


The effect of anesthesia on the magnitude of the postoperative systemic inflammatory response in patients undergoing elective surgery for colorectal cancer in the context of an enhanced recovery pathway

A prospective cohort study

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Abstract

There are reports that the use of regional anesthesia (RA) may be associated with better perioperative surgical stress response in cancer patients compared with general anesthetics (GA). However, the role of anesthesia on the magnitude of the postoperative systemic inflammatory response (SIR) in colorectal cancer patients, within an enhanced recovery pathway (ERP), is not clear.

The aim of the present study was to examine the effect of anesthesia, within an enhanced recovery pathway, on the magnitude of the postoperative SIR in patients undergoing elective surgery for colorectal cancer.

Database of 507 patients who underwent elective open or laparoscopic colorectal cancer surgery between 2015 and 2019 at a single center was studied. The anesthetic technique used was categorized into either GA or GA + RA using a prospective proforma. The relationship between each anesthetic technique and perioperative clinicopathological characteristics was examined using binary logistic regression analysis.

The majority of patients were male (54%), younger than 65 years (41%), either normal or overweight (64%), and were nonsmokers (47%). Also, the majority of patients underwent open surgery (60%) and received mainly general + regional anesthetic technique (80%). On univariate analysis, GA + RA was associated with a lower day 4 CRP (≤ 150 / >150 mg/L) concentration. On day 4, postoperative CRP was associated with anesthetic technique [odds ratio (OR) 0.58; confidence interval (CI) 0.31–1.07; $P = .086$], age (OR 0.70; CI 0.50–0.98; $P = .043$), sex (OR 1.15; CI 0.95–2.52; $P = .074$), smoking (OR 1.57; CI 1.13–2.19; $P = .006$), preoperative mGPS (OR 1.55; CI 1.15–2.10; $P = .004$), and preoperative dexamethasone (OR 0.70; CI 0.47–1.03; $P = .072$). On multivariate analysis, day 4 postoperative CRP was independently associated with anesthetic technique (OR 0.56; CI 0.32–0.97; $P = .039$), age (OR 0.74; CI 0.55–0.99; $P = .045$), smoking (OR 1.58; CI 1.18–2.12; $P = .002$), preoperative mGPS (OR 1.41; CI 1.08–1.84; $P = .012$), and preoperative dexamethasone (OR 0.68; CI 0.50–0.92; $P = .014$).

There was a modest but an independent association between RA and a lower magnitude of the postoperative SIR. Future work is warranted with multicenter RCT to precisely clarify the relationship between anesthesia and the magnitude of the postoperative SIR.

Abbreviations: ASA = American Society of Anesthesiologists, COX-2 = cyclooxygenase-2, CRP = C-reactive protein, ERP = enhanced recovery pathway, GA = general anaesthesia, IL-6 = interleukin-6, IV = Intravenous, mGPS = modified Glasgow Prognostic Score, NSAIDs = nonsteroidal anti-inflammatory drugs, POD = postoperative day, RA = regional anesthesia, SIR = systemic inflammatory response, TAP, transversus abdominal plane, TNM = tumor node metastasis.

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1. Introduction

The perioperative period is a complex process that may influence the outcome of cancer surgery.^[1] In particular, both surgery and anesthesia have been reported to depress the cellular immunity during the postoperative period and to potentiate recurrence and metastasis of cancer.^[2] The surgical stress response and its magnitude are strongly associated with interleukin (IL)-6 and C-reactive protein (CRP).^[3] However, although the impact of surgery on the postoperative systemic inflammatory response (SIR) is well delineated, the impact of anesthesia is not clear.

Regional anesthetic techniques can be used combined with general anesthetics (GA) in most abdominal surgery, which involve either neuraxial or peripheral nerve block. The available evidence suggests the benefits of regional anesthesia (RA) on the surgical stress response, recovery of the gastrointestinal function, and reducing the postoperative pain outcome and opioid consumption.^[4]

Specifically, Alhayyan et al^[5] in systematic review and meta-analysis reported that it was not clear in the literature whether anesthetic technique has an effect on the magnitude of the postoperative SIR. This was due to the heterogeneity and poor quality of identified studies.^[5] Furthermore, these authors, in a retrospective audit of the effect of anesthetic technique on the magnitude of the postoperative CRP in patients undergoing elective open or laparoscopic surgery for colon cancer, reported that the magnitude of the postoperative SIR in particular, POD 2 CRP, was modulated by the induction of RA in patients who underwent open surgery, but not laparoscopic surgery for colorectal cancer.^[6]

With the introduction of enhanced recovery pathways (ERPs), there has been a focus on laparoscopic surgery and early mobilization of patients undergoing surgery for colorectal cancer; however, few studies have examined the effect of anesthetic technique.^[7] In terms of the postoperative SIR, few components of ERP have been proven to reduce the postoperative SIR with the exception of minimally invasive surgery.^[8]

The aim of the present study was to examine the effect of anesthesia using a prospective proforma within the context of ERP, on the magnitude of the postoperative SIR in patients undergoing elective surgery for colorectal cancer.

2. Patients and methods

2.1. Study design

The study was designed by preparing a proforma, including clinicopathological data, all the anesthetic technique or agents and all the medications administered before and after induction of anesthesia such as neuromuscular blockers, steroids, antibiotics, and benzodiazepines in patients who underwent elective surgery for colorectal cancer (Table 1).

2.2. Patients

Five hundred nineteen consecutive patients who underwent elective open or laparoscopic surgery for colorectal cancer from 2015 to 2019 within an ERAS pathway were identified from a

prospectively maintained database at a single center. Of these, only 507 patients had documented anesthetic records. All data were anonymized, and all patients underwent either open (n=304) or laparoscopic surgery (n=203). Propofol had been given for the induction of GA either with or without remifentanyl. Most patients received inhalational anesthesia for the maintenance of anesthesia (n=449), while only few patients received intravenous anesthesia mainly propofol for both induction and maintenance of anesthesia (n=53). In addition, 309 patients underwent colon resection, while 196 patients underwent rectal resection. Anesthetic regimens were grouped according to the anesthetic methods applied into GA or GA + RA. Within the RA technique, 3 groups were included that is, epidural (n=115), spinal (n=213), or local anesthesia (n=80).

All clinicopathological data were anonymized, and all the emergency cases were excluded from the analysis. The preoperative modified Glasgow Prognostic Score (mGPS) from 0 to 2 was used to assess the preoperative SIR. Patients with normal CRP concentration (<10 mg/L)=0, patients with high CRP concentration (>10 mg/L)=1 and patients with high CRP concentration (>10 mg/L) and hypoalbuminemia (<35 g/L)=2.^[9] The magnitude of the postoperative SIR was assessed by the measurement of postoperative C-reactive protein (CRP \leq 150/>150 mg/L), on the second, third, and fourth postoperative days. Tumors were staged according to TNM staging system (tumor, node, and metastasis). The patient comorbidity was assessed by using the American Society of Anaesthesiologists (ASA) grading system, while severity of surgical complications has been classified by using the Clavien-Dindo scale.^[10,11]

Patients data were collected from a prospective database from January to December 2016 from the academic department of surgery at Glasgow Royal Infirmary hospital. The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

2.3. Data analysis

All data were analyzed using SPSS version 25.0 for windows (IBM Corporation, Armonk, NY). On the basis of previous retrospective study, more than 400 patients were recruited to the present study. The X² (Chi-square) statistical method was used to test the statistical significance between the anesthetic regimens and clinicopathological variables. A *P* value of <.05 were considered statistically significant.

Binary logistic regression model was used to examine the relationship between the clinicopathological variables and the postoperative CRP with the calculation of odds ratio (OR) and 95% confidence interval (95% CI). On univariate analysis, all the clinicopathological variables with a *P* value <.10 were included into a multivariate analysis using a backward conditional model to identify independently significant variables.

3. Results

Most patients were male (275, 54%), younger than 65 years (207, 41%), normal or overweight (319, 64%), and were nonsmokers (235, 47%). The majority of patients had the

surgical resection for open colorectal cancer (304, 60%). The GA was only administered to 99 patients, while GA and RA was the most commonly performed technique (408, 80%). The epidural anesthetic technique was given to 115 patients (23%), spinal to 213 patients (42%), and local anesthesia to 80 patients (16%) respectively.

IV dexamethasone was administered at the induction of anesthesia to 373 patients (74%) and 133 patients (26%) did not receive dexamethasone. Also, 489 patients received opioids. In theater, NSAID-COX2 inhibitors were administered to 79 patients and IV local anesthesia such as lidocaine or lignocaine was administered to 54 patients. Preoperative antibiotics were given to most patients (n=491) to reduce the risk of infections. All patients received muscle relaxant and neuromuscular reversal was given to 277 patients. Benzodiazepine medication was administered to 145 patients. In addition, most patients did not receive NSAID-COX2 (n=504) or steroids (n=503) postoperatively. The majority of patients were not systemically inflamed before surgery (322, 65%) and had a CRP <150mg/L on day 2, 3, and 4 following surgery.

The relationship between GA versus GA + RA and clinicopathological data of patients undergoing elective surgery for colorectal cancer is summarized in Table 2. There was a significant association between GA versus GA + RA, surgical approach (P=.02), TNM stage (P=.003), preoperative dexamethasone (P=.05), neoadjuvant therapy (P=.006), and POD 4 CRP (P=.005).

The relationship between GA versus GA + RA and clinicopathological data of patients undergoing elective surgery for colon cancer is summarized in Table 3. There was a significant association between GA versus GA + RA, surgical approach (P=.01), and POD 4 CRP (P=.01).

Binary logistic regression of clinicopathological variables that significantly associated with low (≤150mg/L) versus high (>150mg/L) POD 4 CRP concentration in patients undergoing elective surgery for colorectal cancer is summarized in Table 4. On univariate analysis, POD 4 CRP was associated with anesthetic technique (OR 0.58; CI 0.31–1.07; P=.086), age (OR 0.70; CI 0.50–0.98; P=.043), sex (OR 1.15; CI 0.95–2.52; P=.074), smoking (OR 1.57; CI 1.13–2.19; P=.006), preoperative mGPS (OR 1.55; CI 1.15–2.10; P=.004), and preoperative dexamethasone (OR 0.70; CI 0.47–1.03; P=.072). On multivariate analysis, POD 4 CRP was independently associated with anesthetic technique (OR 0.56; CI 0.32–0.97; P=.039), age (OR 0.74; CI 0.55–0.99; P=.045), smoking (OR 1.58; CI 1.18–2.12; P=.002), preoperative mGPS (OR 1.41; CI 1.08–1.84; P=.012), and preoperative dexamethasone (OR 0.68; CI 0.50–0.92; P=.014).

4. Discussion

The results of the present prospective observational study showed that RA, within the context of an ERP, had a modest and an independent effect on the magnitude of the postoperative SIR in elective surgery for colorectal cancer. This would suggest that there is a role for anesthetic technique in modulating the postoperative SIR.

To date, there has been one previous study that addressed the effect of anesthesia on postoperative CRP within an ERAS program. Chen et al conducted a randomized study and reported that in open colon cancer patients who underwent for fast track protocol, GA combined with epidural anesthesia (n=26) showed

Table 2

The relationship between general versus general + regional anesthesia and clinicopathological variables in patients undergoing elective surgery for colorectal cancer in ERP (n=507).

Characteristic	GA (n=99)	GA + RA (n=408)	P
Age			.80
<65	40 (40)	167 (41)	
65–74	36 (36)	135 (33)	
>75	23 (23)	106 (26)	
Sex			.09
Male	60 (61)	215 (53)	
Female	39 (39)	193 (47)	
BMI			.26
<20	3 (3)	21 (5)	
20–25	38 (39)	104 (26)	
26–30	28 (29)	149 (37)	
>30	28 (29)	125 (31)	
Smoking			.56
Never	45 (47)	190 (47)	
Ex	31 (33)	154 (38)	
Current	19 (20)	60 (15)	
ASA grade			.24
1	10 (10)	37 (9)	
2	47 (47)	208 (53)	
3	35 (35)	138 (35)	
4	7 (7)	10 (2)	
TNM stage			.003
I	26 (28)	79 (20)	
II	41 (44)	129 (32)	
III	20 (21)	155 (39)	
IV	4 (4)	29 (7)	
Surgical approach			.02
Open	50 (51)	254 (62)	
Laparoscopic	49 (49)	154 (38)	
Tumor site			.49
Colon	65 (65)	244 (60)	
Rectum	34 (34)	162 (40)	
Preop mGPS			.61
0	61 (63)	261 (65)	
1	17 (17)	66 (17)	
2	19 (19)	71 (18)	
Opioids			.10
No	1 (1)	17 (4)	
Yes	97 (99)	390 (96)	
Preop Dexamethasone			.05
No	38 (39)	95 (23)	
Yes	60 (61)	313 (77)	
POD 2 CRP > 150 mg/L			.23
No	47 (51)	217 (54)	
Yes	45 (49)	171 (44)	
POD 3 CRP > 150 mg/L			.34
No	47 (55)	222 (58)	
Yes	39 (45)	163 (42)	
POD 4 CRP > 150 mg/L			.005
No	42 (56)	254 (72)	
Yes	33 (44)	98 (28)	
Neoadjuvant therapy			.006
No	90 (94)	339 (84)	
Yes	6 (6)	66 (16)	
Adjuvant therapy			.06
No	59 (61)	212 (52)	
Yes	37 (38)	194 (48)	
Stoma type			.59
No	63 (64)	245 (60)	
Ileostomy	22 (22)	96 (24)	
Colostomy	14 (14)	63 (15)	
Any complication			.30
No	65 (66)	282 (70)	
Yes	33 (34)	123 (30)	
Infective complication			.54
No	75 (76)	311 (76)	
Yes	23 (23)	95 (23)	
Clavien-Dindo grade			.94
0	56 (57)	209 (51)	
1–2	29 (30)	148 (36)	
3–4	10 (10)	45 (11)	
5	3 (3)	4 (1)	

ASA=American Society of Anaesthesiology Grading system, BMI=body mass index, CRP=C-reactive protein, day=G General anesthesia, E=Epidural anesthesia, POD=postoperative, Preop mGPS=preoperative modified Glasgow Prognostic score, RA=Regional anesthesia, Sp=Spinal anesthesia, TNM=Tumour Node Metastases, (0 = no complication, 1–2 = complication with minor intervention, 3–4 = complication with major intervention, 5 = death).

Table 3
The relationship between general versus general + regional anesthesia and clinicopathological variables in patients undergoing elective surgery for colon cancer in ERP (n=309).

Characteristic	GA (n=65)	GA + RA (n=244)	P
Age, yr			.65
<65	25 (38)	84 (34)	
65–74	22 (34)	90 (37)	
>75	18 (28)	70 (29)	
Sex			.43
Male	35 (54)	126 (52)	
Female	30 (46)	118 (48)	
BMI			.29
<20	3 (5)	13 (5)	
20–25	27 (41)	62 (26)	
26–30	14 (21)	87 (37)	
>30	21 (32)	76 (32)	
Smoking			.60
Never	30 (48)	114 (47)	
Ex	22 (35)	98 (41)	
Current	11 (17)	29 (12)	
ASA grade			.11
1	4 (6)	19 (8)	
2	28 (43)	116 (49)	
3	27 (41)	91 (39)	
4	6 (9)	9 (4)	
TNM stage			.14
I	14 (22)	47 (20)	
II	29 (46)	84 (35)	
III	17 (27)	83 (35)	
IV	3 (5)	22 (9)	
Surgical approach			.01
Open	32 (49)	159 (65)	
Laparoscopic	33 (51)	85 (35)	
Preop mGPS			.57
0	36 (57)	141 (59)	
1	11 (17)	47 (20)	
2	16 (25)	50 (21)	
Opioids			.63
No	1 (2)	5 (2)	
Yes	63 (98)	239 (98)	
Preop Dexamethasone			.49
No	26 (40)	68 (28)	
Yes	39 (60)	176 (72)	
POD 2 CRP > 150mg/L			.26
No	31 (48)	124 (53)	
Yes	34 (52)	110 (47)	
POD 3 CRP > 150mg/L			.40
No	32 (53)	128 (56)	
Yes	28 (47)	100 (44)	
POD 4 CRP > 150mg/L			.01
No	27 (53)	146 (70)	
Yes	24 (47)	63 (30)	
Neoadjuvant therapy			.24
No	63 (98)	231 (95)	
Yes	1 (2)	11 (5)	
Adjuvant therapy			.47
No	36 (56)	133 (55)	
Yes	28 (44)	110 (45)	
Stoma type			.22
No	48 (74)	196 (81)	
Ileostomy	13 (20)	34 (14)	
Colostomy	4 (6)	11 (5)	
Any complication			.40
No	43 (66)	166 (69)	

(continued)

Table 3
(continued).

Characteristic	GA (n=65)	GA + RA (n=244)	P
Yes	22 (34)	76 (31)	
Infective complication			.45
No	50 (77)	190 (79)	
Yes	15 (23)	52 (21)	
Clavien-Dindo grade			.81
0	38 (58)	126 (58)	
1–2	19 (29)	90 (37)	
3–4	5 (8)	23 (9)	
5	3 (5)	3 (1)	

ASA=American Society of Anaesthesiology Grading system, BMI=body mass index, CRP=C-reactive protein, day, G=General anesthesia, E=Epidural anesthesia, POD=postoperative, Preop mGPS=preoperative modified Glasgow Prognostic score, RA=Regional anesthesia, Sp=Spinal anesthesia, TNM= Tumour Node Metastases, (0 = no complication, 1–2 = complication with minor intervention, 3–4 = complication with major intervention, 5 = death).

a significant reduction on postoperative day 2 CRP level compared with a group of GA alone (n=27). In contrast, in the pre-ERP era, Papadima et al conducted a randomized study and reported no significant difference in postoperative CRP concentrations in both techniques of anesthesia (GA, n=19 vs combined GA with RA, n=21) in patients underwent open colectomy. Therefore, the present observational study is the largest to date to examine this relationship in the ERP era.

The application of an ERP in colorectal surgery has been studied extensively and now established as a best care method. It is an evidence-based multimodal care pathway that contains several components during the preoperative, intraoperative, and postoperative periods to attain faster recovery and shorter hospital stay with a focus on reducing the postoperative stress response and postoperative complication rates.^[12] A randomized controlled trial conducted by Veenhof et al who examined the effect of fast track and standard care on immune status and stress response within open or laparoscopic surgery for non-metastased colon cancer patients, reported that the immune function was significantly improved for those who underwent for minimally invasive surgery with fast track protocol. This result was consistent with the hypothesis that laparoscopic technique in combination with fast track protocol enhanced the immune function and thereby reducing the stress response and lowering the postoperative concentration of CRP.^[8]

There is a recognition that RA, in particular neuraxial block with epidural technique, has been reported to protect the immune system. This includes modulation of surgical stress response with an optimal postoperative pain relief. With regards to the postoperative outcomes and in patients undergoing abdominal surgery, the most studied technique in RA is the epidural analgesia.^[4,13] The use of RA has been reported to reduce the dose of opioids and thus minimize the risk of immune suppressive effect of opioids.^[14] However, in the present study and even within RA patients, opioids were extensively administered to control pain in the perioperative period. However, the immunosuppressive effects of opioids have been reported in many previous and recent studies. Therefore, there is significant work to be done to reduce the reliance on opioids postoperatively.^[15]

Propofol is the most common intravenous anesthetic agent used for induction by bolus administration and maintenance of anesthesia by continuous infusion. It has been reported that

Table 4**Binary logistic regression of clinicopathological data associated with low versus high POD 4 CRP concentrations in patients undergoing elective surgery for colorectal cancer in ERP (n=507).**

Variables	Univariate analysis OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
Age, yr (<65/65–74/>75)	0.70 (0.50–0.98)	.043	0.74 (0.55–0.99)	.045
Sex (male/female)	1.15 (0.95–2.52)	.074	1.48 (0.94–2.31)	.085
BMI (<20/20–25/26–30/>30)	1.17 (0.89–1.53)	.253	–	–
Smoking (never/ex/current)	1.57 (1.13–2.19)	.006	1.58 (1.18–2.12)	.002
ASA grade (1/2/3/4)	0.82 (0.56–1.20)	.311	–	–
Surgical technique (open/laparoscopic)	0.72 (0.39–1.34)	.310	–	–
TNM stage (I/II/III/IV)	0.93 (0.71–1.21)	.594	–	–
Opioids (no/yes)	1.12 (0.35–3.60)	.842	–	–
Tumor site (colon/rectum)	0.89 (0.74–1.07)	.221	–	–
Preop mGPS (0/1/2)	1.55 (1.15–2.10)	.004	1.41 (1.08–1.84)	.012
GA alone /GA+ RA (no/yes)	0.58 (0.31–1.07)	.086	0.56 (0.32–0.97)	.039
Preop Dexamethasone (no/yes)	0.70 (0.47–1.03)	.072	0.68 (0.50–0.92)	.014

propofol-based IV anesthesia has an anti-inflammatory, antioxidant, and antitumor effect providing some protection against immune suppression.^[16,17] In addition, previous research has established that propofol-based IV anesthesia was favorable in the long-term outcome in patients underwent for surgical resection of gastric, esophagus, and colon.^[18] Therefore, with the appropriate use of propofol, it may be that the use of opioids in the postoperative period may be reduced or removed.^[19,20]

The concept of ERP was introduced by Prof. Kehlet and Wilmore. The role of ERAS has been proven in multiple surgical disciplines and aims to minimize the perioperative surgical stress response, maintain the body physiological function, and facilitate recovery after surgery.^[21]

There is increasing interest in moderating the post-operative SIR using anesthesia to improve recovery from surgery.^[18,22] However, to date, there have been little data to guide how we might proceed, and therefore, there is a pressing need for more information on the effect of anesthesia on the postoperative SIR taking account of other perioperative treatments.^[23] Recently, a retrospective study of 543 patients who underwent for elective curative surgery for CRC examined the relationship between 2 types of anesthesia, inhalational or TIVA within a standardized ERP and the postoperative complications, survival, recurrence, and recovery. The results of this study showed that those patients exposed to inhalational anesthesia had a significant lower chance of discharge and bowel movement per postoperative day, although no significant difference for other outcomes was reported.^[24] Clearly, further studies are required if evidence-based anesthesia is to be practised within an enhanced recovery pathway.

In the present study, in the context of ERP, approximately 19% of patients had GA solely. These patients were less likely to have advanced disease and less likely to have undergone open surgery and therefore is not clear what drives this apparently suboptimal anesthetic practice. However, it may simply reflect existing anesthetic practice.

In major open colorectal surgery, epidural anesthesia is recommended; however, it may be superfluous in laparoscopic colorectal surgery. A recent meta-analysis showed that there was no additional clinical benefit with epidural analgesia for patients undergoing laparoscopic colorectal surgery within an ERP.^[25] Indeed, the commonly used analgesic techniques in laparoscopic abdominal surgery are spinal analgesia, continuous IV local

infusion, and TAP block, which has been a recommended technique in laparoscopic abdominal surgery.^[13,26] A recent randomized clinical study reported that, in a comparison between GA + continuous TAP block performed before laparoscopic colorectal surgery with GA + thoracic epidural anesthesia, both anesthetic techniques were able to significantly attenuate the surgical stress response including IL-6. Also, the continuous TAP-block anesthesia was associated with an acceleration in the recovery of gastrointestinal function and shortened hospital stay.^[27]

The present prospective observational cohort study has some limitations. The use of surgical and anesthetic techniques was variable and it was a single-center study. Also, the administration of preoperative steroids to the majority of patients (74%) may have affected the relationship between the type of anesthesia and the postoperative SIR, as dexamethasone has been shown recently in reducing the postoperative SIR and complications after elective colorectal cancer surgery.^[28] However, this study was carried in a relatively large well documented group of patients undergoing surgery for colorectal cancer.

5. Conclusions

The results of the present study suggest that the application of RA within an ERP reduces the magnitude of the postoperative SIR in patients undergoing elective surgery for colorectal resection. Further studies are needed to examine the relationship between anesthesia and the magnitude of the postoperative SIR in large multicenter randomized trials to provide an optimal ERP in patients undergoing surgery for colorectal cancer.

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Author contributions

The authors A. A., C. R., and D. M. contributed for study concepts and design. The authors A. A., S. M., and D. M. contributed for data acquisition, analysis, and interpretation. All authors contributed for the manuscript preparation, editing, and review.

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