Effects of oxycodone on immune function in patients undergoing radical resection of rectal cancer under general anesthesia

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Abstract

This study aims to explore the effect of oxycodone hydrochloride injection on the immune function of patients who underwent radical resection of rectal cancer under general anesthesia. Eighty patients were enrolled and randomly divided into group A and B (n=40, each). All patients underwent general intravenous anesthesia. At the end of surgery, each patient in group A was injected with 5 mg (5 mL) of oxycodone hydrochloride, while 5 mg (5 mL) of morphine hydrochloride in group B. Venous blood was withdrawn in both groups at different time points. Changes in the numbers of T lymphocyte subsets and natural killer (NK) cells were determined by flow cytometry.

First the numbers of T lymphocyte subsets and NK cells at T1, T2, T3, and T4 decreased in both groups, compared with those at T0, and the differences were statistically significant. Furthermore, the numbers reduced to a minimum at T2 and began to recover at T3. Second the differences between group A and B at T1, T2, T3, and T4 were statistically significant; and the numbers of T lymphocytes and NK cells were higher in group A than in group B at corresponding time points.

Oxycodone hydrochloride and morphine hydrochloride both have inhibitory effects on immune function in patients undergoing radical resection of rectal cancer after surgery. However, oxycodone hydrochloride has a smaller effect compared to morphine hydrochloride.

Abbreviations: BP = blood pressure, HR = heart rate, NK = natural killer, PCEA = patient-controlled epidural analgesia, PCA = patient-controlled intravenous analgesia.

Keywords: analgesia, anesthesia, immune function, morphine hydrochloride, oxycodone hydrochloride

1. Introduction

The incidence of rectal cancer has continuously increased recently. Surgery has become the first choice for the radical treatment of early rectal cancer. However, surgical stimulation and anesthesia can affect the immune function of patients. An impaired immune function after surgery will bring harm to the patient such as increased survival rate of the tumor cell microembolus, high rates of recurrence and metastasis, high rates of systemic and wound infections and sepsis, slow healing of wounds, and the waste of medical resources. Furthermore, a good postoperative analgesia is also necessary, which can reduce and prevent a series of stress reactions caused by surgical trauma, and reduce the incidence of postoperative complications.[1] A strong stress reaction can inhibit the immune function of patients. Hence, a good postoperative analgesia is conducive to the rehabilitation of patients, and in shortening the length of hospital stay and reducing cost. This would provide more comfortable humanistic care, reflecting the new concept of comfortable medical treatment. At present, oxycodone is often used for postoperative analgesia. It has a lasting analgesic effect and can effectively reduce analgesic gaps. All commonly used traditional opioid analgesic drugs have effects on immunity to a different extent.[2] Morphine, fentanyl, and other strong opioid drugs have immunosuppressive effects that can reduce T cells and inhibit the secretions of the hypothalamic-pituitary-adrenal/gonadal axes. The equivalent analgesic dose of oxycodone is two-thirds of morphine.[3] At present, it is believed that the excitation of the kappa receptor can produce an analgesic effect and relieve visceral pain. However, it does not cause euphoria, gastrointestinal motility inhibition, and respiratory inhibition, and does not lead to addiction. Oxycodone does not induce histamine release, does not inhibit the parasympathetic nerve, and does not induce bradyrhythmia.[4] At present, oxycodone is the only clinically used U-K dual receptor agonist.[5,6] An ideal drug should have a good postoperative analgesic effect and little influence on immune function. Few studies on the influence of oxycodone on immunity have been reported, at present. After being absorbed, oxycodone distributes in the whole body, and approximately 45% of it binds with plasma protein, and is converted into oxymorphone, noroxycodone, and its glucuronic acid-bound form via the metabolism of the liver.[7]
2. Information and methods

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of our hospital. Written informed consent was obtained from all participants.

2.1. General information

A total of 80 patients who underwent radical resection of rectal cancer under general anesthesia in Zhongshan Hospital Affiliated to Dalian University, China were enrolled into this study. The age of these patients ranged within 40 to 60 years old. Among these patients, 40 patients were male and 40 patients were female. The included patients had anesthesia ASA grade I or II, and Dukes stage A or B. These patients were randomly divided into 2 groups: groups A and B. At the end of the surgery, each patient in group A was injected with 5 mg (5 mL) of oxycodone hydrochloride, while each patient in group B was injected with 5 mg (5 mL) of morphine hydrochloride. All patients had normal liver function, had no endocrine, immune, and circulatory system diseases, did not receive blood transfusion during the perioperative period, and did not take steroid hormones and opioids. Differences in body weight, age, ASA grade, gender, and operation time between these 2 groups were not statistically significant (Table 1).

2.2. Anesthesia protocol

Thirty minutes before entering the operation room, 3 mg of midazolam was intramuscularly injected. Patients in both groups underwent total intravenous anesthesia. Induction: 0.1 to 0.2 mg/kg of midazolam, 0.5 to 1 μg/kg of sufentanil, 0.2 to 0.3 mg/kg of etomidate, and 0.2 to 0.3 mg/kg of cisatracurium besilate. Maintenance: 4 to 6 mg/(kg·h) of propofol, 0.2 to 0.8 μg/(kg·min) of remifentanil, and 0.15 to 0.3 mg/(kg·h) of cisatracurium besilate. After 5 minutes of assisted ventilation, which began at the onset of the muscle relaxation effect of cisatracurium besilate, tracheal intubation was conducted using a steel-reinforced tracheal tube. Different types of tracheal tubes were chosen according to the situation of the patients. Tidal volume was set at 8 to 10 mL/kg, respiratory rate was set at 13 to 15 times/min, and inspiratory-to-expiratory ratio was set at 1:2. Respiration was controlled using a breathing machine. In the operation, the depth of anesthesia was adjusted according to the surgical stimulation, and the circulatory system was kept stable. At the end of the surgery, each patient in group A was injected with 5 mg (5 mL) of oxycodone hydrochloride, while each patient in group B was injected with 5 mg (5 mL) of morphine hydrochloride.

2.3. Observation indexes

Five time points were set for each group: before injection (T0), 0.5 hours after injection (T1), 6 hours after injection (T2), 12 hours after injection (T3), and 24 hours after injection (T4). Vital signs, heart rate (HR), blood pressure (BP), respiration (R), body temperature (T), and blood oxygen saturation (SpO2) at each time point were observed. At each time point, 2 mL of peripheral venous blood was collected using a vacuum tube with heparin (for anticoagulation), and the percentages of CD4, CD8 positive cells, and natural killer (NK) cells were detected by flow cytometry.

2.4. Statistics processing

All measurement data were statistically analyzed using SPSS 19.0 statistical software. Changes in T lymphocyte subsets and NK cells, as well as other measurement data, were expressed as mean ± standard deviation. Data were evaluated using independent sample t test and analysis of variance. P < .05 was considered statistically significant.

3. Results

Vital signs of patients in the 2 groups: mean blood loss during the operation was 301 ± 40 mL in group A and 296 ± 38 mL in group B, and the difference between these 2 groups was not statistically significant (P > .05). The results of the observations revealed that the BP, HR, R, T, and SpO2 in the 2 groups did not undergo significant changes during the process of anesthesia and perioperative period (P > .05). Changes in the percentages of CD4, CD8 positive cells, and NK cells. First the number of T lymphocyte subsets and NK cells at T1, T2, T3, and T4 decreased in both groups, compared with those at T0; and the differences were statistically significant. Furthermore, these numbers reduced to a minimum at T2, and began to recover at T3. In both groups, the differences between T1 and T2 were statistically significant (P < .05), the differences between T1 and T3 were statistically significant (P < .05), the differences between T1 and T4 were statistically significant (P < .05), the differences between T2 and T3 were statistically significant (P < .05), the differences between T2 and T4 were statistically significant (P < .05), and the differences between T3 and T4 were statistically significant (P < .05). Second the differences between group A and B at T1 (P < .05), T2 (P < .05), T3 (P < .05), and T4 (P < .05) were all statistically significant; and the number of T lymphocytes and NK cells were higher in group A than those in group B at corresponding time points. However, the differences in various indices between groups A and B at T0 were not statistically significant (P > .05, details are shown in Table 2).

4. Discussion

According to the activation stage, T cells can be divided into initial T cells, effector T cells, and memory T cells. Furthermore, according to the expression of CD4 or CD8 molecules, T cells can be generally divided into CD4+ T cells and CD8+ T cells. Th0 cells can further differentiate into different subsets such as Th1 cells, Th2 cells, Th3 cells, and Th17 cells, etc. The effect of Th1 cells is mainly to enhance the
antinfection immunity mediated by phagocytes, in particular, the resistance to intracellular pathogen infections. The effect of Th2 cells is mainly to promote and induce humoral immune response mediated by B cells, and the cytokines secreted by these cells can promote the proliferation and differentiation of B cells and antibody production. CD8+ T cells are mainly killer T cells, and their main function is to specifically and directly kill target cells. NK cells are the primary immune cells for antitumor defense in the body. This kind of cells can directly kill virus-infected cells and some tumor cells without antigen sensitization. Therefore, it plays an important role in the immune response of antitumor, antintracellular parasite infection, and antivirus in the body. Thus, it has a broad spectrum function of killing tumor cells. Kondo et al revealed that the number of NK or T cells and the function of NK or T cells before operation with important significance for predicting the proliferation and metastasis about tumor cells at postoperative intestinal cancer. Therefore, the number of CD4, CD8 positive cells, and NK cells can reflect the immune function level of the body. Oxycodone belongs to the U-K dual receptor agonist.

Opioids are undoubtedly the most commonly used and most effective drugs for the treatment of intraoperative and postoperative acute pains. The pharmacologies of opioid agonists mainly include analgesia, antitussive effect, respiratory depression, constipation induction, antiaxiety, euphoria, etc. Compared with nonsteroidal antiinflammatory drugs, opioid agonists have no risk of gastrointestinal bleeding, and its analgesic effect does not have the “ceiling effect.” However, a number of studies have revealed that the effects of many opioid analgesic drugs on immune function are inhibitory such as fentanyl, sufentanil, and morphine. These drugs often impair the immune function of patients and people often ignore these due to the absence of obvious clinical symptoms. However, many scholars have also observed that opioid drugs increase the susceptibility of the body, and promote and accelerate the spread of cancer cells.

Furthermore, the application of its receptor antagonist, nalme-fene, can improve the survival rate of bacteria. For postoperative patients, poor control of pains can also lead to the inhibition of immune function. Therefore, the balance between opioid drug dosage and pain control should be considered when patients undergo analgesia using opioid drugs after surgery.

In addition, many studies have explored the effects of opioid drugs in different administration routes on immune function. Belin et al revealed that the following 3 methods of analgesia had an effect on immune function in patients after abdominal surgery: patient-controlled intravenous analgesia (PCA) with morphine, intermittent opiate regimen with morphine, and patient-controlled epidural analgesia (PCEA) with local anesthetics and opioid drugs. At 24 hours after surgery, lymphocyte mitogen responses were inhibited in patients in all 3 groups. At 72 hours after surgery, lymphocyte mitogen responses were still in an inhibited state in patients in the PCIA group, and recovered to preoperative level in the PCEA group. Furthermore, IL-1 and IL-6 levels significantly increased in the intermittent opiate regimen and PCIA groups, but these did not change in the PCEA group. In addition, Volk et al reported that the effects of morphine PCIA and sufentanil plus ropivacaine PCEA on immune function were observed in patients after spinal surgery. Compared with PCIA, PCEA maintained a good lymphocyte function, thus, protecting specific immune function. In addition, Yokota et al reported that the effect of 0.5 and 0.1 mg of morphine (subarachnoid space administration), anesthetics (inhalation), and 10 mg of morphine (intravenous injection) were observed on NK cell function in 40 patients. These results revealed that the function of NK cells was significantly lower in patients with a subarachnoid space administration of 0.5 mg of morphine at 24 hours after surgery, compared that before surgery; and this did not significantly change in patients in other 3 groups. However, at 2 and 24 hours after surgery, the visual analogue scale was the lowest in patients who had taken 0.5 mg of morphine. Sacerdote et al reported that the effects of morphine and tramadol on immune function in 30 patients who underwent abdominal uterine tumor surgery were observed. Before and after surgery, as well as at 2 hours after intramuscular injection of tramadol or morphine, the activity of NK cells and lymphocyte proliferation stimulated by phytohemagglutinin were observed. Results revealed that the surgery significantly inhibited phytohemagglutinin-stimulated lymphocyte proliferation in all patients, and at 2 hours after treatment. This proliferation recovered to the preoperative basic value in patients who receiving tramadol treatment, and the proliferation remained lower than that in the preoperative basic value in patients who receiving morphine treatment. Surgery and morphine did not affect NK cell activity, but tramadol could enhance NK cell activity. The improvement degree of postoperative analgesics was evaluated by the numerical rating scale. Different degrees of pain were represented by 0 to 10 numbers. We should ask patients about the degrees of pain, make a marker, or let the patient himself write a number that would mostly be able to represent the degree of pain. This method has been commonly used in clinic, at present. Points are defined as follows: 0 point represents painless, 1 to 3 points represent mild pain (that does not affect sleep), 4 to 6 points represent moderate pain, 7 to 9 points represent severe pain (in which patients cannot sleep or wake up in sleep), and 10 points represents sharp pain. The ideal postoperative analgesic effect should be that the score is controlled at ≤3 points. Oxycodone is commonly used in postoperative analgesia, at present; and its side effects have been a research hotspot for many scholars.
refers to a series of physiological and pathological reactions caused by the stimulation of the disease and the surgical trauma in the body. It manifests as a series of reactions and an unpleasant emotional experience in the mind and behavior. Furthermore, pain has become the 5th vital sign following HR, BP, R, and T.\[2\]

Pain is extremely unfavorable to the postoperative recovery of patients. Pain control is one of the key factors that influence the postoperative recovery speed of patients. With the continuous deepening of the reform for the national health system, and the continuous increase in the public health needs, the requirements of improvement on medical quality, and the reduction of medical costs are increasingly urgent.\[27\] A number of hospitals are actively advocated a painless medicine and comfortable care. The idea of enhanced recovery after surgery, which was derived from Europe more than 10 years ago and currently has been popularized and applied in the world, is in accordance with historical trends. It is a new idea for clinical surgery,\[28\] which is based on the evidence of evidence-based medicine, adopts multimode strategy, optimizes perioperative treatment measures, decreases perioperative stress of surgical patients, and finally accelerates and improves the postoperative recovery speed of surgical patients.\[29\] The enhanced recovery after surgery idea accelerates and improves the postoperative recovery speed of measures; hence, accelerating the postoperative rehabilitation of patients. A drug that can exert a good analgesic function have not been fully understood at home and abroad.\[31\] require. However, the effects of oxycodone on immune urgently required. Oxycodone hydrochloride can fully meet this requirement. Therefore, the effects of oxycodone on immune function have not been fully understood at home and abroad.\[31\]

5. Conclusion
Oxycodone hydrochloride injection and morphine hydrochloride injection both have inhibitory effects on immune function in patients undergoing radical resection of rectal cancer after surgery. However, oxycodone hydrochloride has a lower effect compared to morphine hydrochloride. This has the greatest inhibitory effect on the immune function in patients at 6 hours after the injection, and the immune function begins to recover 6 hours after injection. Therefore, oxycodone is a relative ideal postoperative analgesic drug in clinic, which has small side effects.

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