI ($kg.m^{-2}$)	27 ± 6.4	27 ± 6.3	0.04	27 ± 6.4	27 ± 6.7	0.01
Charlson Score	1.6 ± 2.2	1.6 ± 2.2	0.01	1.6 ± 2.2	1.5 ± 2.2	0.03
ASA (%)			0.24			0.06
I	2 (0.3)	83 (1)		2 (0.3)	19 (0.7)	
II	231 (34)	3133 (44)		230 (34)	1036 (36)	
III	401 (59)	3564 (50)		399 (59)	1610 (56)	
IV-V	50 (7)	347 (5)		50 (7)	197 (7)	
Preoperative medication						
Steroid (%)	201 (29)	2024 (28)	0.02	201 (30)	875 (31)	0.02
Immunosuppressive drug (%)	21 (3)	236 (3)	0.01	21 (3)	89 (3)	0.00
Comorbidities						
Diabetes w/o chronic complications (%)	75 (11)	865 (12)	0.04	75 (11)	309 (11)	0.01
Peripheral vascular disease (%)	42 (6)	382 (5)	0.03	42 (6)	180 (6)	0.01
Coagulopathy (%)	67 (10)	447 (6)	0.13	65 (10)	250 (9)	0.03
Obesity (%)	146 (21)	1204 (17)	0.11	145 (21)	565 (20)	0.04
Other neurological disorders (%)	37 (5)	296 (4)	0.06	37 (5)	131 (5)	0.04
Metastatic cancer (%)	64 (9)	586 (8)	0.04	63 (9)	235 (8)	0.04
Congestive heart failure (%)	20 (3)	250 (4)	0.03	20 (3)	89 (3)	0.01
Valvular disease (%)	26 (4)	281 (4)	0.01	26 (4)	112 (4)	0.00
Hypertension (%)	235 (34)	2680 (38)	0.07	235 (35)	958 (33)	0.02
Renal failure (%)	31 (5)	319 (4)	0.00	31 (5)	131 (5)	0.00
Liver disease (%)	19 (3)	178 (2)	0.02	19 (3)	80 (3)	0.00
Solid tumor w/out metastasis (%)	111 (16)	1577 (22)	0.15	111 (16)	469 (16)	0.00
Deficiency anemias (%)	167 (24)	1409 (20)	0.11	167 (25)	671 (23)	0.03
Drug abuse (%)	23 (3)	91 (1)	0.14	23 (3)	63 (2)	0.07
Psychosis (%)	43 (6)	262 (4)	0.12	42 (6)	151 (5)	0.04
Depression (%)	164 (24)	1095 (15)	0.22	164 (24)	628 (22)	0.05
Surgery duration (minute)	281 (203,376)	237 (173,310)	0.38	281 (203,374)	255 (180,343)	0.21
Laparoscopic surgery (%)	47 (7)	2611 (37)	0.77	47 (7)	238 (8)	0.05
Surgery types (%)			0.35			0.07
Colostomy or colorectal resection	339 (50)	4719 (66)		338 (50)	1516 (53)	
Ileostomy, small bowel resection and other enterostomy	120 (18)	704 (10)		118 (17)	458 (16)	
Lysis of adhesions	33 (5)	247 (3)		33 (5)	133 (5)	
Other procedures	192 (28)	1457 (20)		192 (28)	755 (26)	
Intraoperative information				16 (2)	63 (2)	0.01
Opioids amount – iv morphine equivalent mg	28 (20,38)	30 (22,38)	0.06	28 (20,38)	30 (22,38)	0.05
Acetaminophen use (%)	16 (2)	143 (2)	0.02	16 (2)	63 (2)	0.01
Hypotension (%)	235 (34)	2506 (35)	0.02	235 (35)	980 (34)	0.01
Estimated blood loss (mL)	200 (75,400)	110 (50,275)	0.30	200 (75,400)	200 (50,350)	0.10
Crystalloids (L)	3.2 (2.0,4.3)	2.8 (2.0,3.7)	0.30	3.2 (2.3,4.20	3.0 (2.0,4.00	0.16
Colloids (mL)	0 (0.750)	0 (0.500)	0.18	0 (0.750)	0 (0.500)	0.06
Transfusion	105 (15)	611 (9)	0.21	103 (15)	363 (13)	0.07

Summary statistics are presented as means ± standard deviations, medians (Q1, Q3), or n (%) as appropriate. PCA, Patient Controlled Analgesia; ASD, Absolute Standardized Difference; ASA, American Society of Anesthesiologists physical status; Absolute standardized difference defined as the absolute difference between groups divided by the pooled standard deviation. Variables with an ASD > 0.10 are defined as imbalanced between groups.

intraoperative potential confounding variables was assessed before and after matching using Absolute Standardized Differences (ASDs), defined by the absolute difference between means, mean rankings, or proportions divided by a combined estimate of standard deviation. We considered an ASD > 0.1 after matching as indicative of potential residual confounding and subsequently adjusted for such factors directly in the primary analysis comparing the groups on outcomes.

To assess the adjusted association between postoperative analgesic technique (regional analgesia vs. IV-PCA only) and the composite outcome of serious infections, we used a logistic regression model adjusted for the imbalanced potential confounding factors, if any, among the subset of matched surgeries. The odds ratios (odds of having serious infection with regional analgesia over with IV-PCA-only approach) along with 95% confidence limits were reported. Secondarily, we assessed the association between overall postoperative opioid consumption during the initial 72 postoperative hours and the composite of serious infections in a multivariable logistic regression model.

The significance criterion was $p < 0.05$ for primary and secondary outcomes. All statistical tests were two-tailed.

Power considerations

We planned to retrieve records from approximately 10,000 patients in the colorectal registry. The infection rate for major colorectal surgery at the Cleveland Clinic is about 15%. A 20% reduction in infections would most certainly be clinically important. Assuming 20% of patients received regional anesthesia, we anticipated having approximately 9000 matched patients in total (1500 with regional analgesia and 7500 with IV-PCA only). With a type I error rate of 5%, we would have 80% power to detect an odds ratio of 0.8 (or smaller) for collapsed composite infectious complications comparing the regional analgesia group and PCA-only group.

In fact, there were fewer patients than expected who had regional analgesia. A post-hoc power estimation showed that we had 80% power to detect an Odds Ratio of 0.7 (or smaller) for postoperative serious infection in 681 patients in the regional analgesia group, and 2682 matched only patients in the IV-PCA group.

Results

We identified 7811 patients who met inclusion and exclusion criteria (Fig. 1), including 684 (9%) who had regional anesthesia and 7127 (91%) who had IV-PCA. In the regional anesthesia group, 125 patients had TAP blocks, 552 patients had epidural, and 7 patients had both. Seventy-nine patients who had failed epidurals, 134 patients who had failed TAP blocks, and one who failed both epidural and TAP blocks were considered to be in the IV-PCA group. We successfully matched 681 regional anesthesia patients to 2862 IV-PCA patients based on propensity scores derived from all potential confounding factors listed in Table 1. The balance of confounding variables among matched patients was much better than before matching, but surgery duration and intraoperative volume of crystalloids administered still had ASD > 0.1 (Table 1).

Within the matched groups of patients, there were 82 (12%) in-hospital serious postoperative infections in the regional anesthesia group vs. 285 (10%) in the IV-PCA group. Regional analgesia was not significantly associated with serious infection (OR = 1.14; 95% CI 0.87–1.49; $p = 0.339$), after adjusting for surgical duration and volume of intraoperative crystalloids (Table 2).

We further compared opioid consumption within the matched pairs of patients. The median total amount of postoperative morphine equivalent consumption during the initial 72 postoperative hours was 169 mg ([Q1, Q3] = [97, 313]) in patients given regional analgesia vs. 202 mg ([Q1, Q3] = [109, 342]) in the PCA group (p-value = 0.005). After excluding postoperative epidural opioids, the median total amount of opioid consumption in 72 hours was 79 (25, 230) mg IV morphine equivalents in the regional analgesia group and 198 (107, 340) mg in the PCA group. Opioid consumption was therefore significantly lower in the regional analgesia group than the PCA group (p-value < 0.001).

Among all eligible patients, including both PCA and regional analgesia, increase in postoperative opioid consumption was significantly associated with higher odds of serious infection. The estimated odds ratio related with a 50-mg increase in morphine equivalent opioid consumption was 1.03 (97.5% CI 1.01, 1.05; $p = 0.002$), adjusted for all confounding variables listed in Table 1.

Discussion

We did not observe an association between postoperative regional analgesia and a composite of serious infectious complications compared to patient-controlled analgesia with opioids. Our findings extend previous work by Park et al.[25] who studied the effect of epidural analgesia on perioperative outcomes in a randomized trial of 1021 patients having intra-abdominal surgery. There was no difference in the incidence of pneumonia and sepsis in patients given general anesthesia and postoperative analgesia with parental opioids compared with epidural analgesia. Recent analyses of the Healthcare Cost and Utilization Project Nationwide Inpatient Sample evaluated associations between epidural analgesia and postoperative outcomes in patients who had open[26] and laparoscopic[27] colorectal surgery. These retrospective studies were unable to identify associations between epidural analgesia and postoperative pneumonia, anastomotic leak, or wound complications.

We observed a weak association of postoperative opioid consumption with serious infectious complications which might not be clinically important. A 50-mg increase in intravenous morphine equivalents was associated with 3% increase in the odds of serious infectious complications, roughly equivalent to a quarter percent increase in the absolute difference of incidence. Patients given postoperative regional analgesia used similar amounts of total opioids when including epidural opiates, i.e., despite reducing the use of IV and PO opioids, the use of regional analgesia did not significantly reduce total opioid use.

The CPT coding for procedures used for our analysis limited our ability to further classify and match procedures based upon their complexity. Regional analgesia is most likely to be offered to patients having larger and more complex surgery who will presumably have more pain. These patients are also most likely to develop infections. Although our analysis was

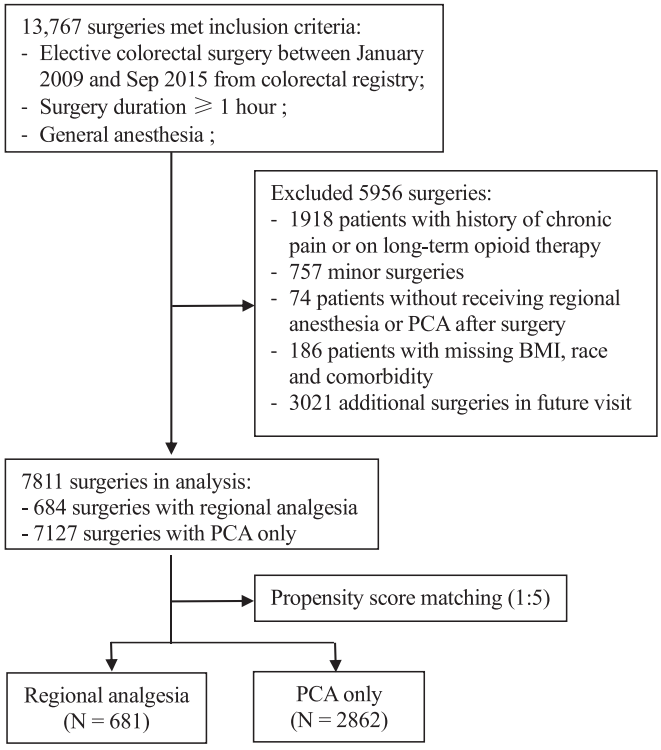

Figure 1 Study flow diagram.

adjusted for duration of surgeries, there could be other attributes of surgical complexity which remained unadjusted, resulting in unobserved confounding which might have diminished putative benefit from regional analgesia. Our analysis included surgeries conducted in our hospital across 6 years during which collateral changes in infection prevention protocols, surgical teams, perioperative pain management strategies, as well as changing trends of utilization of regional analgesia as primary postoperative pain management modalities have been apparent. These, in addition to other unknown confounders, may have affected the results of our analysis.

In conclusion, our analysis demonstrated that the use of regional analgesic techniques was not associated with lower risk of postoperative serious infections, compared with patient-controlled analgesia with opioids. However, opioid consumption after colorectal surgery was associated with a small increase in the odds of serious infection. Hence, regional analgesia should not be selected as postoperative analgesic technique to reduce infections.

Glossary of terms

IV-PCA, Intravenous Patient Controlled Analgesia; TAP, Transversus Abdominis Plane; PACU, Post Anesthesia Care Unit; SSI, Surgical Site Infections; ASD, Absolute Standardized Differences; Q1, First Quartile; Q3, Third Quartile; CI, Confidence Interval; CPT, Current Procedural Terminologies.

Table 2 Association between regional analgesia vs. PCA only and postoperative serious infection after colorectal surgery.

Outcome	Incidence – n (%)		Odds ratio (95% CI)[a] (Regional vs. PCA)	*p*-value[b]
	Regional (n = 681)	PCA only (n = 2862)		
Serious infection	82 (12.0)	285 (10.0)	1.14 (0.87, 1.49)	0.339
Abscess – Intra-abdominal	21 (3.1)	72 (2.5)		
Abscess – Pelvic	28 (4.1)	104 (3.6)		
Clostridium Difficile	5 (0.7)	29 (1.0)		
Pneumonia	10 (1.5)	29 (1.0)		
Pneumonia (Aspiration)	2 (0.3)	6 (0.2)		
Sepsis	16 (2.3)	70 (2.4)		
SSI – deep (Facia)	2 (0.3)	6 (0.2)		
SSI – organ space	40 (5.9)	139 (4.9)		

[a] Odds Ratio was estimated from matched cohort using logistic regression, adjusted for surgery duration and total volume of intraoperative Crystalloid fluid.
[b] Significant criterion was p-value < 0.05. Correspondingly, 95% Confidence Interval (95% CI) was presented with Odds Ratio.
PCA, Patient Controlled Analgesia; CI, Confidence Interval; SSI, Surgical site infection.

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Conflicts of interest

The authors declare no conflicts of interest.

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