Effects of Depth of Anesthesia Monitored by IoC on Patients Undergoing Laparoscopic Radical Resection of Colorectal Cancer

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Index of consciousness (IoC) consisting of IoC1 and IoC2, is a new analgesia monitoring indicator in anesthesia evaluation in the laparoscopic radical resection of colorectal cancer. Although the precise anesthetic dosage adjusted by IoC1 has been confirmed to enhance the recovery and reduce the complications of anesthesia, the most appropriate range of IoC2 during anesthesia remains unclear. To investigate the correlation between IoC2 and peri-operative indicators of patients during laparoscopic radical resection of colorectal cancer, the current randomized, controlled, and single-blinded clinical trial was performed. Participants were divided randomly into three groups with different anesthesia depth monitored by IoC2 during their laparoscopic radical resections. Primary outcomes included the dosage of remifentanil. Secondary outcomes included other physiological indexes and complications. The remifentanil dosage and the awakening time increased as IoC2 decreased. The incidences of hypotension and hypoxemia decreased with the elevated IoC2, but the risk of intra-operative awareness also increased. The impact caused by anesthesia to the immune system and health-related life quality of the patients descended with reduced anesthetic level. The IoC2 range of 35–45 could represent the most appropriate anesthetic depth during laparoscopic radical resection, which provides a new perspective for the clinical treatment of colon cancer.

INTRODUCTION

Colorectal cancer causes almost 700,000 deaths annually, making it the world's fourth most deadly carcinoma.[1–3] The increasing incidence of colorectal cancer among the adolescent and young adults has drawn great attention of the oncology community.[4,5] Due to its less invasiveness and higher safety, laparoscopic radical resection has been widely used for the treatment of colorectal cancer since 1980s.[6] Because laparoscopic radical resection can bring strong discomfort to the patient, anesthesia is a necessary procedure for the operation.[7] However, inappropriate administration of intravenous anesthesia during the resection can lead to unfavorable physical reactions such as vomiting, choke coughing, and other incontrollable movements, raising the risks of the surgery, and even severe complications such as hypertension, hypotension, and bradycardia.[8,9] The bispectral index (BIS) has been approved as the first method by the US Food and Drug Administration to monitor the depth of anesthesia and evaluate the effects of narcotics.[10,11] However, since the past two decades, the BIS monitoring system has been reported to be severely affected by the variation of anesthetic agents and patients' ages.[12] Besides, researchers have also revealed that hypothermia, neurological impairment, and other medical devices decreased the accuracy of the BIS because of their interference with the electroencephalographs (EEGs) of the patients.[13,14] It is, therefore, urgent for us to identify a more stable and universal evaluation system for the administration of anesthesia in clinic.

Index of consciousness (IoC) is a recent advanced monitoring technology, which is composed of a hazy inference system with several pre-defined parameters and a dynamic EEG extraction system with a nonlinear analysis algorithm.[15,16] IoC1 and IoC2 are two categories of IoC that represent the analgesic depth and consciousness level of patients, respectively.[17,18] Recent research has revealed that IoC1 functions as an estimator of the dosage of anesthetic agents during the procedure and the post-operative recovery time.[19] However, the clinical standard and medical significance of IoC2 remain unclear.

In this study, we used IoC2 to monitor the correlation between anesthesia depth and patients' peri-operative physiological indicators, inflammatory response, cognitive function, and health-related quality of life (HRQL). Since the validity of IoC1 has been considered to reflect the depth of anesthesia, we hypothesized that the value of IoC2 during this surgery was closely related to the peri-operative indicators and long-term recovery of patients. We believe that our research has pioneered the importance of IoC2 in laparoscopic radical resection and provided a new perspective for the clinical treatment of colon cancer.

RESULTS

Flow Chart of the Research

As shown in Figure 1, we assessed a total of 215 eligible patients in our clinical trial. 35 patients were excluded at the beginning of the study, and the remaining 180 patients proceeded in the next stage of our
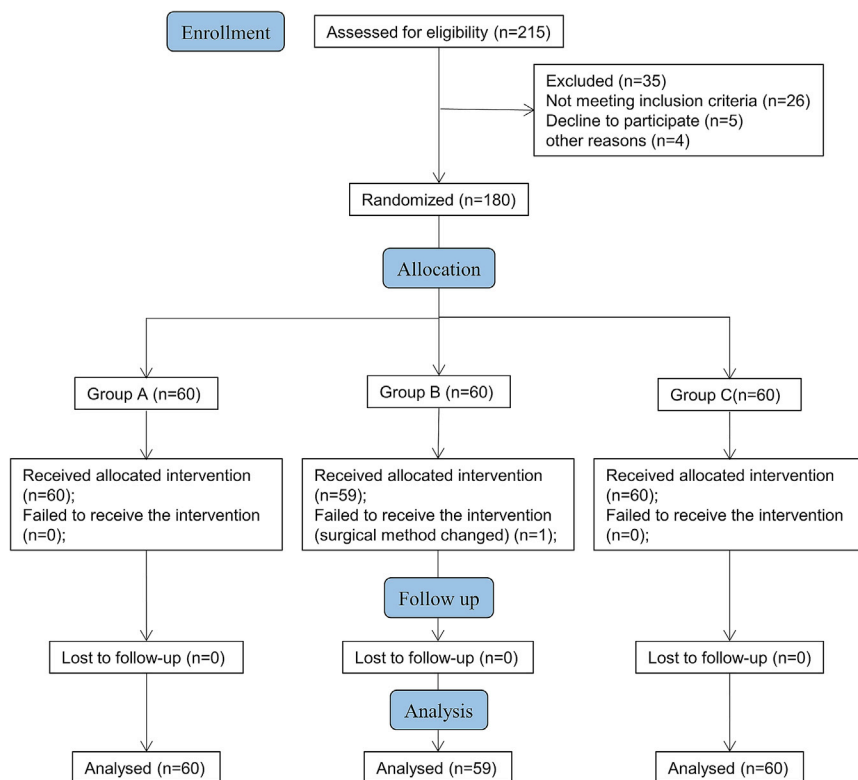
hypoxemia was statistically higher in group A than in groups B and C. On the contrary, the incidence of hypertension was higher in group B and C than in group A (Table 3). Only one case of body movement during the surgery was observed in group C, suggesting that anesthetic awareness was closely related to an IoC2 of 45–50.

IoC, MAP, and HR Values

As shown in Table 4, the values of IoC1 and IoC2 both decreased with the anesthesia and recovered to normal levels in the absence of analgesic agents. However, there was a statistical difference between the values of IoC2 at time point 0 (T0) and T4 in group A, indicating a longer recovery time from the anesthesia for patients with a peri-operative IoC2 of 25–35. Additionally, the heart rate (HR) and mean arterial pressure (MAP) of patients in all groups decreased with the deepening of anesthesia.

Cortisol, Prolactin, IL-6, and IL-10

Anesthesia during the surgery could induce the activation of the stress response system in the patient's body and cause fluctuations in hormone and interleukin (IL) levels, which could be detected by testing blood samples. As shown in Table 5, the levels of circulating cortisol and prolactin both increased during the surgery, indicating the activation of the stress response system. However, the levels of circulating cortisol and prolactin in groups B and C were much higher than in group A, suggesting that the peri-operative endocrine stress response decreased with reduced anesthesia level. In addition, the levels of IL-6 and IL-10 both increased after the surgery. Contradictory to the endocrine fluctuation, the levels of circulating IL-6 and IL-10 were higher in group A than in both groups B and C, suggesting that deeper anesthesia was more favorable for the prognosis.

Effect of Depth of Anesthesia on Cognitive Function

The recovery of cognitive function of the patients in the three groups were evaluated with the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Trail-Making Test, Part A (TMT-A) (Table 6), and there were no statistical differences in the scores of these tests among the three groups.

EORTC QLQ-C30 Scores

HRQL was evaluated by EORTC QLQ-C30 scores. As shown in Table 7, role function, social function, and global quality of life (QoL) scores decreased dramatically with the deepening of anesthesia, suggesting that inappropriate levels of anesthesia could impact the HRQL of patients in the long term.

trial. They were divided randomly and equally into 3 groups, with 60 subjects per group: group A with IoC2 ranging from 25 to 35, group B with IoC2 ranging from 35 to 45, and group C with IoC2 ranging from 45 to 55. Eventually, 60 patients in group A, 59 in group B, and 60 in group C received the scheduled laparoscopic radical resection with different modes of anesthesia administration and were included in the final statistics and analysis.

Demographic and Clinical Data

As shown in Table 1, there were no significant differences in the demographic, obstetrical characteristics, and baselines among the three groups, including age, sex, weight, ASA (American Society of Anesthesiologists) class, and surgery time.

Comparison of Remifentanil Dosage and Awakening Time among Groups

The dosage of remifentanil and awakening time were analyzed in Table 2. Compared to group A, the average dose of remifentanil used during the procedure decreased dramatically in groups B and C. However, there was no significant difference in the dosage of remifentanil between groups B and C. Similarly, the awakening time of the patients was also prolonged with the deepening of anesthesia.

Peri-operative Adverse Reactions

Generally, the incidence of peri-operative adverse reactions increased with the deepening of anesthesia. The paroxysm of hypotension and

Table 1. Demographic and Clinical Data of the Participants

Variable	Group A (n = 60)	Group B (n = 59)	Group C (n = 60)	p
Sex, male/female	27/33	31/28	26/34	0.347
Age, in years	60.2 ± 11.5	64.8 ± 13.6	63.4 ± 9.7	0.459
Weight, in kilograms	62 ± 9	63 ± 8	63 ± 10	0.632
n (%) in ASA classification				0.343
II	27 (45.0)	29 (49.2)	29 (48.3)	
III	33 (55.0)	30 (50.8)	31 (51.7)	
n (%) in indicated stage				0.408
I	11 (18.3)	13 (22.0)	10 (16.7)	
II	32 (53.3)	30 (50.8)	33 (55.0)	
III	17 (28.4)	16 (27.2)	17 (28.3)	
Surgery time, in minutes	261 ± 62	243 ± 59	244 ± 40	0.035

ASA, American Society of Anesthesiologists.

Table 2. Comparison of Remifentanil Dosage and Awakening Time among Groups

	Group A (n = 60)	Group B (n = 59)	Group C (n = 60)	p
Mean dose of remifentanil ($\mu g/kg \cdot h$)	0.20 ± 0.05	0.17 ± 0.02**	0.15 ± 0.02**	0.047
Awakening time, in minutes	6.7 ± 2.5	5.4 ± 2.3**	4.8 ± 2.1**	0.034

**p < 0.01, when compared with group A.

DISCUSSION

Anesthesia, including general and regional anesthesia as well as a combination of the two techniques, plays a critical role in modern surgeries.[20] It is estimated that almost 60% of patients in the United States received tumor resection, and 80% of them were administrated with anesthesia in 2018 in the United States.[9] Increasing evidence has revealed the close correlation among the inflammatory reaction, the proliferation and migration of cancer cells, the fluctuation of the hormones, and the surgical anesthesia, indicating that the choice and dosage of analgesic agents utilized during carcinoma resection would affect the long-term recurrence of cancers.[21–23] However, due to the lack of solid prospective evidence, the current analgesic procedure often ignores the diverse impacts of similar analgesic strategy and analgesic agents and/or adjuvants on different patients. In our research, we performed a randomized clinical trial to use IoC, an advanced anesthesia monitoring method, to identify a new strategy for the determination of appropriate analgesic dosage in laparoscopic radical resection for colorectal cancer. We aimed to explore the most favorable range of IoC2 during the resection in order to minimize the complications and the endocrine and immune stress responses caused by anesthesia.

Conventional anesthesia monitoring methods, including BIS, auditory evoked potential, and Narcotrend have been widely used in clinic for decades. However, the morbidity and complications induced by improper use of analgesic agents and adjuvants remain relatively high. For instance, the accidental awareness during general anesthesia determines the success or failure of the surgery.[24,25] Previous research has revealed that the emergence of unintended awareness during the procedure of laryngoscopy is 1/25, and the collection of spontaneously self-reported awareness intra-operative of patients by the Royal College of Anesthetist Nation Audit Project showed that the incidence of surgical responsiveness was up to 1/800 in the United States in 2018.[26,27] BIS, which was previously considered as the most accurate anesthesia monitoring strategy, has been suggested to be affected by the variations in analgesic agents and patients' age, causing several complications such as hypertension, hypotension, hypoxemia, and accidental awareness during the surgery.[28,29]

IoC is a new type of anesthesia depth monitoring technique that relies on epidermal electrodes to record the EEG signal.[30] The EEG signal is amplified, purified, and digitized by a low-pass filter, and the digitized signal is transmitted from the amplifying digitizer to the microprocessor.[31] The value of IoC is calculated as an indicator to evaluate the level of patient's consciousness during anesthesia. Accumulating research has indicated the superiority of IoC over traditional anesthesia monitoring methods. For example, it is reported that IoC is a better predictor than BIS for representing patient's consciousness during the anesthesia induction and maintenance with sevoflurane and remifentanil.[32] Monitoring anesthesia through IoC makes the whole procedure more controllable and effectively reduces adverse events during the operation.[33]

The current clinical research on IoC mainly focuses on IoC1. The value of IoC1 can intuitively reflect the patient's anesthesia depth in laparoscopic radical resection. IoC1 monitoring can effectively protect the patient's anesthesia safety and reduce the occurrence of intra-operative recovery and post-operative complications. However, the current clinical research on IoC2 is quite inadequate, and the understanding of the clinical role of IoC2 is very limited. At present, IoC2 is mainly used as a cofactor of IoC1 to monitor the patient's anesthesia depth. However, the detailed relationship between the value of IoC2 and the peri-operative indicators of patients and the incidence of post-operative complications is still unknown. In this research, we creatively designed a clinical experiment and explained the relationship between the range of IoC2 during laparoscopic radical resection and various physiological indexes, inflammatory response, cognitive function, and HRQL of post-operative colorectal cancer patients. We believe that our findings provide a new perspective on the procedure of laparoscopic radical resection. Controlling the value of intra-operative IoC2 between 35 and 45 can effectively improve the quality of surgery and reduce the occurrence of complications. We hope that our research can deepen clinicians' understanding of IoC2 and provide a basis for the application of IoC2 monitoring in similar operations.

The stress response system is activated under the stimulation of trauma and injuries through a complex cooperation of the hormonal,

Table 3. Peri-operative Adverse Reactions of Different Groups

| | No. (and %) from: | | | |
	Group A (n = 60)	Group B (n = 59)	Group C (n = 60)	p
Hypotension	16 (26.7)	10 (16.9)[a]	9 (15)[a]	0.032
Hypertension	0 (0)	5 (8.5)[a]	6 (10)[a]	0.025
Bradycardia	10 (16.7)	9 (15.3)	9 (15)	0.647
Tachycardia	8 (13.3)	8 (13.6)	7 (11.7)	0.832
Body movement	0 (0)	0 (0)	1 (1.7)	0.671
Hypoxemia	10 (16.7)	3 (5.4)[a]	2 (3.3)[a]	0.036
Therapy interruption	0 (0)	0 (0)	0 (0)	–
Nausea	0 (0)	0 (0)	0 (0)	–
Vomiting	0 (0)	0 (0)	0 (0)	–
Aspiration	0 (0)	0 (0)	0 (0)	–
Intra-operative awareness	0 (0)	0 (0)	0 (0)	–

The significance level was set at $p < 0.05$.
[a]Significantly different when compared with group A.

Table 4. Comparison of IoC with MAP and HR Values among Groups

IoC and Time Points	Group A (n = 60)	Group B (n = 59)	Group C (n = 60)	p
IoC1				
T0	98.2 ± 1.6	98.0 ± 1.4	97.9 ± 1.6	0.575
T1	41.5 ± 7.2[##]	42.6 ± 6.5[##]	39.5 ± 7.2[###]	0.321
T2	47.7 ± 6.9[##]	49.8 ± 8.7 [a,##]	51.3 ± 6.5[a,b,##]	0.096
T3	50.4 ± 8.0[##]	53.1 ± 8.5[a,##]	54.8 ± 7.9[a,##]	0.048
T4	95.8 ± 2.5	96.3 ± 3.4	97.2 ± 2.5	0.876
IoC2				
T0	97.5 ± 2.3	97.8 ± 1.9	98.1 ± 1.6	0.563
T1	35.2 ± 7.8[###]	34.9 ± 9.5[###]	35.1 ± 7.3[###]	0.476
T2	33.4 ± 4.5[###]	41.1 ± 11.5[a,###]	47.2 ± 4.5[a,b,##]	0.044
T3	37.6 ± 4.7[###]	43.2 ± 5.3[a,###]	52.5 ± 5.5[a,b,##]	0.027
T4	95.5 ± 1.7[#]	98.0 ± 1.2	97.9 ± 1.4	0.679
MAP, in mmHg				
T0	89.2 ± 8.8	87.8 ± 8.5	90.5 ± 7.9	0.509
T1	75.8 ± 7.9[##]	75.2 ± 8.6[##]	77.3 ± 8.7[##]	0.192
T2	74.3 ± 7.4[##]	77.5 ± 9.8[##]	79.5 ± 9.6[a,b,##]	0.047
T3	77.6 ± 8.2[##]	82.4 ± 10.2[a,#]	85.5 ± 9.4[a,b,#]	0.015
T4	81.6 ± 8.4[#]	86.5 ± 8.7	84.6 ± 8.8[a,b,#]	0.037
HR, in Beats per Minute				
T0	80.0 ± 9.3	79.3 ± 9.0	80.7 ± 9.4	0.418
T1	72.1 ± 8.0[##]	70.4 ± 8.1[##]	71.6 ± 9.2[##]	0.285
T2	72.7 ± 9.9[##]	72.8 ± 9.7[##]	74.9 ± 10.0[a,b,##]	0.044
T3	74.7 ± 8.9[##]	75.6 ± 9.5[##]	78.5 ± 8.3[a,b,##]	0.027
T4	76.8 ± 8.2[#]	78.3 ± 8.8	79.1 ± 7.5[a]	0.043

IoC, index of consciousness. MAP, mean arterial pressure. HR, heart rate. T, time point.
[a]Significantly different when compared with group A.
[b]Significantly different when compared with group B. The significance level was set at $p < 0.05$.
[#]$p < 0.05$, [##]$p < 0.01$, and [###]$p < 0.001$, when compared with T0.

neural, immune, and physiologic alterations. Among all the regulatory pathways, the impact caused by the over-secretion of stress-related hormones (e.g., adrenaline, noradrenaline, antidiuretic hormone, adrenocorticotropic hormone, cortisol, and prolactin) is rather drastic and profound.[34] Accumulating evidence indicates that the endocrine stress response during a variety of surgeries can be modulated by the anesthesia procedure during the operation. In addition, the long-term recovery of patients is closely correlated with both the analgesic agents and dosage used in surgery and the secretive fluctuation of stress responding hormones, especially cortisol and prolactin. For example, it was reported that the levels of circulating cortisol and prolactin could be affected by changing the combination of analgesic agents such as propofol-fentanyl and isoflurane-fentanyl.[34] Moreover, altered levels of interferon gamma (IFN-γ) and IL-2 receptor during general anesthesia were found to impact the blood levels of cortisol and prolactin.[35] In our research, we reported that the levels of cortisol and prolactin were increased during the surgery. Our study is also the first instance to compare the alterations in stress-related hormones at different IoC2 values and come to the conclusion that higher IoC2 value (40–50) leads to relieved endocrine pressure and is beneficial for the recovery of the patients from the anesthesia.

In recent years, the immune reaction caused by anesthesia and surgery in cancer treatment has drawn great research attention, and increasing studies have focused on the alterations in the behaviors of immunocytes caused by the anesthesia procedure, such as thymus-dependent lymphocytes (T cells) and bursa-dependent lymphocytes (B cells).[36] For instance, plasma IL-6 and IL-10 have been reported to be affected by different analgesic strategies, such as total intravenous anesthesia or isoflurane anesthesia during the operation of colorectal cancer.[37] In addition, it was reported that the intra-operative anesthesia and analgesia could impact the behavior of the natu-

ral killer cells, which was closely related to the prognosis of patients after the resection.[38] Our research is the first of its kind to compare the levels of IL-6 and IL-10 at different peri- and post-operative time points. The levels of IL-6 and IL-10 increased with elevated analgesic depth, indicating that the immune response was enhanced with a higher dosage of anesthesia agents.

Conclusions

In conclusion, our clinical trial is the first to explore the most appropriate range of IoC2, and our data have increased the accuracy and efficiency of anesthesia in the laparoscopic radical resection of colorectal cancer. By analyzing the complications caused by anesthesia and the endocrine and immune responses, we finally conclude that the most appropriate IoC2 range is 35–45, which highlights the importance of IoC2 in laparoscopic radical resection and provides a new perspective for the clinical treatment of colon cancer.

Table 5. Comparison of Cortisol, Prolactin, IL-6, and IL-10 among Groups

Level and Time Point	Mean ± SD for:			
	Group A (n = 60)	Group B (n = 59)	Group C (n = 60)	p
Circulating Cortisol (nmol/L)				
T0	467.75 ± 30.89	482.03 ± 35.77	475.44 ± 35.69	0.278
T3	823.45 ± 42.51[##]	912.13 ± 34.74[##]	945.23 ± 44.41[##]	0.076
T4	982.00 ± 46.32[##]	1,045.21 ± 37.22[a,##]	1,047.00 ± 35.42[a, ##]	0.043
T5	1,026.72 ± 42.54[##]	1,094.07 ± 43.52[##]	1,105.84 ± 45.23[a,##]	0.032
T6	532.14 ± 26.23	562.57 ± 25.31	568.74 ± 27.64	0.175
T7	522.27 ± 27.93	512.80 ± 22.78	523.45 ± 21.34	0.432
Circulating Prolactin (mU/L)				
T0	268.23 ± 18.03	255.62 ± 13.20	252.35 ± 16.21	0.392
T3	2,387.43 ± 79.31[##]	2,936.41 ± 81.29[a,##]	3,037.15 ± 92.31[a,b,###]	0.056
T4	1,483.03 ± 77.20[##]	1,864.03 ± 88.93[a,##]	2,214.88 ± 97.37[a,b,##]	0.009
T5	759.01 ± 76.38[##]	992.56 ± 83.79[a,##]	1,183.56 ± 87.97[a,b,##]	0.000
T6	325.77 ± 31.65[#]	343.26 ± 38.11[#]	318.49 ± 25.98[#]	0.146
T7	287.75 ± 31.65	296.58 ± 44.61	283.63 ± 29.37	0.387
IL-6 (pg/mL)				
T0	7.71 ± 5.71	8.24 ± 4.83	8.18 ± 4.24	0.474
T3	156.95 ± 27.84[###]	143.05 ± 21.11[###]	137.75 ± 15.67[###]	0.225
T4	279.62 ± 33.20[###]	254.24 ± 34.86[a,###]	244.69 ± 33.64[a,###]	0.174
T5	346.95 ± 39.14[###]	335.62 ± 35.94[a,###]	320.35 ± 31.66[a,b,###]	0.042
T6	125.05 ± 19.24[###]	118.23 ± 14.07[###]	110.62 ± 15.37[###]	0.036
T7	45.95 ± 9.14[##]	42.71 ± 9.02[##]	34.69 ± 10.00[##]	0.343
IL-10 (pg/mL)				
T0	5.2 ± 0.5	5.0 ± 0.4	5.2 ± 0.3	0.153
T3	10.2 ± 0.4	9.1 ± 0.5	10.1 ± 0.4	0.732
T4	19.68 ± 6.85[###]	18.73 ± 7.24[###]	17.14 ± 6.96[###]	0.183
T5	76.18 ± 14.35[###]	73.90 ± 16.06[###]	72.44 ± 19.93[b,###]	0.048
T6	46.31 ± 11.17[##]	41.40 ± 12.58[a,##]	36.52 ± 9.82[a,##]	0.067
T7	14.15 ± 6.24[#]	13.24 ± 9.21[#]	15.42 ± 7.63[#]	0.269

IL, interleukin. T, time point.
[a]Significantly different when compared with group A. The significance level was set at p < 0.05.
[b]Significantly different when compared with group B. The significance level was set at p < 0.05.
[#]p < 0.05, [##]p < 0.01, and [###]p < 0.001 when compared with T0.

Table 6. Effect of Depth of Anesthesia on Cognitive Function of Participants of Different Groups

	Mean ± SD for:			
	Group A (n = 60)	Group B (n = 59)	Group C (n = 60)	p
MMSE, Score				
Preop	27.31 ± 2.25	27.41 ± 1.84	27.37 ± 2.18	0.674
ΔPreop	−0.17 ± 0.72	0.45 ± 0.84	0.39 ± 0.87	0.149
MoCA, Score				
Preop	26.32 ± 1.15	25.94 ± 1.32	26.35 ± 1.24	0.251
ΔPreop	0.17 ± 0.44	0.03 ± 0.65	0.97 ± 0.83	0.232
TMT-A, in Seconds				
Preop	41.5 ± 10.5	43.5 ± 12.4	43.0 ± 11.3	0.730
ΔPreop	1.6 ± 9.0	0.7 ± 11.3	−1.2 ± 1.6	0.451

MMSE, Mini-Mental State Examination. MoCA, Montreal Cognitive Assessment. TMT-A, Trail-Making Test, Part A. The significance level was set at p < 0.05.

system by anesthetic drugs and improving the recovery of cognization and life quality of the patients undergoing the surgery.

We recruited a total of 215 patients with colorectal cancer who were scheduled for the laparoscopic radical resection in Quanzhou First Hospital Affiliated to Fujian Medical University from 2016 to 2018 to to explore the proper anesthetic level. This study was approved by the Ethics Committee of Quanzhou First Hospital Affiliated to Fujian Medical University. Patients with colorectal cancer were asked to join our clinical trial during their first time of antepartum examination, and all the patients participating in the study signed the informed consent forms.

Among all the applicants, only patients who met the following 5 criteria were chosen to join in our study: patients had to (1) be over 18 years old; (2) have an American Society of Anesthesiologists (ASA) Physical Status Classification of II or III; (3) be scheduled to undergo a laparoscopic radical resection for colorectal cancer; (4) have no other major diseases or mental illnesses; and (5) have no history of propofol or remifentanil allergy. Patients were excluded from the trial if they: (1) were under 18 years old; (2) presented with heart, liver, kidney, and/or lung dysfunction; (3) had a history of drug allergy or alcohol abuse; (4) weighed more than 20% of the average weight; (5) had endocrine or immunological diseases or were undergoing chemoradiation or immunotherapy; (6) were using drugs that impacted the nervous system within 7 days before the surgery; and (7) had a mental illness.

Among the 215 patients, 26 people were excluded because they did not meet the aforementioned conditions, 5 people refused to participate in the study, and 4 people could not participate in the study due to other reasons. The remaining 180 patients were randomly divided into three groups: group A (60 people), group B (60 people), and group C (60 people). All patients in group A received our scheduled intervention (IoC2 values were maintained at 25–35 during their

MATERIALS AND METHODS
Study Design and Participants
A prospective, randomized, and single-blinded clinical trial was performed in this research (trial number: ChiCTR2000032867). We aimed to investigate the relationships between the variation of anesthetic depth in the laparoscopic radical resection of colorectal cancer and the stress response, immune system, anesthetic recovery, cognization, and HRQL of the patients. Only in this way could we identify the correspondingly appropriate analgesic depth for the laparoscopic radical resection to decrease the awakening time and the dose of anesthetic agents, thereby reducing the repression of the patients' immune

Table 7. EORTC QLQ-C30 Scores of Different Groups

	Mean ± SD for:			
	Group A (n = 60)	Group B (n = 59)	Group C (n = 60)	p
Physical Function				
Preop score	79.8 ± 11.4	80.3 ± 9.7	76.9 ± 9.8	0.268
ΔPreop score	−26.7 ± 8.6[&&]	−21.1 ± 7.8[&&]	−20.0 ± 8.3[&&]	0.292
Role Function				
Preop score	76.5 ± 7.8	78.4 ± 9.7	76.7 ± 8.1	0.424
ΔPreop score	−35.7 ± 12.1[&&&]	−24.8 ± 10.0[a,&&]	−18.8 ± 10.7[a,b,&&]	0.005
Cognitive Function				
Preop score	85.6 ± 11.8	86.1 ± 11.0	86.4 ± 9.3	0.532
ΔPreop score	−5.8 ± 1.7[&]	−4.3 ± 2.1[&]	−4.0 ± 2.0[&]	0.451
Emotional Function				
Preop score	72.7 ± 6.2	73.3 ± 7.0	72.8 ± 8.1	0.676
ΔPreop score	−0.4 ± 0.3	1.3 ± 0.5[&]	1.0 ± 0.5[&]	0.075
Social Function				
Preop score	87.5 ± 9.8	88.5 ± 9.7	87.3 ± 9.2	0.473
ΔPreop score	−15.5 ± 4.8[&&]	−8.9 ± 4.3[a,&&]	−7.8 ± 5.0[a,&&]	0.032
Global QoL				
Preop score	67.7 ± 7.6	68.6 ± 8.3	65.1 ± 7.8	0.518
ΔPreop score	−9.8 ± 4.4[&&]	−6.0 ± 3.5[a,&]	−5.9 ± 2.7[a,&&]	0.046

[&]p < 0.05, [&&]p < 0.01, and [&&&]p < 0.001 when compared with baseline (pre-operative [preop] score).

For functional scales and the global quality of life (QoL), a high score denotes a high level of function, while a negative difference from baseline denotes a deterioration of health-related quality of life (HRQL). The significance level was set at p < 0.05.

[a]Significantly different when compared with group A.

[b]Significantly different when compared with group B.

laparoscopic radical resection). 59 patients in group B received allocated intervention (IoC2 values were maintained at 35–45 during laparoscopic radical resection). All patients in group C received our scheduled intervention (IoC2 values were maintained at 45–55 during laparoscopic radical resection). Therefore, data for a total of 179 patients were collected and analyzed.

Anesthesia

For anesthesia induction, patients were injected intravenously with analgesic agents containing 0.05 mg/kg midazolam, 1 mg/kg propofol, and 2 μg/mL remifentanil until they lost consciousness. 0.6 mg/kg rocuronium was then injected intravenously, and the oxygen saturation level was kept at 100% until the IoC1 maintained at 35–45 and IoC2 at 30. Endotracheal intubation was then performed, and a Drager-Fabius anesthesia ventilator was connected to the tube to analyze the concentration of CO_2 in the breathing end to keep the partial pressure of CO_2 at 35–45 mmHg.

For intra-operative anesthesia maintenance, propofol was pumped into the patient's vein to keep the IoC1 stable at 40–60. Increased propofol was injected into the vein when the IoC2 was higher than the upper limit and the amount of propofol was 0.5 μg/mL per adjust-

ment. When the physical motions were severe, the dosage of propofol was 1 μg/mL per adjustment. The dosage of propofol decreased to 0.5 μg/mL per adjustment when the IoC2 was lower than 40. Blood pressure, HR, finger pulse oxygen saturation, end-tidal carbon dioxide partial pressure, and anesthesia depth were all monitored during the procedure. Ephedrine and atropine were utilized when necessary. The muscle relaxant was stopped 30 min before the end of the operation, and propofol and remifentanil were discontinued when suture was started. The patient was routinely treated with parecoxib sodium at a dosage of 40 mg.

For post-operative treatment, at the end of the operation, the patient was transferred to the post-,operative recovery room to monitor extubation. The muscle relaxant antagonist was routinely used and the anesthesia continued to be observed. The endotracheal tube was removed, and the time of recovery and extubation was recorded. 600 mg tramadol, 20 mg dextrozine, and 0.6 mg ramosetron were used for the post-operative analgesia.

Complications and Management

The awakening time of the patients was defined as the period between the end of the surgery and when the patient responded to a general voice calling his or her name and opened his or her eyes.[39] Hypotension was diagnosed when the patient's blood pressure was lower than 90/60 mmHg, and 1 mg metaraminol was utilized to treat the hypotension.[40] Hypertension was diagnosed when blood pressure was higher than 140/90 mmHg, and 10 mg urapidil was injected. Bradycardia was defined as HR below 50 beats per minute. In that case, 1 mg atropine was injected intravenously. HR higher than 100 beats per minute was defined as tachycardia, and 1 mg/kg esmolol was administered in that case.[41] Hypoxemia was diagnosed as oxygen saturation level below 90%; all procedures had to be stopped when hypoxemia lasted more than 3 min, and the assisted breathing mask would be used in that case.[42]

Outcomes

The primary outcomes of this trial were the dosage of remifentanil and the values of IoC1 and IoC2. The secondary outcomes of the trial included the incidences of complications in blood pressure; HR and blood oxygen concentration; patient's awakening time, and the serum levels of cortisol and prolactin, IL-6, and IL-10. Other outcomes included the scores of the MMSE, the results of the TMT, the EORTC QLQ-C30 scores, and MAP.

Collection of Data

The dosage of propofol and remifentanil and the awakening time of the patients were recorded. The IoC1, IoC2, MAP, and HR were monitored during the whole length of the surgery, and their values were recorded at the following time points: patient's entering the operating room and before the anesthesia (T0); before the cutting (T1); 2 min after the cutting (T2); 2 h after the beginning of the surgery (T3); at the end of the surgery (T4); 2 h after the surgery (T5); 24 h after the surgery (T6); and 48 h after the surgery (T7). Blood samples of the patients were collected at T0, T3, T4, T5, T6, and

T7. The serum levels of cortisol and prolactin and the survival rates of T cell subsets (CD3+, CD4+, CD8+, CD4+/CD8+) and natural killer cells were measured. The MMSE and TMT were administered on the day before the surgery and 1 week after the surgery to evaluate the recovery of cognition. The EORTC QLQ-C30 test was performed on the day before the surgery and 2 weeks after the surgery to evaluate the HRQL.

Randomization and Blinding

All patients participating in the trial were randomly given a number from among 1, 2, and 3 by a computer program. The patients with the number 1 composed group A, with IoC2 ranging from 25 to 35. Group B, with IoC2 ranging from 35 to 45, consisted of patients who were given number 2. Group C, with IoC2 ranging from 45 to 55, consisted of patients who were given number 3. Additionally, all the parameters were recorded by anesthetists and doctors who were blind to the group assignment of the patients.

Statistical Analysis

The expression of categorized variables was frequency or percentage, and the expression of continuous variables was mean ± standard deviation. The chi-square test (or Fisher's exact test) was used to compare the categorized variables. One-way ANOVA and Tukey's post hoc test were used to analyze the continuous variables, and contingency table chi-square test was acquired for the comparison of outcomes among different groups. The statistical analysis was performed by SAS v.9.3 software (SAS Institute, Cary, NC, USA).

AUTHOR CONTRIBUTIONS

J.Z. and Z.K. carried out the molecular genetic studies, participated in the sequence alignment, and drafted the manuscript. W.X. carried out the immunoassays. H.L. and Y.L. participated in the sequence alignment. H.L. and Y.L. participated in the design of the study and performed the statistical analysis. Z.K. conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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