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The effect of the enhanced recovery after surgery protocol and the reduced use of opioids on postoperative outcomes in elderly patients with colorectal cancer

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Abstract. – OBJECTIVE: The study aimed to assess the impact of the enhanced recovery after surgery (ERAS) pathways and the reduced use of opioids on postoperative outcomes in elderly colorectal cancer (CRC) patients who underwent laparoscopic surgery under general anesthesia (GA).

PATIENTS AND METHODS: Clinical data from 99 elderly patients who underwent laparoscopic CRC surgery in the First Affiliated Hospital of Hebei North University from April 2021 to April 2023 were retrospectively analyzed and grouped based on the method of pain control measures received. Of 99 patients, 51 received conventional doses of opioid drugs (conventional group), and 48 patients were treated with reduced doses of opioids based on the principles of ERAS (low-dose group). Perioperative characteristics, postoperative pain level, cognitive function, serum biochemical index levels, and adverse reactions were compared between the two groups.

RESULTS: The first exhaust time, defecation time, and bedtime activity time of the low-dose group were compared to the conventional group ($p<0.05$). On the first day after the surgery, the mini-mental state examination (MMSE) score of the low-dose group was higher than the conventional group ($p<0.05$). After the surgery, the levels of serum brain-derived neurotrophic factor (BDNF) decreased in both groups, while the levels of neuron-specific enolase (NSE) and 5-hydroxytryptamine (5-HT) increased. However, compared to the conventional group, the low-dose group had higher levels of BDNF and lower levels of NSE and 5-HT ($p<0.05$). The incidence of adverse reactions in the low-dose group was lower than that in the conventional group ($p<0.05$).

CONCLUSIONS: ERAS protocol and the reduced use of opioid drugs in CRC patients who underwent surgery under GA is associated with an analgesic effect that is comparable to that of conventional opioid use. Reduced dosage of opioid drugs lessened cognitive impairment and lowered the incidence of adverse reactions in surgical patients with CRC.

Key Words:
Enhanced recovery after surgery, Opioid drugs, General anesthesia, Postoperative, Colorectal cancer.

Introduction

Recent changes in the lifestyle habits and aging of the general population led to a gradually increasing number of elderly patients with colorectal cancer (CRC)[1,2]. Surgery alone or in combination with adjuvant chemotherapy is the main mode of treatment for CRC patients. However, it is associated with a high rate of complications due to frailty and comorbidity of the elderly population of patients[3]. Therefore, effective management during the perioperative period is of great significance in reducing the rate of potential adverse effects of the surgery[3,4].

Opioids are commonly used in elderly patients undergoing general anesthesia (GA) and are beneficial not just for analgesia, but also for inhibiting stress response, and protecting organ functions. However, opioid drugs are associated with adverse reactions, including vomiting, nausea, respiratory depression, cognitive impairment[5,6], etc. Therefore, the enhanced recovery after surgery (ERAS) clinical practices that promote reducing the dosage of opioid drugs and implementing multimodal analgesia have gradually become an important trend for elderly patients undergoing GA surgery[7,8].

Based on the ERAS concept, lowering opioid use in patients undergoing surgery under GA is beneficial for improving the effectiveness and safety of analgesia, thus laying a solid foundation for postoperative rehabilitation and prognosis[9]. The main goal of this study is to evaluate the impact of ERAS

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protocols and the reduced use of opioid drugs on postoperative outcomes in elderly CRC patients who undergo laparoscopic surgery under GA.

Patients And Methods

Clinical records of 99 elderly patients (49 males and 50 females) who underwent laparoscopic CRC surgery in the First Affiliated Hospital of Hebei North University from April 2022[1] to April 2023 were selected. The Ethics Committee of our hospital approved this study on May 23rd, 2023. The age of the cohort ranged from 61 to 83 years old, with an average age of 70.2 ± 5.0 years. Based on the American Society of Anesthesiologists (ASA) grading, 58 patients were classified as Grade II, and 41 patients as Grade III. The body mass index (BMI) of the patients ranged between 17.9 and 28.7 kg/m^2, with an average BMI of 23.6 ± 2.7 kg/m^2. Of 99 patients in the cohort, 51 received conventional doses of opioid drugs and were assigned to the conventional group, and 48 patients received low-dose opioid drugs based on the ERAS concept and were assigned to the low-dose group.

Anesthesia Management

Specific differences between the conventional and the ERAS approaches, and doses of opioids and other medications administered are summarized in Table I.

Inclusion Criteria

- Complete clinical data.
- Age ≥ 60 years old.
- The American Society of Anesthesiologists (ASA) grades II to III.
- Preoperative Minimal Intelligence State (MMSE) score ≥ 24 points.

Exclusion Criteria

- Speech communication disorder and cognitive dysfunction.
- Presence of coagulation dysfunction.
- Infection or trauma at the puncture site.
- Previous history of drug abuse and alcohol intoxication.
- Mental system diseases.
- A history of stroke.
- Renal and liver organ dysfunction.
- Cardiovascular and cerebrovascular diseases.
- Use of sedatives, opioid drugs, anti-anxiety and anti-depression medications.
- A history of allergies to opioids and local anesthetics.

Observation Indicators

1) Perioperative conditions, including surgical duration, frequency of patient-controlled intravenous analgesia (PCIA) compressions, rescue analgesia frequency, first exhaust time, first defecation time, and first ambulation time. 2) At 12 hours, 24 hours, and 48 hours after the surgery, the pain level in both static and dynamic states was evaluated using the visual analogue scale (VAS), with a score range of 0-10 points (the higher the score, the stronger the pain sensation). 3) Cognitive function was evaluated using the MMSE scale at preoperative, postoperative 1 day, postoperative 3 days, and postoperative 7 days, with a total score of 30 points (the higher the score, the better the cognitive function). 4) Levels of brain-derived neurotrophic factor (BDNF), neuron-specific enolase (NSE) and 5-hydroxytryptamine (5-HT) were measured before and 1 day after the surgery. Briefly, fasting venous blood was collected, centrifuged (3,500 r/minute, 10 minutes), and the supernatant was taken. The levels of the above indicators were measured by enzyme-linked immunosorbent assay. The kit was provided by Shanghai mlbio Biotechnology Co., Ltd. (Shanghai, China) 5) The incidence of adverse reactions, including vomiting, dizziness, nausea, and hypoxemia.

Statistical Analysis

All data analysis was conducted using SPSS 25.0 software (IBM Corp, Armonk, NY, USA). The normality of the data was evaluated using the Shapiro-Wilk test. The data of normal distribution were expressed by mean ± standard deviation, and the inter-group comparison was performed by independent sample *t*-test. The data of non-normal distribution were expressed by median and interquartile interval, and the Mann-Whitney *U* test was used for inter-group comparison. The counting data were represented by the number of use cases, and the Chi-squared test was used. $p < 0.05$ indicated statistical significance.

Results

A total of 99 patients were included in this study. Of them, 51 were in the conventional group and 48 patients were in the low-dose group. There was no significant difference in the baseline data between the two groups ($p > 0.05$) (Table II).

There was no significant difference between the two groups in terms of surgical duration,

Table I. Comparison of anesthesia methods between low-dose and conventional-dose opioid drugs based on ERAS concept.

Item	Based on the ERAS concept, reduce the use of opioid (Low-dose group)	Conventional dose opioid drugs (Conventional group)
Preoperative education	Oral or WeChat mini program video explanation of various related matters, informing patients of preset discharge standards, follow-up time arrangements, etc.	Regular education to inform patients of medical procedures.
Preoperative examination and evaluation	Routine preoperative examination. Color Doppler ultrasound, vascular ultrasound, coronary CTA, Holter monitor, chest CT, pulmonary function examination, etc. can be considered according to the condition. Anesthesiologists comprehensively evaluate the patient's condition of heart, lung, brain, and other diseases.	Routine preoperative examination. Other examinations are selected by the attending physician based on the patient's condition. Routine anesthesia preoperative visit.
Preoperative preventive Analgesic	Take 1 tablet of Lesong orally 8 hours before surgery.	Unconventionally administer preoperative analgesia.
Preoperative fasting	Forbid solid food for 8 hours before surgery and drink for 2 hours before surgery; Drink clear liquid (5 ml/kg) 8 hours before surgery and 5 ml/kg 2 hours before surgery.	Preoperative fasting for 8 hours; It is not recommended to drink electrolyte drinks regularly.
Type of anesthesia	Use general anesthesia to assist with nerve block and promote local infiltration of anesthesia drugs in the wound.	General anesthesia with conventional Tracheal intubation was used.
Auxiliary nerve block	Ultrasound-guided bilateral quadratus lumborum block. Blocking drug 20 ml Ropivacaine (0.33%) +10 mg dexamethasone.	Not assisting with nerve block.
Intraoperative use of Analgesic	Before anesthesia induction, 0.6 gμ/kg dexmedetomidine was given, pumped within 15 minutes, and 2.5 μg/kg fentanyl+1.2 mg/kg propofol +0.2 mg/kg atracurium cisneneneba benzenesulfonate +1.5 mg/kg Lidocaine was given intravenously. After anesthesia induction, intravenous infusion of 30 mg ketorolac tromethamine and 1 mg butorphanol, and intravenous pump infusion of 0.4 μg/kg/h dexmedetomidine.	Intravenous infusion of 5 μg/kg fentanyl +1.2 mg/kg propofol +0.2 mg/kg atracurium cisneneneba benzenesulfonate. Intravenous infusion of 30 mg ketorolac tromethamine and 1 mg butorphanol after anesthesia induction; Intravenous infusion of 0.4 μg/kg/h dexmedetomidine.

Table continued

Table I *(Continued).* Comparison of anesthesia methods between low-dose and conventional-dose opioid drugs based on ERAS concept.

Item	Based on the ERAS concept, reduce the use of opioid drugs (Low-dose group)	Conventional dose opioid drugs (Conventional group)
Application of analgesics in post-operative wards	In addition to the intravenous analgesia pump, 50 mg Tramadol was given intravenously within 3 to 4 days after the operation; Other appropriate analgesics were added according to the patient's pain.	According to the patient's pain situation, appropriate analgesics should be given, and drugs should be given as needed.
Preventing post-operative nausea and vomiting	The combination of 5-HT receptor antagonists and dexamethasone during surgery prevents postoperative nausea and vomiting.	Apply a 5-HT receptor antagonist antiemetic once after routine surgery.
Preventing intra-operative hypothermia Avoid fluid overload	Routine monitoring of body temperature during surgery and proactive insulation measures are taken to ensure that the patient's body temperature during surgery does not fall below 36.0°C. Strengthen monitoring, implement targeted liquid therapy strategies, and avoid liquid overload.	Passive insulation measures, only use active heating devices when the temperature monitoring is below 36.0°C. Liquid management is carried out by anesthesiologists based on their own experience.
Promote the recovery of gastrointestinal function	2 to 4 hours after surgery, patients are encouraged to take clear liquid orally without nausea or vomiting, and their food intake should not exceed 200ml. After 3-4 hours, it is possible to gradually transition to a liquid diet based on gastrointestinal tolerance, increasing the frequency and amount of food intake.	It is recommended that patients start eating after their first bowel movement.
Early postoperative ambulation	Based on the patient's objective situation, plan and implement the patient's daily activity volume. From the first day, guide the patient to get out of bed and move (walk>30-60 minutes daily, twice).	Arrange out of bed activities based on the patient's personal wishes and recovery situation.

Table II. Comparison of baseline data between two groups.

Group	Gender (Male/Female)	Age (years)	ASA grade (II/III)	BMI (kg/m^2)
Low-dose group (n = 48)	26/22	69.9 ± 5.1	25/23	23.9 ± 2.8
Conventional group (n = 51)	23/28	70.4 ± 5.0	33/18	23.3 ± 2.6
χ^2/t	0.814	-0.449	1.624	1.076
p-value	0.367	0.654	0.203	0.285

American Society of Anesthesiologists (ASA), body mass index (BMI).

PCIA compression frequency, and rescue analgesia frequency ($p > 0.05$). The time to first exhaust, first bowel movement time, and first ambulation time were significantly shorter in the low-dose group compared to the conventional group ($p < 0.05$) (Table III).

There was no significant difference in VAS scores in the static and dynamic states between the two groups at 12, 24, and 48 hours after the surgery ($p > 0.05$) (Table IV).

There was no significant difference in MMSE scores between the two groups before the surgery ($p > 0.05$). On the first day after the surgery, the MMSE score of the low-dose group was higher than that of the conventional group ($p < 0.05$). There was no significant difference in MMSE scores between the two groups at 3 and 7 days after the surgery ($p > 0.05$) (Table V).

Serum levels of BDNF, NSE, and 5-HT were comparable in both groups before the surgery

Table III. Comparison of pain levels between two groups (scores).

Group	Surgical duration (minutes)	PCIA press times (times)	Remedial analgesia frequency (times)	First exhaust time (hours)	First bowel movement time (hours)	Time for first time out of bed activity (hours)
Low-dose group (n = 48)	149.7 ± 17.2	8 (6, 9)	3 (2, 4)	34.9 ± 6.5	38.7 ± 7.0	46.3 ± 6.5
Conventional group (n = 51)	144.5 ± 18.2	7 (5, 9)	3 (2, 5)	37.5 ± 5.9	42.2 ± 6.8	50.9 ± 6.2
t/Z	1.464	-1.027	-0.856	-2.145	-2.456	-3.653
p-value	0.146	0.304	0.392	0.034	0.016	< 0.001

Table IV. Comparison of pain levels between two groups (scores).

State	Group	12-hours after surgery	24-hours after surgery	48-hours after surgery
Static state	Low-dose group (n = 48)	3 (2, 3.5)	2.5 (2, 3)	2 (2, 2)
	Conventional group (n = 51)	3 (2, 4)	2 (2, 3)	2 (2, 2)
	Z	-0.510	-0.744	-0.671
	p-value	0.610	0.457	0.502
Trend state	Low-dose group (n = 48)	3 (3, 4)	3 (3, 3.5)	3 (2, 3)
	Conventional group (n = 51)	3 (3, 4)	3 (2,3)	3 (2, 3)
	Z	-0.528	-0.384	-0.301
	p-value	0.598	0.701	0.761

Table V. Comparison of cognitive function between two groups (scores).

Group	Preoperative	1-day after surgery	3-day after surgery	7-day after surgery
Low-dose group (n = 48)	28.5 (28, 30)	28 (27, 29)	28 (27, 29)	28 (28, 29.5)
Conventional group (n = 51)	28 (27, 30)	27 (26, 28)	28 (27, 29)	28 (27, 29)
Z	-1.318	-2.221	-1.940	-1.897
p-value	0.188	0.026	0.052	0.058

($p > 0.05$). Serum BDNF levels in both groups decreased after the surgery and were significantly lower in the conventional group. While the levels of NSE and 5-HT were overall higher after the surgery compared to the preoperative levels, they were significantly lower in the low-dose group compared to the conventional group ($p < 0.05$) (Table VI).

The incidence of adverse reactions in the low-dose group (4.2%) was lower than that in the conventional group (15.7%) ($p < 0.05$) (Table VII).

Discussion

This study shows that the reduced use of opioids based on the ERAS concept can achieve the same analgesic effect as the use of conventional opioid doses in elderly CRC patients undergoing laparoscopy under GA. Lower opioid doses were associated with earlier recovery of body functions and a lower rate of adverse events. Similar to our results, Bhatia and Buvanendran[10] showed that using the ERAS protocol and reducing the dosage of opioid drugs can effectively lower the rate of opioid-related side effects, shorten the time required for patients' functional recovery, and lower postoperative hospitalization rates. However, a study by Brandal et al[11] indicated that implementing ERAS protocols did not significantly affect opioid use in patients. These discrepancies may be related to the conventional dosage of opioid drugs used. Ferrara et al[12] used ERAS-based analgesia regimen in patients undergoing orthognathic surgery and showed that while there was no significant change in the total surgical time, the blood loss was significantly reduced. Moreover, the postoperative hospitalization rate of patients who received ERAS protocol with lower opioid dose decreased by 8.35%, and the total hospitalization time was shorter than that of patients in the conventional group. Together, these results further show that anesthesia protocols, based on the ERAS concept, are effective in minimizing pain and optimizing surgical conditions during the perioperative period. Additionally, they minimize the degree of stress response, reduce the stimulation response caused by invasive surgical procedures, reduce the occurrence of complications, and improve the quality of postoperative rehabilitation[10-12]. Jandali et al[13] found that while ERAS reduces the dosage of narcotics, it still maintains a good analgesic effect and, at the same time, shortens the postoperative rehabilitation time, which is consistent with the conclusion of this study.

Cognitive impairment is a common type of severe complication after GA surgery[14]. At present, the specific pathogenesis of this adverse event is unclear but is generally believed to be related to anesthetic drugs, invasive surgical operations, internal environment disorders, and systemic stress reactions[14,15]. Qiu et al[16] showed that BDNF, a brain neuroprotein, can inhibit

Table VI. Comparison of serum biochemical index levels between two groups.

Time	Group	BDNF (ng/ml)	NSE (μg/L)	5-HT (ng/ml)
Preoperative	Low-dose group (n = 48)	4.31 ± 0.54	11.3 ± 1.9	118 ± 19
	Conventional group (n = 51)	4.49 ± 0.53	11.1 ± 2.2	124 ± 21
	t	-1.735	0.531	-1.333
	p-value	0.086	0.596	0.186
Postoperative	Low-dose group (n = 48)	2.60 ± 0.65	13.2 ± 2.2	143 ± 19
	Conventional group (n = 51)	2.14 ± 0.71	15.8 ± 2.6	165 ± 21
	t	3.317	-5.337	-5.436
	p-value	0.001	< 0.001	< 0.001

Brain-derived neurotrophic factor (BDNF), neuron-specific enolase (NSE), 5-hydroxytryptamine (5-HT).

Table VII. Comparison of adverse reaction rates between two groups.

Group	Vomit	Dizziness	Nausea	Hypoxemia	Incidence
Low-dose group (n = 48)	0 (0.0)	1 (2.1)	1 (2.1)	0 (0.0)	2 (4.2)
Conventional group (n = 51)	2 (3.9)	2 (3.9)	3 (5.9)	1 (3.33)	8 (15.7)
χ^2					4.550
p-value					0.033

neuronal apoptosis, accelerate nervous system development, and maintain normal physiological functions of the nervous system. There is a significant correlation between serum levels of BDNF and neuropathological status. Olmezturk et al[17] showed that NSE is an important marker of nerve injury. Serum levels of NSE are relatively low under normal physiological conditions but rise in the event of damage to the nervous system. 5-HT has an important role in pain management in the central nervous system. Studies[18] show that stress induces the release of 5-HT from mast cell, platelets and chromaffin cells into the blood. 5-HT then binds to 5-HT receptors in primary afferent fibers, which excites and sensitizes nociceptors, leading to increased pain levels after the surgery. In our study, the MMSE score of the low-dose group on the first day after the surgery was higher than that of the conventional group, and the serum levels of BDNF, NSE, and 5-HT were better than those of the conventional group. This confirms that reducing the use of opioid drugs based on the ERAS concept can also help alleviate the cognitive impairment caused by anesthesia and GA surgery in elderly patients.

Limitations

This is a single-center retrospective study that only included 99 patients, with limited number of collected indicators and no long-term follow-up data. Further multi-center studies with larger cohorts and longer follow-ups are needed to verify our conclusions.

Conclusions

The ERAS protocol with low opioid use can achieve similar analgesic effects as the conventional approach but is associated with reduced cognitive impairment, earlier recovery of postoperative functions and reduced incidence of adverse reactions in elderly CRC patients, undergoing laparoscopic surgery under GA.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

XS conceived and designed the study. TF, YW, FW and XL collected the data and performed the analysis. XS was involved in the writing of the manuscript. JZ edited the manuscript. All authors have read and approved the final manuscript.

Ethics Approval

The Ethics Committee of The First Affiliated Hospital of Hebei North University approved this study (Approval No.: 2023523; Date: May 23, 2023). This article has been conducted following the Helsinki declaration and its latest amendments.

Informed Consent

Written informed consent was obtained from the patient or legal guardian.

Conflict of Interest

The authors declare that they have no competing interests.

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