Cohort Study

Effects of Hypovitaminosis D on Preoperative Pain Threshold and Perioperative Opioid Use in Colorectal Cancer Surgery: A Cohort Study

Jun Xia, MD[1], Dai Li,PhD[1], Guanyu Yu, PhD[2], Bing Xu, PhD[1], Xianhua Gao, PhD[2], Han Wang, MD[1], Yu Ma, PhD[1], Xiujuan Li, MD[1], and Yuanchang Xiong, PhD[1]

From: [1]Department of Anesthesiology, Changhai Hospital, Naval Medical University, Shanghai, China; [2]Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China

Address Correspondence:
Yuanchang Xiong, PhD
Department of Anesthesiology
Changhai Hospital
Naval Medical University
Changhai Rd 168
Shanghai, 200433
China
E-mail: proychxiong@163.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 01-06-2022
Revised manuscript received: 03-25-2022
Accepted for publication: 04-11-2022

Free full manuscript: www.painphysicianjournal.com

Background: Postoperative pain after colorectal cancer surgery has a significant impact on postoperative physical and mental health. Vitamin D deficiency has been correlated with both acute pain states, including postoperative and post-traumatic pain, and several chronic pain diseases. The effects of hypovitaminosis D on preoperative pain threshold and perioperative opioid use in colorectal cancer surgery still need to be studied.

Objectives: To find the relationship between hypovitaminosis D on pain threshold, perioperative opioid use, and postoperative complications in colorectal cancer surgery.

Study Design: A total of 112 patients, who were enrolled in this prospective, observational trial, were divided into 2 groups based on their preoperative serum 25-hydroxyvitamin D (25 [OH] D3) levels: (1) group D: vitamin D-deficient group (< 20 ng/mL); and (2) group S: vitamin D-sufficient group (≥ 20 ng/mL).

Methods: Primary outcomes were pain threshold indexes, perioperative dosages of opioid use, and postoperative pain. Secondary outcomes were other postoperative complications.

Results: Preoperative serum level of vitamin D was 14.94 ± 3.10 ng/mL in group D and 24.20 ± 4.80 ng/mL in group S. Significant differences were showed in the 3 indexes of pain threshold and analgesic consumption between the 2 groups ($P < 0.05$). A low 25 (OH) D3 level was associated with a higher opioid dose of sufentanil. There was an association between 25 (OH) D3 and pain enduring threshold (PET), beta coefficient $\beta = 0.532$, 95% confidential interval (0.440, 0.623), $P < 0.001$. The history of diabetes mellitus (DM) and vitamin C and vitamin D levels may be risk factors of surgical site infections (SSI), and the binary logistics regression model is statistically significant, $\chi^2 = 35.028$, $P < 0.001$.

Limitations: There is room for further expansion in the sample size. Our study lacked objective indicators to measure pain threshold. Intestinal recovery time and total hospital stay were not included in the final analysis. In the follow-up study, the vitamin D supplementation group should be set and the specific site of colorectal cancer surgery also needs to be divided more carefully.

Conclusions: On the basis of the study results, hypovitaminosis D is associated with increased perioperative opioid consumption in colorectal cancer surgery. Sensory perception and pain threshold of patients with insufficient 25 (OH) D3 concentration were more sensitive, and PET was lower. History of DM, vitamin D, and vitamin C may be factors related with SSI. Future studies are needed to investigate their relationship further and discover if postoperative pain and pain threshold can benefit from vitamin D supplementation in these patients.

Key words: Hypovitaminosis D, pain threshold, opioid, colorectal cancer

Pain Physician 2022: 25:E1009-E1019

Colorectal cancer is the third most common cancer worldwide, estimated to have caused nearly 1,000,000 deaths in 2020 (1). Surgery is still the mainstay of treatment for colorectal cancer. Postoperative pain is a kind of acute pain, which has been reported in most patients undergoing colorectal cancer surgeries. This unrecognized problem is often caused by stimulation of skin incision, internal organ incision, and drainage, and causes consequent complex postoperative complications, such as hemorrhage, impaired wound healing, and cardiovascular and cerebrovascular accidents, that may bring a great burden to patients both physically and psychologically, leading to a longer hospital stay and more medical cost. The severity of postoperative pain is associated with age, gender, preoperative pain, pain threshold, and surgical features.

It has been reported that vitamin D, with its anti-inflammatory and immune-modulatory effects, may play a crucial role in pain perception and in several chronic pain states. In previous studies (2,3), vitamin D deficiency has been correlated with both acute pain states, including postoperative and post-traumatic pain, and several chronic pain diseases, including headache, abdominal pain, inflammatory pain, neuropathic pain, and cancer. In one study (4) focused on patients with chronic pain, the level of serum 25-hydroxyvitamin D (25 [OH] D3) was significantly negatively correlated with mechanical pain sensitivity. Clinical trials have shown different results regarding the effects of vitamin D supplementation on improvement of pain scores in patients with various chronic pain diseases. Nevertheless, the effect of hypovitaminosis D on postoperative pain is not very clear. A few observational studies (5,6) conducted on patients undergoing bariatric surgery and knee arthroplasty showed conflicting results.

Despite a possible relationship between vitamin D and pain (7,8), no studies, to our knowledge, have covered the indexes of pain threshold and carry on the trial among colorectal cancer patients. The effects of hypovitaminosis D on preoperative pain threshold and perioperative opioid use in colorectal cancer surgery are still not studied. Based on the discovery that insufficient vitamin D levels are one of the risk factors of colorectal cancer, we designed an observational study in colorectal patients undergoing surgeries to investigate the relationships between the levels of vitamin D with preoperative pain threshold, opioid consumption, and postoperative pain in patients with colorectal cancer surgery. We hypothesized that low 25 (OH) D3 levels are associated with lower pain threshold, higher opioid dosages, and higher Visual Analog Scale (VAS) scores. As a secondary aim, we also wanted to investigate if there was an association between 25 (OH) D3 levels and postoperative complications.

Methods

Ethic Committee, Informed Consent, and Patients

The study protocol for this study was approved by the Shanghai Changhai Hospital Ethics Committee, which was registered on the Chinese Clinical Trial Registry (ChiCTR2100044781) on March 3, 2021. Written informed consent was obtained from all patients prior to inclusion.

Adult patients who were 30~75 years; body mass index (BMI) 18.5~25kg/m^2; American Society of Anesthesiologists 1~2 grade, with diagnosed colorectal cancer; and were prepared for colorectal cancer resection, from October 2020 to December 2021, were included in this observational clinical trial study. The exclusion included previous participation in other clinical trials; patients using drugs affecting the levels of calcium, phosphorus, and vitamin D, such as vitamin D supplement, calcitonin, and estrogen or its analogs, etc one month before enrollment; hyperparathyroidism or receiving parathyroidectomy before enrollment; diseases affecting vitamin D absorption, such as long-term diarrhea, chronic pancreatitis, biliary obstruction, colitis, partial resection of the small intestine, etc; severe liver and kidney diseases; severe peripheral or central neuropathy; serious complications, such as heart failure, pneumonia, etc; fasting or parenteral nutrition patients; patients requiring postoperative stoma; patients with other acute and chronic pain diseases; and patients who refused to join the study.

Measurement of Vitamin D

The characteristics of 25 (OH) D3 are relatively longer half-life than 1.25 (OH)2 D3, stability, strong detection repeatability, and no biological activity. Generally, systemic levels of the more stable 25 (OH) D3 are considered to be the best index to reflect status of vitamin D in the individual patient. According to the recommendations from the Institute of Medicine in the United States (9), serum levels of 25 (OH) D3 below 20 ng/mL are considered to be insufficient, as hypovitaminosis D in this study. Serum level of 25 (OH) D3 was measured the day before elective operation and 24 hours after operation through blood tests in the hospital.

Pain Threshold Measurement

The measurement was conducted by pain threshold measuring instruments at the admission time. Three indexes: sensory perception (SP), pain threshold (PT), and pain enduring threshold (PET) were recorded, and the average value was taken for 3 consecutive times. Specific measurement site is under the navel. During the measurement, the measurement indicators and operation mode were explained. The specialized researcher instructed the patients to use earplugs and eye masks to avoid other factors interfering with the determination of pain threshold. Three indexes were expressed as seconds of time.

Anesthesia Implementation

All patients had no preanesthesia medication. After entering the room, routine peripheral veins and basic monitoring were established. Intravenous induction anesthesia was performed on the day of elective operation, and intravenous-inhalation combined anesthesia was used for intraoperative maintenance. Intravenous induction drugs: midazolam 1~2 mg; etomidate 0.3 mg/kg or propofol 2~4 mg/kg; sufentanil 0.3~0.4 μg/kg; and rocuronium 1.0 mg/kg were given. Bilateral transverse abdominal muscle plane block was performed after intubation with 0.375% ropivacaine, 20mL on each side. According to basic conditions of patients and surgical requirements, internal jugular vein puncture and radial artery puncture catheterization were conducted. Intraoperative intravenous maintenance drugs are propofol 0.5~1.0 mg/(kg/min) and remifentanil 0.05~0.1 ug/(kg/min). Sevoflurane was inhaled and the minimum alveolar concentration was maintained at 0.7~0.8. The dosage of intravenous drugs was adjusted to maintain the bispectral index of electroencephalography between 40 and 60, and the surgical pleth index used as the analgesic index between 20 and 50. Add sufentanil 0.1~0.2 μg/kg as needed to maintain the stability of hemodynamics (the change of mean arterial pressure and heart rate compared with the basic value is < 20%). If the decrease of heart rate or blood pressure is not obvious after adding sufficient opioids, vasoactive drugs, such as ebrantil 5~10 mg (when the change of mean arterial pressure from the basic value is > 20%) or esmolol 10 mg (when the change of basic value of heart rate is > 20% or the heart rate is > 120 beats/min) can be added. If the patient's blood pressure is low, ephedrine or deoxyepinephrine can be used. Vasoactive drugs can be added or continuously pumped in a single time according to the patient's response to vasoactive drugs.

All the patients enrolled received pain medication through patient-controlled analgesia (PCA). The analgesic pump was used 10 minutes before finishing stitching, and the formula was fentanyl 0.22 mg/kg, flurbiprofen axetil 5 mg/kg, and metoclopramide 20 mg.

Outcome Assessment

The 25 (OH) D3 levels were detected the day before and the first day after surgery, respectively. Our primary outcomes were pain threshold, perioperative dosages of opioid use, and postoperative pain. Intraoperative opioid dosage was recorded by a professional anesthesiologist. The VAS scores at 6 hours, 12 hours, 24 hours, and 48 hours and the dosages of analgesic drugs in the analgesic pump at 24 hours and 48 hours were recorded by the anesthesia nurse responsible for follow-up. Secondary outcomes were postoperative nausea and vomiting (PONV) and surgical site infections (SSI). All the statistics were recorded in a standardized questionnaire.

Statistical Analysis

Data were entered by 2 persons and the data consistency was checked. Statistical tests were performed using SPSS version 21 (IBM Corporation, Armonk, NY) and Graphpad Prism version 8.00. $P < 0.05$ was statistically significant. The measurement data of normal distribution are expressed as mean (standard) deviation, and the group t test is used for the comparison between the 2 groups. The measurement data of abnormal distribution are expressed in the form of median (25%, 75%). For the 2 groups, the nonparametric Mann-Whitney U test is used. The counting data is expressed in frequency. Multiple linear analysis was used to analyze the vitamin C and D levels and main indexes of pain threshold. Logistic statistical analysis was used to analyze the secondary outcome of SSI. Since this was a pilot study with the aim to obtain data for a future interventional study, no power calculation was carried out.

Results

Patients

A total of 115 patients were assessed in this trial, 2 were excluded due to regular hormone medication and

1 was excluded due to massive hemorrhage. Finally, 112 patients were recruited of 42 women and 70 men, 70 patients in group D (< 20 ng/mL), and 42 patients in group S (≥ 20 ng/mL). The median age was 59 years old (range 30~74). The disposition of the patients throughout the study was shown in Fig. 1. Basic conditions and surgical data were recorded in Table 1. There was no significant difference in age, gender, weight, BMI, complications, and other basic characteristics between the 2 groups ($P > 0.05$).

Primary Outcomes

Relationship Between 25 (OH) D3 Level and Pain Threshold, Opioid Use, and Postoperative Pain

Table 2 showed the perioperative 25 (OH) D3 level, daily sunshine time, pain threshold, perioperative opioid use, and postoperative pain.

The 25 (OH) D3 levels in group D and group S decreased compared with that before the operation, and the difference was 1.70 ± 2.08 ng/mL and 2.67 ± 2.13 ng/mL, respectively. There was no significant difference in the degree of decline ($P > 0.05$). There was no significant difference in sunlight time between the 2 groups ($P > 0.05$).

Three pain threshold indexes are SP, PT, and PET. Significant differences were showed in the 3 indexes between the 2 groups ($P < 0.05$). The duration seconds of SP in group D and group S were 11.1 seconds (10.6, 11.5) and 12.0 seconds (11.2, 12.8), and duration seconds of PT were 15.6 seconds (14.5, 16.8) and 17.5 seconds (15.6, 18.9), respectively. SP and CPT were more sensitive in group D ($P < 0.05$). The duration seconds of PET in group D and group S were 27.0 seconds (24.7, 28.9) and 30.0 seconds (28.4, 32.9), respectively, and the PET in group D was lower ($P < 0.05$).

When analyzing the intraoperative opioid dosages, a significant difference was found in the dosage of sufentanil ($P < 0.05$); however, no difference was found in the dosage of remifentanil ($P > 0.05$). The same results appeared in the comparison of opioid dosage per unit body weight. Since the drug dosage in the analgesic pump was calculated according to the patient's body weight, we covered not only the dosage, but also the milliliters of consumption. There were significant differences in consumption (mL) of PCA at both 24 hours and 48 hours and fentanyl dosage (mg) of PCA at 24 hours after operation between the 2 groups ($P < 0.05$). Nevertheless, we didn't find a significant difference in fentanyl dosage (mg) of PCA at 48 hours after operation ($P > 0.05$). VAS scores were higher at 6 hours, 12 hours, and 48 hours in group D ($P < 0.05$), but no significant difference was found in VAS at 24 hours ($P > 0.05$). Tendency of postoperative VAS at 6 hours, 12 hours, 24 hours, and 48 hours were described in Fig. 2.

Multiple Linear Regression

In this study, the effects of vitamin C level, vitamin D level, and age on PET were discussed by using multiple linear regression methods. The final linear model was univariate and statistically significant ($F = 132.439$, $P < 0.001$) in Fig. 3. Moreover, 54.6% of the PET data variation of the dependent variable could be explained by vitamin D level (corrected $R^2 = 0.542$), and the partial regression coefficient of vitamin D level $\beta = 0.532$, 95% confidential interval (CI) (0.440, 0.623), $P < 0.001$.

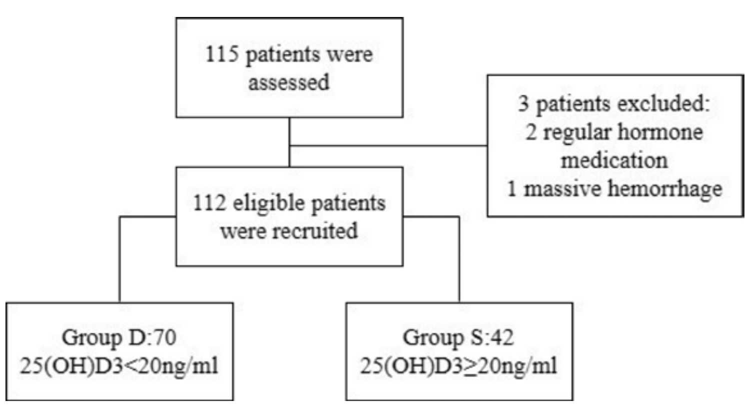

Fig. 1. *Flow chart of patients in the cohort study.*

Table 1. *Characteristics of patients (basic, tumor, and anesthesiology related).*

Serum 25 (OH) D3 Concentration, ng/mL				
Classification		Group D (< 20)	Group S (≥ 20)	*P* value
		70	42	
Basic Characteristics	Age, y, mean (25%,75%)	60 (55.67)	56 (50.65)	0.106[c]
	Gender, women, n (%)	30 (42.9)	12 (28.6)	0.090[b]
	Weight, kg, mean (SD)	65.08 (9.24)	66.83 (9.23)	0.680[a]
	BMI, kg/m^2, mean (SD)	23.55 (2.85)	23.46 (2.23)	0.848[a]
	Smoking, n (%)	10 (14.3)	11 (26.8)	0.148[b]
	Alcohol, n (%)	15 (21.4)	11 (26.8)	0.663[b]
	Hypertension, n (%)	20 (28.6)	8 (19.0)	0.296[b]
	Diabetes, n (%)	15 (21.4)	8 (19.0)	0.823[b]
	Coronary heart disease, n (%)	12 (17.1)	4 (14.3)	0.802[b]
	Cerebrovascular disease, n (%)	3 (4.3)	1 (2.4)	0.992[b]
	Lung disease, n (%)	7 (10.0)	4 (7.14)	0.849[b]
	Vitamin C, ng/mL, mean (SD)	30.85 (2.57)	31.29 (1.98)	0.301[a]
Tumor Related	Weight loss, kg, mean (SD)	0.58 (1.41)	0.76 (1.81)	0.592[a]
	Size over 2 cm, n (%)	68 (97.1)	40 (95.2)	0.992[b]
	Position, rectum, n (%)	36 (51.4)	29 (69.0)	0.052[b]
	Right hemicolon, n (%)	19 (27.1)	8 (19.4)	
	Left hemicolon, n (%)	15 (21.4)	5 (11.9)	
	Liver metastasis, n (%)	6 (8.6)	2 (4.8)	0.690[b]
	Bone metastasis, n (%)	0	0	
	Lymphatic metastasis, n (%)	39 (55.7)	23 (54.8)	0.908[b]
	Chemotherapy, n (%)	2 (2.9)	3 (7.1)	0.542[b]
Anesthesiology	NYHA grade 1, n (%)	40 (57.1)	29 (69.0)	0.133[b]
	ASA grade 1, n (%)	24 (34.3)	21 (50)	0.073[b]
	Operation time, min, mean (25%,75%)	158 (129.181)	161 (139.180)	0.588[c]
	Anesthesia time, min, mean (25%,75%)	196 (165.220)	199 (179.221)	0.641[c]

Abbreviations: 25 (OH) D3, 25-hydroxyvitamin D; SD, standard deviation; BMI, body mass index; NYHA, New York Heart Association; ASA, American Society of Anesthesiologists.
Result from [a]independent sample t test, [b]χ^2 test, or [c]Mann-Whitney U test
X significant at the 0.05 level.

Intraoperative Conditions

This study also compared intraoperative complications, infusion, urine volume, blood loss, and use of vasoactive drugs. No significant difference was found in intraoperative conditions ($P > 0.05$) and results were recorded in Table 3.

Secondary Outcomes

Relationship Between 25 (OH) D3 Level and PONV and SSI

According to Table 2, the incidences of PONV in the 2 groups were 47.1% and 26.2%, respectively, and the difference was statistically significant ($P < 0.05$). The incidences of SSI in the 2 groups were 38.5% and 9.5%, respectively, and the difference was statistically significant ($P < 0.05$).

Factors Influencing PONV

Taking the patients into 2 groups according to the presence of PONV and compare between the 2 groups. There were significant differences in the gender, BMI, hypotension, vitamin D level, and fentanyl (mg) use 24 hours after operation ($P < 0.05$). No significant difference was found in the dosage of PCA (mL) 24 hours after operation ($P > 0.05$).

Table 2. *Perioperative 25 (OH) D3 level, perioperative opioid use, and pain threshold.*

Serum 25(OH) D3 concentration, ng/mL				
Classification		**Group D (< 20)**	**Group S (≥ 20)**	***P* value**
		70	**42**	
Perioperative 25 (OH) D3 Level	Preoperative, ng/mL, mean (SD)	14.94 (3.10)	24.20 (4.80)	0.000[a]
	Postoperative, ng/mL, mean (SD)	13.25 (3.56)	21.53 (3.34)	0.000[a]
	D value, ng/mL, mean (SD)	1.70 (2.08)	2.67 (2.13)	0.020[a]
	Sunlight Time, min, mean (25%,75%)	139 (90,180)	152 (120,180)	0.355[c]
Pain Threshold	Sensory Perception, s, mean (25%,75%)	11.1 (10.6,11.5)	12.0 (11.2,12.8)	0.036[c]
	Pain Threshold, s, mean (25%,75%)	15.6 (14.5,16.8)	17.5 (15.6,18.9)	0.000[c]
	Pain Enduring Threshold, s, mean (25%,75%)	27.0 (24.7,28.9)	30.0 (28.4,32.9)	0.000[c]
Opioid Use	Sufentanil, ug, mean (25%,75%)	55.3 (50,57.5)	53.5 (50,55)	0.017[c]
	Sufentanil/Weight, ug/kg, mean (25%, 75%)	0.86 (0.80,0.92)	0.82 (0.76,0.88)	0.023[c]
	Remifentanil, μg, mean (25%,75%)	1800 (1720,1860)	1750 (1680,1860)	0.231[c]
	Remifentanil/Weight, μg /kg, mean (25%, 75%)	27.49 (24.75,29.96)	27.47 (24.95,28.85)	0.661[c]
Postoperative Analgesic Drug Dosage Consumption	24h, mL, mean (SD)	52.5 (3.47)	49.1 (3.10)	0.000[a]
	24h, mg, mean (SD)	0.75 (0.14)	0.71 (0.08)	0.038[a]
	48h, mL, mean (SD)	90 (2.18)	88.7 (2.54)	0.006[a]
	48h, mg, mean (SD)	1.29 (0.19)	1.29 (0.19)	0.874[a]
Postoperative VAS	6h, mean (25%,75%)	2.07 (1.93,2.21)	1.57 (1.38,1.77)	0.000[c]
	12h, mean (25%,75%)	3.40 (3.25,3.55)	3.10 (2.90,3.29)	0.016[c]
	24h, mean (25%,75%)	2.81 (2.62,3.01)	2.64 (2.45,2.84)	0.242[c]
	48h, mean (25%,75%)	1.74 (1.64,1.85)	1.45 (1.30,1.61)	0.002[c]
Postoperative SSI and PONV	SSI, n (%)	27 (38.5)	4 (9.5)	0.001[b]
	PONV, n (%)	33 (47.1)	11 (26.2)	0.028[b]

Abbreviations: 25 (OH) D3, 25-hydroxyvitamin D; VAS, visual analog scale; SSI, surgical site infections; PONV, postoperative nausea and vomiting; SD, standard deviation.
Result from [a]independent sample t test, [b]χ^2 test, or [c]Mann-Whitney U test.
X significant at the 0.05 level.

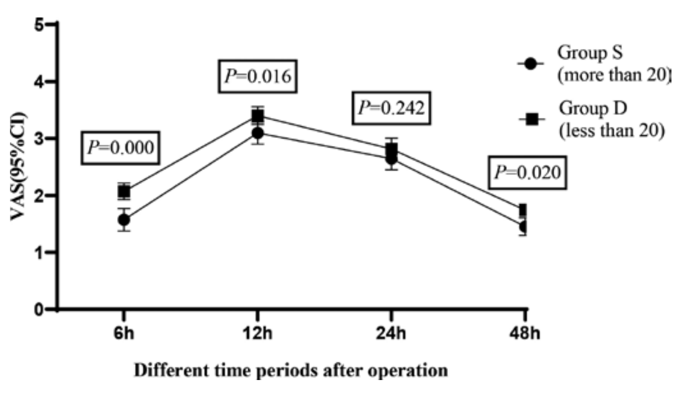

Fig. 2. ***Comparison of mean (95% CI) VAS score over time in 2 groups.***
CI, confidential interval; VAS, visual analog scale.

Factors Influencing SSI

In this study, binary logistics regression was used to assess the impact of age, gender, tumor location, diabetes mellitus (DM) history, vitamin C level, and vitamin D level on postoperative infection. The Box-Tidwell method was used to test whether the conversion value between the continuous independent variable and dependent variable logit was linear. Nine items were included in the linear test model, and the significance level after Bonferroni correction was 0.0056. The linear test results showed that there was a linear relationship between all continuous independent variables and the logit conversion value of dependent variables. Finally, the obtained logistic model is statistically significant, $\chi^2 = 35.028$, $P < 0.001$. The model can correctly classify 77.7% of the research objects. The sensitivity, specificity, positive predictive value, and negative predictive value of the model were 94.4%, 46.9%, 34.8%, and 80.9%, respectively.

Among the 6 independent variables included in the model, the history of DM (odds ratio [OR] = 4.151, 95% CI 1.304~13.215, $P < 0.05$), vitamin C level (OR = 0.632, 95% CI 0.467~0.857, $P < 0.05$), and vitamin D level (OR = 0.839, 95% CI 0.747~0.943, $P < 0.05$) were statistically significant, specific values were in Table 4. The history of DM will increase the risk of SSI. The lower the vitamin C level, the lower the vitamin D level, and the higher the risk of SSI. The result is statistically significant ($P < 0.05$).

Discussion

In this prospective cohort of Chinese patients undergoing colorectal cancer surgery, 62.5% had preoperative hypovitaminosis D. According to previous studies (10-12), a low concentration of 25 (OH) D3 was considered a risk factor for colorectal adenoma and colorectal adenocarcinoma, with ORs of 4.875 and 2.925, respectively (10). A higher predicted vitamin D score was significantly associated with a lower colorectal cancer risk (11,12). In the prognosis of colorectal cancer, a meta-analysis (13) also found that low circulating 25 (OH) D3 levels were associated with mortality. Colorectal cancer patients with higher circulating 25 (OH) D levels may have a better prognosis (14).

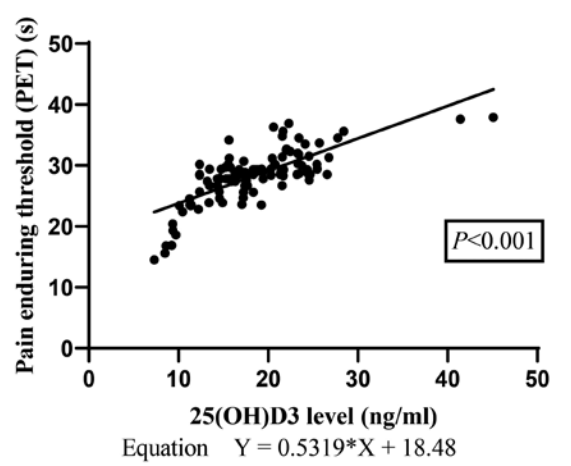

Fig. 3. *Univariate linear model of 25 (OH) D3 level and PET.*
25 (OH) D3, serum 25-hydroxyvitamin D; PET, pain enduring threshold.

Table 3. *Intraoperative complications, infusion, urine, blood loss, and vasoactive drugs.*

Serum 25 (OH) D3 concentration, ng/mL				
Classification		**Group D (< 20)**	**Group S (≥ 20)**	***P* value**
		70	**42**	
Intraoperative Complications	Hypotention, n (%)	18 (25.7)	11 (26.2)	0.952[b]
	Hypertension, n (%)	15 (21.4)	9 (21.4)	1.000[b]
	Tachycardia, n (%)	0	0	
	Bradycardia, n (%)	33 (47.1)	21 (50.0)	0.736[b]
	Intraoperative Awareness, n (%)	0	0	
Intraoperative Infusion, Urine Volume and Blood Loss	Urine Volume,	634 (300.875)	596 (400.700)	0.733[c]
	Blood Loss, mL, mean (25%,75%)	149 (100.150)	124 (75.150)	0.576[c]
	Crystal Liquid, mL, mean (25%,75%)	1337 (1100.1600)	1353 (1100.1600)	0.840[c]
	Colloidal Liquid, mL, mean (25%,75%)	766 (500.1000)	756 (500.1000)	0.822[c]
Vasoactive Drugs	Ephedrine, mg, mean (25%,75%)	9.4 (6.12)	8.3 (3.12)	0.356[c]
	Deoxyepinephrine, mean (25%,75%)	165 (100.200)	153 (100.250)	0.512[c]

Abbreviation: 25 (OH) D3, 25-hydroxyvitamin D.
Result from [b]χ^2 test or [c]Mann-Whitney U test.
X significant at the 0.05 level.

Table 4. *Binary logistic regression of infection factors.*

		β value	OR	95% CI	*P* value
Age		-0.028	0.972	0.924 ~1.022	0.270
Gender	Men	0.065	1.067	0.374 ~3.055	0.904
Tumor Position	Rectum				0.695
	Right Hemicolon	-0.018	0.982	0.254 ~3.795	0.979
	Left Hemicolon	-0.525	0.592	0.126 ~2.779	0.506
Diabetes	Yes	1.423	4.151	1.304 ~13.215	0.016
Vitamin C		-0.458	0.632	0.467 ~0.857	0.003
Vitamin D		-0.176	0.839	0.747 ~0.943	0.003

Abbreviations: OR, odds ratio; CI, confidential interval.
X significant at the 0.05 level.

Vitamin D is now considered to be an active pleiotropic hormone in the brain, which plays a role of hormone paracrine or autocrine in the brain (15,16). Sunlight time is one of the factors influencing vitamin D status. Effective ultraviolet (UV) doses are equated to oral vitamin D3 doses. Some experts have recommended that increased sun/UV radiation b exposure is an effective and inexpensive approach to maintaining adequate vitamin D levels. However, this point of view has been criticized because UV radiation is a known human carcinogen linked to the development of both melanoma and nonmelanoma skin cancers (17). According to our current data, no slight relevance was found in 25 (OH) D3 levels and sunlight time. On one hand, the number of patients we recruited is limited. On the other hand, according to other research, the reasons affecting vitamin D photosynthesis and bioavailability include season, geographical latitude, daily illumination time, atmospheric composition, skin color, use of sunscreen, clothing, etc (18). It is suggested that our results may be affected by the specific time of patients' outdoor activities, the use of sunscreen clothes and sunscreen cream, and different weather conditions. The deviation of patients' memory and understanding is also a possible factor. This is not our main focus and can be studied in the future.

A recent study (19) showed that patients with 25 (OH) D3 levels lower than 20 ng/mL had a higher incidence of pain. In the hypovitaminosis D group, the motor nerve amplitude of the median nerve, ulnar nerve, and tibial nerve increased, and the conduction velocity of the ulnar nerve and peroneal nerve decreased. We found that compared with 25 (OH) D3 of more than 20 ng/mL, SP and CPT of insufficient vitamin D concentration were more sensitive, and PET was lower. No other previous articles have discussed the relationship between the adequacy of 25 (OH) D3 and pain threshold in patients prepared for surgery. The results of some previous animal experiments (20-22) suggested the effects of vitamin D deficiency on SP and pain in rats. Rats receiving vitamin D-deficient diets for 2~4 weeks showed mechanical deep muscle hypersensitivity (20). Vitamin D deficiency may lead to selective alterations in target innervation, resulting in presumptive nociceptor hyperinnervation of skeletal muscle, which, in turn, is likely to contribute to muscular hypersensitivity and pain (21). Although our limited data suggest that there may be a linear regression relationship between preoperative 25 (OH) D3 levels and PET, it could only explain about 50% of the data. We didn't find any related research on the relationship between vitamin D and PET. It is still necessary to expand the sample size to further explore the relationship between 25 (OH) D3 and SP, CPT, and PET. Some studies (20-22) have focused on the positive effects of vitamin D supplementation on animal pain threshold, mainly discussed SP and pain perception. Cholecalciferol supplementation improved mechanical nociceptive threshold in monoarthritic animals and reduced mechanical hyperalgesia and cold allodynia in a model of mononeuropathy. Transcriptomic analysis of cerebrum, dorsal root ganglia, and spinal cord tissues indicate that cholecalciferol supplementation induces a massive gene dysregulation, which, in the cerebrum, is associated with opioid signaling (23 genes), nociception (14 genes), and allodynia (8 genes), and, in the dorsal root ganglia, with axonal guidance (37 genes) and nociception (17 genes). Among the identified cerebral dysregulated nociception-, allodynia-, and opioid-associated genes, 21 can be associated with vitamin D metabolism (20). The specific mechanism is still unknown and remains to be explored. Vitamin D also contributes to myelin regeneration in a rat model of nerve injury (22). Whether vitamin D supplementation has a positive effect on the pain threshold of surgical patients remains to be verified. In addition, during the study, in order to ensure the accuracy of the patient's pain threshold measurement, we arranged full-time personnel to measure, explain the specific measurement methods to the patients, and keep the environment quiet. Nevertheless, the pain threshold measurement value is still a reflection of subjective feelings, and there will be some deviations due to the different understanding degree of the patients.

Previous studies (5,6) showed contradictory outcomes in the relationship between 25 (OH) D3 levels and opioid use. As far as our research, there is no significant difference in the basic characteristics of the 2 groups, such as age, gender, weight, and past disease history. Hypovitaminosis D may cause a larger consumption of sufentanil during operation and a larger use of PCA fentanyl during 24 hours after operation. Considering that the dosage is mainly calculated according to body weight, our study also calculated the dosage of sufentanil per unit body weight and the results are consistent with the dosage of sufentanil. Remifentanil, a widely used analgesic agent in anesthesia, has a rapid onset and short duration of action. According to previous research (23,24), increased use of intraoperative remifentanil is associated with increased postoperative analgesic requirements and opioid consumption. There was no significant difference in the dosage of remifentanil between the 2 groups. Since many factors may affect the dosage of remifentanil, the relationship between use of remifentanil and 25 (OH) D3 levels needs to be explored in the future. The data suggested that the incidence of PONV in group S with relatively sufficient vitamin D is lower. The incidence of PONV may be related to gender, BMI, hypotension, vitamin D level, and fentanyl dosage (mg) 24 hours after operation. Previous studies (25) have shown that gender, BMI, and postoperative opioid dosage are important influencing factors of PONV. More research data are needed to find the concrete role of vitamin D levels in the incidence of PONV.

SSI is one of the most important factors, which not only affects the prognosis of patients, but also increases the economic burden of patients. Analysis of secondary outcome infection suggested possible impact of a history of DM, vitamin C, and vitamin D on wound infection. A recent meta-analysis (26) showed the overall effect of DM on SSI (OR, 1.53; 95% CI, 1.11~2.12; I2, 57.2%), supporting DM as an independent risk factor for multiple surgical types of SSI. Efforts should be made to improve the outcome of diabetic patients. A prospective cross-sectional study (27) involving 300 adult patients found that preoperative level of 25 (OH) D3 was confirmed as statistically significant independent predictors of SSI. In a hepatobiliary surgery unit, high serum levels of vitamin D are a protective factor against SSI (OR, 0.99) (28). Vitamin D affects the human immune system in many ways, such as inducing the synthesis of antimicrobial peptides on the mucosal surface and immune cells (29). Vitamin D's antimicrobial and wound healing effects have been recently shown in animal models and in laboratory settings. Several randomized controlled trials (30-32) have also shown the beneficial effect of vitamin D supplementation on infection. More recently, vitamin C has emerged as a potential therapeutic agent to treat sepsis. However, there haven't been any studies designed on the relationship between preoperative vitamin C levels and postoperative SSI.

Since our study is the first, as far as we know, that focuses on the relationship between hypovitaminosis D and pain threshold in colorectal cancer, our study had many limitations. First of all, there are many influencing factors on vitamin D levels, pain threshold, and postoperative complications in patients with colorectal cancer, so the sample size should be further expanded for classification research. Second, as a subjective index, we didn't measure the indicators related to pain in the blood at the same time, so there existed a lack of objective indicators to measure pain threshold. Third, we only included postoperative pain, PONV, and SSI in postoperative complications. Intestinal recovery time and total hospital stay were not included in the final analysis. Fourth, no vitamin D supplementation group was established to further confirm the relationship between vitamin D and pain threshold, perioperative opioid dosage, and postoperative complications. Finally, the specific operation method of colorectal cancer tumor resection needs to be adjusted according to the specific location and size of the tumor, which should be further refined in future research.

Conclusions

This cohort study found a high prevalence of preoperative hypovitaminosis D in colorectal cancer. Vitamin D deficiency may lead to a lower pain threshold, increased perioperative opioid dosage, and a higher incidence of PONV and SSI. SP and CPT of insufficient 25 (OH) D3 concentration were more sensitive, and PET was lower. History of DM, hypovitaminosis D, and hypovitaminosis C are likely to be risk factors in postoperative SSI. It is suggested that increasing the level of vitamin D before the operation may help to reduce postoperative pain, the incidence of PONV, and postoperative SSI, which provides some new ideas on how to optimize the perioperative period of patients with colorectal cancer.

Patents

Data Availability Statement: The data presented in this study are available on request from the corresponding author (DL). The data are not publicly available due to privacy or ethical restrictions.

Acknowledgments

This work has not been previously published and has not been submitted elsewhere for consideration. This study was funded by the National Natural Science Foundation of China (81600955, 81971048), Shanghai Pujiang Program (2020PJD059), "Deep Blue 123" Military Medical Research Special Key Research Project (2019YSL008), and Youth Cultivation Project for Special Basic Medical Research of the First Affiliated Hospital of Naval Medical University (2021JCQN02).

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