ORIGINAL RESEARCH

Is preoperative hypocholesterolemia a risk factor for severe postoperative pain? Analysis of 1,944 patients after laparoscopic colorectal cancer surgery

Tak Kyu Oh[1]
Sung-Bum Kang[2]
In-Ae Song[1]
Jung-Won Hwang[1]
Sang-Hwan Do[1]
Jin Hee Kim[1]
Ah-Young Oh[1]

[1]Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, [2]Department of Surgery, Seoul National University Bundang Hospital, Seoul, South Korea

Correspondence: In-Ae Song
Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 166 Gumi-ro, Bundang-gu, Seongnam, Gyeonggi 463 707, South Korea
Tel +82 31 787 7499
Fax +82 31 787 4063
Email songoficu@outlook.kr

Purpose: This study aimed to identify the effect of preoperative serum total cholesterol on postoperative pain outcome in patients who had undergone laparoscopic colorectal cancer surgery.

Methods: We retrospectively reviewed the medical records of patients diagnosed with colorectal cancer who had undergone laparoscopic colorectal surgery from January 1, 2011, to June 30, 2017, to identify the relationship of total cholesterol levels within a month prior to surgery with the numeric rating scale (NRS) scores and total opioid consumption on postoperative days (PODs) 0–2.

Results: We included 1,944 patients. No significant correlations were observed between total cholesterol and the NRS (POD 0), NRS (POD 1), and oral morphine equivalents (PODs 0–2) ($P>0.05$). There was no significant difference between the low (<160 mg/dL), medium (160–199 mg/dL), and high (≥200 mg/dL) groups in NRS scores on PODs 0, 1, or 2 ($P>0.05$). Furthermore, there was no significant association in multivariate linear regression analysis for postoperative opioid consumption according to preoperative serum total cholesterol level (coefficient 0.08, 95% CI –0.01 to 0.18, $P=0.81$).

Conclusion: This study showed that there was no meaningful association between preoperative total cholesterol level and postoperative pain outcome after laparoscopic colorectal cancer surgery.

Keywords: cholesterol, analgesia, colon, rectum, laparoscopy

Introduction

Enhanced recovery after surgery (ERAS) is a concept that has been consistently emphasized for rapid recovery of postoperative patients.[1,2] In particular, many studies have been conducted on colorectal surgery in relation to the importance of ERAS.[1–3] Above all, effective pain control is the most significant element in perioperative management.[4] Even though colorectal surgery through a minimally invasive laparoscopic approach has been generally conducted,[5] trocar incision sites or visceral pain remain problematic.

Cholesterol is known to be one of the important factors that may influence opioid effects.[6,7] This is because the μ-opioid receptor is located on the cell membrane as a cholesterol-rich lipid-raft microdomain together with G-protein-coupled receptors[8,9] and acts as the main mediator of morphine analgesia.[10] In addition, similar to the widely accepted association of G-protein-coupled receptors with lipid rafts,[11] the relationship between cholesterol and opioid signaling has been reported and

1057

confirmed by laboratory tests: reducing cholesterol levels through disruption of the lipid raft by methyl-β-cyclodextrin results in signaling impairments in the μ-opioid receptor in neuronal cells.[12] Moreover, a report from a laboratory study suggested a significant connection between cholesterol and opioid signaling,[13] and the result of another study indicated that the cholesterol level was directly critical for μ-opioid-receptor binding.[14] A similar contribution of cholesterol to signaling of the μ-opioid receptor was reported in an in vitro study[13] and an animal study.[12] Recently, the first study on the relationship between opioid doses and cholesterol levels in patients with advanced lung cancer was conducted.[15] This study reported that the opioid doses administered for pain control had a negative correlation with total cholesterol levels, ie, patients with a low total cholesterol level used greater amounts of opioids.

In the postoperative setting, we recently reported that there was no significant association between postoperative pain outcome and preoperative total cholesterol in patients with laparoscopic gastric cancer.[16] The study was the first to focus on the contribution of total cholesterol in postoperative pain outcome. However, laparoscopic colorectal surgery differs from laparoscopic gastric cancer surgery with regard to incision level[17] and position (Trendelenburg). These differences suggest that pain outcome after laparoscopic colorectal cancer surgery would differ from that after laparoscopic gastric cancer surgery.

Therefore, this study aimed to investigate the correlation between cholesterol levels and postoperative pain outcome after laparoscopic colorectal surgery and whether cholesterol levels could be an independent risk factor that can deteriorate postoperative pain outcome. We assumed that postoperative pain scores and opioid usage after laparoscopic colorectal surgery would differ depending on preoperative total cholesterol levels.

Methods

This was a retrospective observational study conducted with the approval of the institutional review board of Seoul National University Bundang Hospital (SNUBH) (B-1707/411-101). Informed consent was waived, as this was a retrospective review of patient medical records, and all patients' data were anonymized for analysis. The data used in the study were medical records of the patients who had been diagnosed with primary colorectal cancer, admitted to SNUBH, and had undergone elective laparoscopic colorectal surgery from January 1, 2011, to June 30, 2017. Data excluded from the analysis were: incomplete medical records; intraoperative open conversion; resection of other organs, except for the colon or rectum (appendices were allowed); intraoperative conversion to Hartmann's operation, Miles's resection, or perineal resection; absence of preoperative total cholesterol result within 1 month; laparoscopic subtotal or total colectomy cases; chronic opioid use; and additional operation conducted within 2 days of the initial operation. SNUBH is a tertiary-care hospital accommodating 1,360 beds, and all its medical records have been preserved and managed through an electronic medical record system since 2003.

Postoperative care for laparoscopic colorectal surgery at SNUBH

SNUBH has a well-experienced colorectal surgical team that has been conducting numerous colorectal surgeries with a laparoscopy-guided standardized technique using five ports since prior to the study period.[5] General anesthesia was administered by professional anesthetists using an inhalation agent and the intraoperative remifentanil-infusion technique. Postoperative management of patients, including pain control, was performed in accordance with the clinical pathway designed for early recovery.[18] Intravenous (IV) patient-controlled analgesia (PCA) was used in patients in the recovery unit immediately after their surgery. IV PCA consisted of 100 mL normal saline with a mixture of 10 μg/mL fentanyl and 150 mg ketorolac. The initial setting of IV PCA was a continuous dose of 1 mL/h, bolus 1 mL, and lockout time of 10–15 minutes. The dose was either increased or decreased as requested by patients. Epidural analgesia was not performed, and after IV PCA had been used, oral or IV opioids were additionally administered for pain control upon request by patients. As a rule, acetaminophen or nonsteroidal anti-inflammatory drugs were not additionally used within 2 days of surgery.

Data collection and outcomes

The data collected for this study were age, body mass index (BMI; kg/m^2), American Society of Anesthesiologists (ASA) classification, history of hypertension or diabetes mellitus, type of surgery, preoperative total cholesterol within 1 month (mg/dL), surgery duration (minutes), length of hospital stay (days), total opioid usage (postoperative day [PODs] 0–2), and postoperative pain score (PODs 0–2). ASA classification was examined before surgery for preoperative evaluation, and history of hypertension/diabetes mellitus was defined as using regular medication for the respective condition before surgery. Length of hospital stay was calculated from POD

0 to discharge date. Postoperative opioid usage by patients was converted into the oral morphine equivalent (OME) using the standard conversion ratio[19] (Table S1). Postoperative pain scores were regularly measured at least four times a day by registered nurses using a numeric rating scale (NRS). Once all daily NRSs had been measured, the daily average NRS (PODs 0–2) was calculated. The collection of all data was conducted by medical record technicians of the Medical Informatic Team of SNUBH in a manner blinded to the study's purpose. The principal investigators of the study also remained blinded to the data until the main statistical outcome was obtained.

The primary outcome of the study pertained to the difference in postoperative pain outcome according to preoperative total cholesterol levels. In this study, 160 mg/dL and 200 mg/dL, which are known to be clinically significant, were used as the cutoff points for total cholesterol level. Patients were assigned to three groups (low [<160 mg/dL], medium [160–199 mg/dL], and high [≥ 200 mg/dL] cholesterol levels) to examine the difference in postoperative pain outcome by group.[20,21]

Statistical methods

To compare the three groups of different cholesterol levels (low, medium, and high), categorical variables were compared using the χ^2 test, and continuous variables were compared using one-way analysis of variance. In addition, to analyze correlations between total cholesterol and NRS scores and OME on PODs 0–2, controlling for covariates, partial Pearson correlation analysis was conducted. Subsequently, analysis of covariance (ANCOVA) was used to compare NRS scores on PODs 0–2 by group, which were the primary outcomes of the study, and covariates with significant differences in demographic and clinical characteristics in the three groups were controlled in the process. In this ANCOVA analysis, a linear regression model was used to derive the adjusted scores. Last, coefficients among OMEs on PODs 0–2 and total cholesterol were calculated through multivariate linear regression analysis. In this process, we initially constructed multivariate model 1 using all variables, then the backward variable-selection method with an elimination criterion of 0.1 in multivariate model 1 was used to fit multivariable model 2. Overall, $P<0.05$ was considered statistically significant, and SPSS version 23.0 (IBM, Armonk, NY, USA) was used for the analyses.

Results

From January 1, 2011, to June 30, 2017, a total of 2,478 patients were admitted to SNUBH, diagnosed with colorectal cancer, and underwent elective laparoscopic colorectal surgery. Among the 2,478 patients, 534 were excluded from the analysis for the following reasons: other organ resection, except colon or rectum (148); intraoperative open conversion (65); Miles's resection, Hartmann's resection, or including perineal resection (15); laparoscopic subtotal or total colectomy (eight); absence of preoperative total cholesterol result within 1 month (279); preoperative chronic opioid use (six); and additional operation conducted within 2 days of surgery (13). A total of 1,944 patients were finally included in the analysis (Figure 1). First, patients were assigned into groups of 565, 785, and 594, respectively, according to the three preoperative total cholesterol levels (low, medium, and high). The demographic and clinical characteristics of these patients are presented in Table 1.

Relationship between total cholesterol and postoperative pain outcome

The relationship between preoperative total cholesterol level and postoperative pain outcome (NRS and OME on PODs 0–2) was analyzed with partial Pearson correlation analysis, and the relevant data are presented in Table 2. Total cholesterol, NRS (POD 0), NRS (POD 1), and OME (PODs 0–2) all showed nonsignificant positive coefficients ($P>0.05$).

Postoperative pain outcomes using ANCOVA and multivariate linear regression analysis

Postoperative NRS scores on PODs 0–2 are shown in Table 3, where sex, age, ASA class, hypertension, and type of surgery, which showed significant differences among the three groups in Table 1, were adjusted by ANCOVA and regression analysis. There was no significant difference in NRS scores on PODs 0–2 among the three groups after adjusting for covariates ($P=0.272$ on POD 0, $P=0.768$ on POD 1, $P=0.561$ on POD 2, and $P=0.192$ on OME on PODs 0–2; Table 3 and Figure 2).

In multivariate linear regression model 1, age, BMI, ASA class, and total cholesterol showed $P<0.1$ and were selected to fit multivariate linear regression model 2. In the final multivariate linear regression model 2, total cholesterol was not associated with OME on PODs 0–2 (coefficient 0.08, 95% CI –0.01 to 0.18; $P=0.81$; Table 4). Additionally, there was no significant association between preoperative total cholesterol level and OME on PODs 0–2 ($P>0.05$) when dividing patients in the three cholesterol groups (low, medium, high). Additionally, female sex (coefficient –22.41, 95% CI –29.63 to –15.19; $P<0.001$), age (coefficient –1.23, 95% CI –1.54 to –0.93; $P<0.001$), and BMI (coefficient 2.33, 95% CI
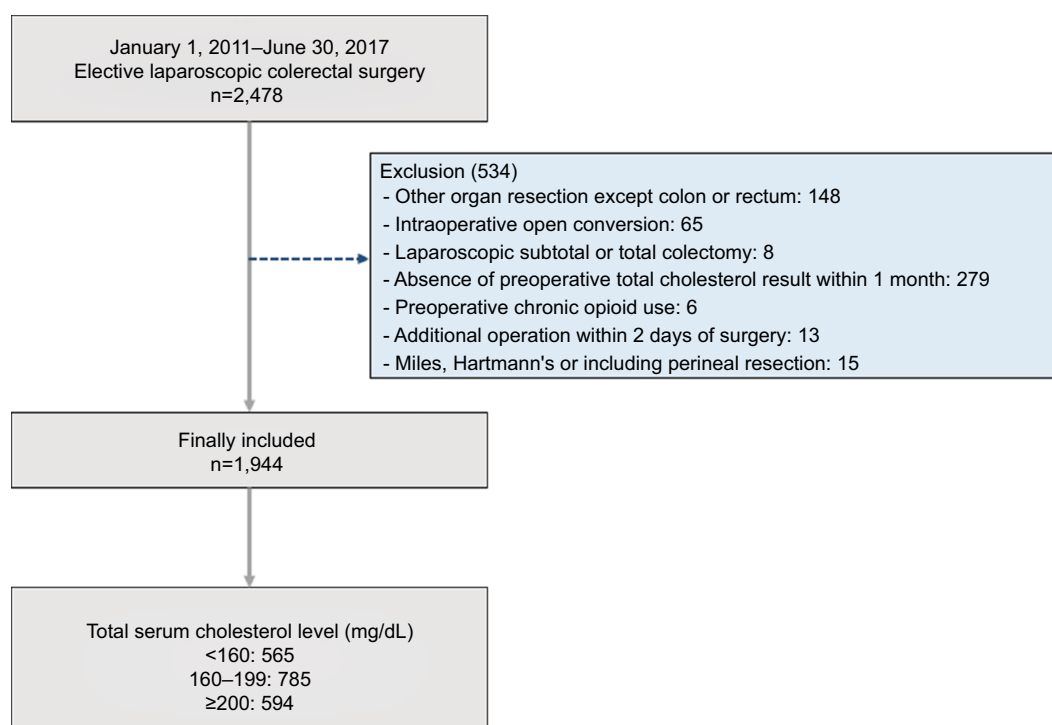
Figure 1 Flowchart for patient selection.

Table 1 Demographic and baseline characteristics of patients

Characteristics		Preoperative cholesterol group (mg/dL)			P-value*
		<160 (n=565)	160–199 (n=785)	≥200 (n=594)	
Total cholesterol		137.44 (17.51)	179.91 (11.36)	225.95 (21.98)	<0.001
Male		375 (66.4%)	491 (62.5%)	300 (50.5%)	<0.001
Age (years)		65.22 (12.20)	62.81 (11.65)	61.41 (10.54)	<0.001
BMI (kg/m²)		23.78 (3.62)	23.56 (3.58)	23.85 (3.04)	0.262
ASA class		1.89 (0.56)	1.69 (0.55)	1.56 (0.54)	<0.001
Hypertension	Yes	266 (47.1%)	289 (36.8%)	174 (29.3%)	<0.001
Diabetes	Yes	27 (4.8%)	24 (3.1%)	16 (2.7%)	0.112
Surgery					
Organ	Colon	378 (66.9%)	506 (64.5%)	359 (60.4%)	0.067
	Rectum	187 (33.1%)	279 (35.5%)	235 (39.6%)	
Laparoscopic AR		155 (27.4%)	225 (28.7%)	168 (28.3%)	0.004
Laparoscopic hemicolectomy		190 (33.6%)	231 (29.4%)	142 (23.9%)	
Laparoscopic low AR		220 (38.9%)	329 (41.9%)	284 (47.8%)	
Surgery time (minutes)		175.13 (68.05)	171.04 (65.08)	169.04 (61.44)	0.265
Length of hospital stay		8.29 (3.14)	8.04 (3.43)	7.79 (3.05)	0.033
Postoperative PACU		496 (87.8%)	746 (95.0%)	578 (97.3%)	<0.001
Postoperative ICU		65 (12.2%)	36 (5.0%)	12 (2.7%)	

Notes: *One way analysis of variance (Scheffe post hoc). Data presented as mean (SD) or n (%).
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; AR, anterior resection; PACU, postanesthesia care unit; ICU, intensive care unit.

1.31–3.34; $P<0.001$) were factors independently associated with postoperative OME on PODs 0–2.

Discussion

This study was performed to investigate the correlation between cholesterol levels and postoperative pain outcome in a postoperative setting. Contrary to the findings of a previous study by Huang et al,[15] we found a nonsignificant correlation between total cholesterol level and postoperative opioid consumption. There was no significant difference in NRS scores on PODs 0–2 or OME on PODs 0–2 among the cholesterol groups after adjustment with ANCOVA. In addition, there was no significant association between total cholesterol and opioid consumption on PODs 0–2 in multivariate linear

Table 2 Partial Pearson correlation analysis for variables

Variables	Total cholesterol (mg/dL)	NRS (POD 0)	NRS (POD 1)	NRS (POD 2)
NRS (POD 0)	0.040 (P=0.084)			
NRS (POD 1)	0.031 (P=0.182)	0.197 (P<0.001)		
NRS (POD 2)	0.001 (P=1.000)	0.055 (P=0.017)	0.589 (P<0.001)	
TOME (PODs 0–2)	0.025 (P=0.269)	0.068 (P=0.003)	0.090 (P<0.001)	0.050 (P=0.028)

Note: Covariates controlled for analysis were age, body mass index, American Society of Anesthesiologists classification, surgical organ, type op operation, surgery time, history of hypertension or diabetes mellitus.
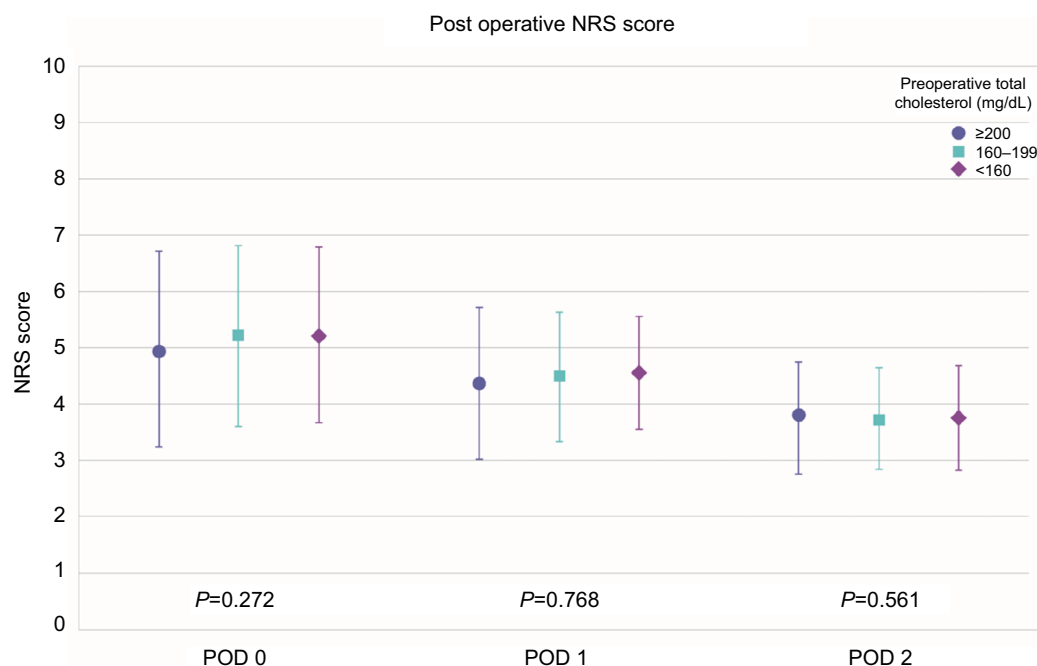**Abbreviations:** NRS, numeric rating scale; POD, postoperative day; TOME, total oral morphine equivalent.

Table 3 Postoperative NRS in PODs 0–2 according to cholesterol group before and after covariate adjustment

Variables	Cholesterol group	Mean (SD)	P-value	Adjusted P-value*
NRS score (POD 0)	>160	5.08 (1.75)	0.016	0.272
	160–199	5.31 (1.65)		
	≥200	5.32 (1.59)		
NRS score (POD 1)	>160	4.46 (1.36)	0.033	0.768
	160–199	4.56 (1.18)		
	≥200	4.64 (1.03)		
NRS score (POD 2)	>160	3.83 (0.96)	0.953	0.561
	160–199	3.84 (0.94)		
	≥200	3.83 (0.96)		
	>160	120.48 (79.84)	0.296	0.192
OME (POD 0–2)	160–199	123.63 (83.79)		
	≥200	120.21 (81.01)		

Note: *Analysis-of-covariance regression used to adjust for covariates of sex, age, American Society of Anesthesiologists class, hypertension, and type of surgery.
Abbreviations: NRS, numeric rating scale; PODs, postoperative days; OME, oral morphine equivalent.

Figure 2 Postoperative NRS on PODs 0, 1, and 2 according to cholesterol group after adjusting for covariates.
Note: Analysis-of-covariance regression used to adjust for covariates of sex, age, ASA class, hypertension, type of surgery.
Abbreviations: NRS, numeric rating scale; PODs, postoperative days; ASA, American Society of Anesthesiologists.

regression analysis. These results are in agreement with those of our previous work in laparoscopic gastric cancer surgery.[16] Importantly, medications, such as statins, are very commonly used, and considering that reducing cholesterol level reduces the risk of cardiovascular disease,[22] stroke,[23] and cancer,[24] the assumption that a low cholesterol level

Table 4 Multivariate linear regression analysis for OME (mg) in PODs 0–2 after laparoscopic colorectal surgery

Variables		Multivariate model 1				Multivariate model 2			
		Coefficient	95% CI		*P*-value	Coefficient	95% CI		*P*-value
Female		−21.45	−28.77	−14.14	<0.001	−22.41	−29.63	−15.19	<0.001
Age		−1.34	−1.72	−1.04	<0.001	−1.23	−1.54	−0.93	<0.001
Body mass index		2.04	0.99	3.08	<0.001	2.33	1.31	3.34	<0.001
ASA class		4.85	−2.67	12.36	0.206				
Surgical organ: rectum (vs colon)		−0.84	−10.50	8.83	0.865				
History of hypertension		−2.77	−11.34	5.80	0.526				
History of diabetes mellitus		0.81	−19.07	20.69	0.936				
Operation time		0.04	−0.20	0.10	0.183				
Serum total cholesterol (mg/dL)		0.10	0.00	0.19	0.051	0.08	−0.01	0.18	0.81
160–199	Reference <160	3.59	−5.06	12.24	0.416				
≥200	Reference <160	2.76	−2.10	7.63	0.379				

Note: For multivariate model 2, backward variable-selection method with an elimination criterion of 0.1 was performed to fit multivariate model 1.
Abbreviations: OME, oral morphine equivalent; PODs, postoperative days; ASA, American Society of Anesthesiologists.

may be associated with an increase in opioid consumption could potentially create complications in clinical practice.[15] However, our study indeed showed that this assumption may not be clinically meaningful.

There are a few considerations in interpreting the results of this study, which vary from those of Huang et al.[15] First, this study was conducted with patients who had undergone a similar type of incision used consistently in all patients, while Huang et al's study was conducted with patients with advanced lung cancer. The characteristics of postoperative pain and cancer pain vary in many aspects. For postoperative pain control, many hospitals, including the study site, use PCA in general. PCA is used in combination with IV bolus at the patient's discretion whenever continuous IV infusion is insufficient.[25] However, this is not usually the case for cancer-pain control. Unlike in this study, where the possibility was high for patients to have received similar types of incisions and experienced similar types of pain, in Huang et al the types of pain would have varied according to different clinical characteristics of cancer, even if the patients had the same type of lung cancer. In addition, Huang et al did not use IV PCA-based opioids, but mainly used transdermal or oral opioids instead. This leads to the possibility that opioid-dose titration would have failed repeatedly in that study, whereas in ours, with the fast-onset IV opioids that were used, this would not have happened. Moreover, the matter of how efficiently the breakthrough pain – a frequent issue in cancer pain – is controlled can be an important concern in a study conducted with patients with advanced cancer.[26] In conclusion, a direct comparison was not available, due to the different features of pain and different main routes of opioid administration.

Notably in this study, we obtained results consistent with those of a similar study that we reported recently.[16] Preoperative cholesterol levels were not associated with postoperative pain outcomes in laparoscopic gastric cancer surgery. At SNUBH, the incision level for laparoscopic colorectal surgery includes a lower part of the abdomen than laparoscopic gastric cancer surgery. In addition, sometimes laparoscopic gastric cancer surgery requires four port sites, while laparoscopic colorectal surgery usually requires five port sites for trocar insertion. Therefore, the characteristics of postoperative pain would differ after the two types of surgery. From the two studies,[16] we can conclude that there is no significant association between preoperative total cholesterol level and pain outcome after major laparoscopic gastrointestinal surgery.

The cutoff points (160 and 200 mg/dL) that assigned patients into the three cholesterol-level groups can also be an important issue. The reason that in this study the cutoff points were set at 160 and 200 mg/dL was that previous studies had set these values as the points at which a change was observed in patients' risk for other diseases according to their cholesterol levels.[20,21] A total cholesterol level of 240 mg/dL is also known to be an important value that may increase the mortality of patients.[27] However, previous studies have reported that a low cholesterol level increases the risk of greater opioid consumption to achieve the same pain control. Therefore, this study focused on a low cholesterol level of <160 mg/dL. Although previous research has used the measurement unit of millimoles per liter, which is different from that used in this study, it defined its low-cholesterol group in a similar manner, in which the dose for women was 168 mg/dL and that for men 158 mg/dL

when converted.[15] Moreover, when establishing these standards, a similar result was obtained, indicating that there was a serious concern regarding postoperative pain control where statins were used, which may reduce total cholesterol levels to below 160 mg/dL. There have been reports that the preoperative use of statins can reduce overall mortality after cardiac surgery[28] and noncardiac surgery.[29] This is considered very important information in the current trend, in which the use of statins for preventive purposes is becoming increasingly common.

This study has a few limitations. First, there may have been biases in the study process, due to the retrospective design. Second, as this study was conducted at a single center, there may be an issue with generalization. Third, even though most opioids were fentanyl-based IV PCA, other types of opioids were also used, and opioid conversion was necessary for this reason. While the standard conversion ratio was used for opioid conversion, its accuracy remains controversial.[19]

Conclusion

This study showed that there was no meaningful association between preoperative total cholesterol levels and postoperative pain outcomes after laparoscopic colorectal cancer surgery. There is a need for future studies that will examine other types of surgeries and patients in a nonperioperative setting.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Forsmo HM, Erichsen C, Rasdal A, Körner H, Pfeffer F. Enhanced recovery after colorectal surgery (ERAS) in elderly patients is feasible and achieves similar results as in younger patients. *Gerontol Geriatr Med*. 2017;3:2333721417706299.
2. Helander EM, Webb MP, Bias M, Whang EE, Kaye AD, Urman RD. A comparison of multimodal analgesic approaches in institutional ERAS protocols for colorectal surgery: pharmacological agents. *J Laparoendosc Adv Surg Tech A*. 2017;27(9):903–908.
3. Lv L, Shao YF, Zhou YB. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. *Int J Colorectal Dis*. 2012;27(12):1549–1554.
4. Chemali ME, Eslick GD. A meta-analysis: postoperative pain management in colorectal surgical patients and the effects on length of stay in an enhanced recovery after surgery (ERAS) setting. *Clin J Pain*. 2017;33(1):87–92.
5. Kang SB, Park JW, Jeong SY, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol*. 2010;11(7):637–645.
6. Zheng H, Pearsall EA, Hurst DP, et al. Palmitoylation and membrane cholesterol stabilize μ-opioid receptor homodimerization and G protein coupling. *BMC Cell Biol*. 2012;13:6.
7. Zheng H, Zou H, Liu X, et al. Cholesterol level influences opioid signaling in cell models and analgesia in mice and humans. *J Lipid Res*. 2012;53(6):1153–1162.
8. Patel HH, Murray F, Insel PA. G-protein-coupled receptor-signaling components in membrane raft and caveolae microdomains. *Handb Exp Pharmacol*. 2008;(186):167–184.
9. Qiu Y, Wang Y, Law PY, Chen HZ, Loh HH. Cholesterol regulates μ-opioid receptor-induced β-arrestin 2 translocation to membrane lipid rafts. *Mol Pharmacol*. 2011;80(1):210–218.
10. Klein G, Rossi GC, Waxman AR, et al. The contribution of MOR-1 exons 1–4 to morphine and heroin analgesia and dependence. *Neurosci Lett*. 2009;457(3):115–119.
11. Chini B, Parenti M. G-protein coupled receptors in lipid rafts and caveolae: how, when and why do they go there? *J Mol Endocrinol*. 2004;32(2):325–338.
12. Huang P, Xu W, Yoon SI, et al. Agonist treatment did not affect association of mu opioid receptors with lipid rafts and cholesterol reduction had opposite effects on the receptor-mediated signaling in rat brain and CHO cells. *Brain Res*. 2007;1184:46–56.
13. Huang P, Xu W, Yoon SI, Chen C, Chong PL, Liu-Chen LY. Cholesterol reduction by methyl-β-cyclodextrin attenuates the delta opioid receptor-mediated signaling in neuronal cells but enhances it in non-neuronal cells. *Biochem Pharmacol*. 2007;73(4):534–549.
14. Andre A, Gaibelet G, le Guyader L, Welby M, Lopez A, Lebrun C. Membrane partitioning of various δ-opioid receptor forms before and after agonist activations: the effect of cholesterol. *Biochim Biophys Acta*. 2008;1778(6):1483–1492.
15. Huang Z, Liang L, Li L, et al. Opioid doses required for pain management in lung cancer patients with different cholesterol levels: negative correlation between opioid doses and cholesterol levels. *Lipids Health Dis*. 2016;15:47.
16. Oh TK, Kim HH, Park DJ, et al. Association of preoperative serum total cholesterol level with postoperative pain outcomes after laparoscopic surgery for gastric cancer. *Pain Pract*. Epub 2017 Nov 23.
17. Duggan J, Drummond GB. Activity of lower intercostal and abdominal muscle after upper abdominal surgery. *Anesth Analg*. 1987;66(9):852–855.
18. Lee TG, Kang SB, Kim DW, Hong S, Heo SC, Park KJ. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial. *Dis Colon Rectum*. 2011;54(1):21–28.
19. Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. *Palliat Med*. 2011;25(5):504–515.
20. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. *Arch Intern Med*. 1992;152(7):1490–1500.
21. Sempos CT, Cleeman JI, Carroll MD, et al. Prevalence of high blood cholesterol among US adults: an update based on guidelines from the second report of the National Cholesterol Education Program Adult Treatment Panel. *JAMA*. 1993;269(23):3009–3014.
22. National Institute for Health and Care Excellence. *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease*. London: NICE; 2008.
23. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361(9364):1149–1158.

24. Jukema JW, Cannon CP, de Craen AJ, Westendorp RG, Trompet S. The controversies of statin therapy: weighing the evidence. *J Am Coll Cardiol*. 2012;60(10):875–881.

25. Walder B, Schafer M, Henzi I, Tramèr MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain: a quantitative systematic review. *Acta Anaesthesiol Scand*. 2001;45(7):795–804.

26. Davies A, Zeppetella G, Andersen S, et al. Multi-centre European study of breakthrough cancer pain: pain characteristics and patient perceptions of current and potential management strategies. *Eur J Pain*. 2011;15(7):756–763.

27. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA*. 1994;272(17):1335–1340.

28. Collard CD, Body SC, Shernan SK, et al. Preoperative statin therapy is associated with reduced cardiac mortality after coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg*. 2006;132(2):392–400.

29. London MJ, Schwartz GG, Hur K, Henderson WG. Association of perioperative statin use with mortality and morbidity after major noncardiac surgery. *JAMA Intern Med*. 2017;177(2):231–242.

Supplementary material

Table S1 Equianalgesic opioid-conversion table

Opioid analgesics	Administration route	Dose equivalent to 10 mg oral morphine (mg)
Morphine	Oral	10
Morphine	Intravenous	3.3
Morphine	Epidural	0.33
Hydromorphone	Oral	2
Fentanyl	Intravenous	0.03
Oxycodone	Oral	7
Codeine	Oral	80
Tramadol	Oral	40