Comparative effects of target-controlled infusion of anesthetic sufentanil and remifentanil on inflammatory factors and oxidative stress indicators in patients of colorectal cancer

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Abstract
This study was designed to compare the recovery of target-controlled infusion of sufentanil and remifentanil in patients of colorectal cancer. In total, 104 patients were randomly divided into sufentanil and remifentanil groups. One group was given target-controlled infusion of sufentanil, while the other group received remifentanil. Inflammatory factors and oxidative stress indicators were measured at 10 min before induction of anesthesia (T1), 1 h (T2), 24 h (T3), and 72 h (T4) after surgery. Adverse reactions were also compared. The extubation and recovery time of sufentanil group was longer than remifentanil group. The levels of CRP, IL-8, and IL-4 in sufentanil group and remifentanil group increased continuously. CRP contents at T3, T4, and IL-8 and IL-4 contents at T2, T3, and T4 of remifentanil group were lower (\(P<0.05\)). The incidence of adverse reactions in sufentanil group was 15.4%, which was significantly (\(P<0.05\)) lower than remifentanil group (28.8%). The recovery and extubation time of sufentanil were longer than remifentanil, while the remifentanil can effectively reduce the levels of inflammatory factors and oxidative stress.

Keywords
inflammatory factors, oxidative stress, remifentanil, sufentanil

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Introduction
Surgical treatment is the main treatment for colon cancer. With the widespread use of surgical treatment, the improvement of anesthesia quality has gained more attention in clinical practice. However, surgical injury, hemodynamic changes, and stress reaction triggered by severe pain, can cause inflammatory reaction and oxidative stress index increase, which has an impact on the surgery outcome and prognosis of the operation.1 The changes of inflammatory reaction and oxidative stress index in peroperative period were related to anesthesia and anesthetics.2

Remifentanil is a potent selective \(\mu\)-opioid receptor agonist and was first approved for use as an analgesic agent during induction and maintenance of general anesthesia in 1996. In 2002, remifentanil received approval from the European...
Medicines Agency for provision of analgesia for duration of up to 3 days in mechanically ventilated ICU patients, aged 18 years or older. It has the characteristics of rapid onset and quick elimination, because of its unique chemical structure.3

Sufentanil, an opioid analgesic, is an analogue of fentanyl and has been used for the induction and maintenance of anesthesia and for postsurgical analgesia. It has shorter distribution and elimination half-lives, and is a more potent analgesic than fentanyl.4 Furthermore, target-controlled infusion can adjust the anesthetic dosage according to the plasma concentration, which has better anesthetic effect. Hence, the target-controlled infusion anesthesia is the main anesthetic method for laparoscopic radical resection of colorectal cancer.5 At present, studies have shown that6 the recovery time and extubation time of target-controlled infusion of sufentanil are longer than that of target-controlled infusion of remifentanil, but the incidence of postoperative adverse reactions is low. However, there are few reports about the combined anesthesia effect of target-controlled infusion of sufentanil and remifentanil on inflammatory response and oxidative stress index in patients who underwent laparoscopic radical resection of colorectal cancer. The aim of this study is to compare the effects of target-controlled infusion of sufentanil and remifentanil on inflammatory response and oxidative stress in patients who underwent laparoscopic radical resection of colorectal cancer.

**Table 1.** Comparison of general data between the two groups (n=52).

| Group        | Male/female | Average age (years) | Classification of ASA |
|--------------|-------------|---------------------|-----------------------|
|              |             |                     | Type I | Type II |
| Sufentanil   | 31/21       | 52.2 ± 2.3          | 41     | 11      |
| Remifentanil | 29/23       | 52.6 ± 2.7          | 39     | 13      |
| X²/t         | 0.361       | 1.452               | 0.127   |         |
| P            | >0.05       | >0.05               | >0.05   |         |

After entering the operation room, the vital signs of patients were monitored routinely, and 5 L/min of oxygen was given at the same time. Subsequently, internal jugular vein puncture was performed, and the upper extremity vein was opened, and followed by continuous infusion of 10 mL/(kg H) sodium lactate and 6% hydroxyethyl starch until the end of operation. Then, the anesthetic induction was performed with 3 µg/mL propofol and 0.25 mg atropine, and the induction was stopped after the patient did not respond to the instruction. After the corresponding concentration was recorded, rocuronium was injected into the patient for rapid induction, and the standard 0.6 mg/kg was injected into the patient.

The plasma concentration of propofol in sufentanil group was 4 mg/L, and the effect chamber concentration was 0.4 µg/L. When the concentration of the drug reached equilibrium, mechanical ventilation was given to the patient at a tidal volume of 8–10 mL/kg, 15 times per minute. During the operation, the concentration of propofol was adjusted in the range of 3.5–4.5 mg/L and intermittent injection of rocuronium was performed on the basis of the actual anesthesia. Three percent sevoflurane was inhaled within 1 h before operation, and sufentanil was stopped within 40 min before operation.
The concentration of the effect chamber of remifentanil group was 4 µg/L, and remifentanil was stopped within 40 min before operation, and the rest process was the same as sufentanil group. During the operation, the amount of fluid and bleeding were taken as the basis for rational adjustment of the volume and speed of fluid infusion. When the patient is conscious, the catheter is removed.

**Observation index**

The extubation time, postoperative recovery time, and adverse reactions during the anesthesia recovery period were statistically analyzed and observed in the two groups. The indications for extubation were as follows: patients can follow verbal instructions, can open eyes, the tidal volume is more than 300 mL 16–25/min, respiratory rate, and blood oxygen saturation (SpO2) > 95%.

Professional nurses are responsible for recording extubation and recovery time. Postoperative adverse reactions such as nausea, vomiting, chills, and cough were observed by specially assigned person. The indication for extubation implies that patients can follow verbal instructions, and be able to open eyes, with the tidal volume of more than 300 mL and respiratory frequency of 16–25/min. In addition, the blood oxygen saturation (SpO2) is also required more than 95%.

The indicators of inflammatory factors and oxidative stress were measured by training professionals in our hospital at 10 min before induction of anesthesia (T1), 1 h after surgery (T2), 24 h after surgery (T3), 72 h after surgery (T4), and other time points.

Among them, inflammatory factors including plasma C-reactive protein (CRP), IL-8, and IL-4 levels were all detected by enzyme-linked immunosorbent assay (ELISA), and all kits were purchased in Shanghai letter Biological Technology Co., Ltd.

Oxidative stress indexes included plasma malondialdehyde (MDA) and superoxide dismutase (SOD) J. Plasma MDA was determined by thiobarbituric acid colorimetric assay (TBA), and plasma SOD was determined by hydroxylamine method. The kits were purchased from Guangzhou Jian Lun Biotechnology Co., Ltd.

**Ethical consideration**

This study was approved from the institutional ethical review board of Hexi University, Gansu, China. All the experiments were conducted as per Helsinki’s declaration for human volunteers. All subjects gave informed, signed consent to participate in the study by themselves. The reference number is 1009/ERB-HU/2016.

**Statistical analysis**

SPSS 20.0 statistical software was adopted for analysis. Comparison of measurement data between groups was conducted using the variance analysis. The comparison between two groups was analyzed by LSD-t test, and the measurement data were conducted using the chi-square test. Finally, all statistical tests were two-sided probability test with the level of α = 0.05.

**Results**

**Comparison of extubation time and recovery time**

The extubation time and recovery time of sufentanil group were longer than those of remifentanil group, and the difference was statistically significant (P < 0.05), as shown in Table 2.

| Group      | Extubation time (min) | Recovery time (min) |
|------------|-----------------------|---------------------|
| Sufentanil | 23.4 ± 2.3            | 17.2 ± 7.6          |
| Remifentanil | 11.8 ± 2.1            | 9.3 ± 3.8           |

**Comparison of inflammatory factors**

The levels of CRP, IL-8, and IL-4 in sufentanil group and remifentanil group increased continuously at T2, T3, and T4, when compared with T1. In addition, compared with sufentanil group, CRP content at T3 and T4, as well as the IL-8 and IL-4
content at T2, T3, and T4 of remifentanil group was lower (P < 0.05) (Table 3).

Comparison of oxidative stress indexes
Relative to T1, the MDA content of sufentanil group and remifentanil group increased continuously at T2, T3, and T4, while the content of SOD decreased continuously (P < 0.05). Compared with sufentanil group, the MDA content of remifentanil group was lower at T2, T3, and T4, and the SOD content was higher at T3 and T4 (P < 0.05) (Table 4).

Comparison of adverse reactions
Incidence of adverse reactions in sufentanil group was 15.4% (8/52), including three cases of nausea and vomiting, cough in three cases, one case of chill, and tachycardia in one case. Among the remifentanil groups, nausea and vomiting were found in four cases, cough in six cases, chills in four cases, tachycardia in one case, and incidence of adverse reactions was 28.8% (15/52). The incidence of adverse reactions in sufentanil group was significantly lower than that in remifentanil group, and the difference was statistically significant.

Discussion
Laparoscopic radical resection of colorectal cancer is the main surgical treatment for colorectal cancer. The postoperative therapeutic effect is closely related to the choice of anesthetic drugs and methods. Sufentanil and remifentanil are common anesthetic drugs for laparoscopic radical resection of colorectal cancer at present. The target-controlled infusion technique is called targeted intravenous infusion. Target-controlled infusion can effectively control the dosage of narcotic drugs, improve the accuracy of anesthesia, and reduce the pain of patients. In this study, the influence of target-controlled infusion of sufentanil and remifentanil on postoperative recovery in patients who underwent laparoscopic radical resection of colorectal cancer was compared. From these findings, the recovery

Table 3. Comparison of inflammatory factors between two groups (n = 52).

| Index      | Group     | T1 (mg/dL) | T2 (mg/dL) | T3 (mg/dL) | T4 (mg/dL) |
|------------|-----------|------------|------------|------------|------------|
| CRP        | Sufentanil| 0.22 ± 0.17| 0.46 ± 0.15| 0.63 ± 0.28| 0.99 ± 0.27|
|            | Remifentanil| 0.23 ± 0.19| 0.44 ± 0.21| 0.42 ± 0.25| 0.61 ± 0.26|
| T          | Sufentanil| 0.714      | 1.106      | 5.672      | 5.438      |
|            | Remifentanil| >0.05      | >0.05      | <0.05      | <0.05      |
| P          | Sufentanil| >0.05      | >0.05      | <0.05      | <0.05      |
| IL-8 (kU/L)| Sufentanil| 211.64 ± 26.73| 276.41 ± 36.5| 314.07 ± 43.68| 357.95 ± 45.12|
|            | Remifentanil| 209.45 ± 27.85| 244.02 ± 35.2| 285.51 ± 41.03| 308.47 ± 41.55|
| IL-4 (pg/mL)| Sufentanil| 13.15 ± 2.09| 20.18 ± 2.44| 24.09 ± 3.25| 28.07 ± 3.12|
|            | Remifentanil| 13.26 ± 2.13| 17.93 ± 2.08| 19.16 ± 3.01| 21.18 ± 3.45|

Table 4. Comparison of oxidative stress indexes (n = 52).

| Index      | Group     | T1 (mmol/L) | T2 (mmol/L) | T3 (mmol/L) | T4 (mmol/L) |
|------------|-----------|------------|------------|------------|------------|
| MDA        | Sufentanil| 4.14 ± 0.43| 5.02 ± 0.37| 5.91 ± 0.61| 7.23 ± 0.75|
|            | Remifentanil| 4.18 ± 0.45| 4.16 ± 0.43| 5.08 ± 0.54| 5.54 ± 0.37|
| T          | Sufentanil| 0.306      | 5.172      | 7.000      | 6.179      |
|            | Remifentanil| >0.05      | <0.05      | <0.05      | <0.05      |
| P          | Sufentanil| >0.05      | <0.05      | <0.05      | <0.05      |
| SOD        | Sufentanil| 97.43 ± 12.38| 88.54 ± 9.88| 82.75 ± 8.16| 77.41 ± 7.62|
|            | Remifentanil| 98.26 ± 13.02| 89.25 ± 7.64| 86.01 ± 7.96| 83.36 ± 6.83|
| T          | Sufentanil| 0.551      | 1.732      | 5.904      | 6.622      |
|            | Remifentanil| >0.05      | >0.05      | <0.05      | <0.05      |

MDA: malondialdehyde; SOD: superoxide dismutase.
and extubation time of remifentanil group were significantly lower than sufentanil. We can conclude that the recovery and extubation time of remifentanil group were significantly lower than sufentanil group. However, the incidence of adverse reactions was significantly higher than sufentanil group. These results indicate that target-controlled infusion of remifentanil can shorten postoperative recovery time and extubation time, but may increase the risk of postoperative adverse reactions. In contrast, target-controlled infusion of sufentanil may lead to an increase in postoperative recovery time and extubation time, but it is beneficial to reduce the incidence of postoperative adverse reactions. The occurrence of this result should be related to the characteristics of the two anesthetics themselves. Remifentanil has a shorter half-life and faster clearance. At the end of the operation, the patient can recover spontaneously breathing and consciousness at a faster rate, and can pull out the tube as early as possible. While the sufentanil takes a long time, and even after stopping the infusion immediately, it still takes longer to regain consciousness. In addition, compared with the incidence of adverse reactions, the incidence of adverse reactions of remifentanil was higher. This may be related to the hemodynamic instability of remifentanil. Remifentanil is a typical opioid which causes the increase in pain sensitivity in patients, so the adverse reactions are higher. Sufentanil is a strong analgesic drug, and can be used repeatedly; in addition, it does not produce accumulation effect and thereby the impact on the cardiovascular system is weak.7

Anesthesia and surgery can cause intense stress response and in stress stimulation of surgery and tumor; the patients will release a large number of inflammatory factors which have important influence on the therapeutic effect and prognosis of surgery. Previous studies show that the mechanism of systemic inflammatory response caused by surgery is very complex.9 Th1/Th2 index can effectively reflect the overall inflammatory state of the body, and it presents abnormal expression in patients with colon cancer surgery. It is reported that surgery can lead to the release of a large number of proinflammatory cytokines into the blood and the increase in IL-8 content during and after surgery.10 The results of this study suggest that target-controlled infusion of remifentanil anesthesia can reduce the stress response and reduce inflammatory markers in patients who underwent surgery, which is beneficial to the operation effect and postoperative recovery.

It is reported that remifentanil-combined anesthesia can relieve stress reaction in patients who underwent abdominal surgery.11 The results of this study indicate that target-controlled infusion of remifentanil can improve the antioxidant capacity and relieve oxidative stress damage in patients with colon cancer.

As a conclusion, in laparoscopic radical resection of colorectal cancer, the two anesthesia methods have their respective advantages and disadvantages. The target-controlled infusion of remifentanil can effectively reduce postoperative inflammatory cytokines levels and oxidative stress response.

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