Effect of dexmedetomidine combined with oxycodone patient-controlled intravenous analgesia on the levels of inflammatory cytokine in patients with rectal cancer

Junnian Song[1], Na Wei[1], Jing Zhang[1] and *Gang Wang[2]
[1]First Operating Room, the First Hospital of Jilin University, Changchun, PR China
[2]Second Operating Room, the First Hospital of Jilin University, Changchun, PR China

Abstract: This study was designed to discuss the clinical effects of dexmedetomidine combined with oxycodone patient-controlled intravenous analgesia for patients with laparoscopic radical resection of rectal cancer. A total of 90 patients with rectal cancer undergoing laparoscopic radical resection surgery were selected. The patients were divided into A, B and C group using a random number table method, 30 cases in each group. Patients in group A received oxycodone (O) alone postoperatively; patients in group B received dexmedetomidine combined with oxycodone (DO) postoperatively; and patients in group C received dexmedetomidine (D) alone postoperatively. The Visual Analog Scale (VAS) score and Ramsay sedative score at 2h, 6h, 24h and 48h after surgery were evaluated, and the effective compressions number of controlled intravenous analgesia (CIA) was recorded. The occurrence of side effects including fever, nausea, vomiting, drowsiness, dizziness, itchy skin, respiratory depression and other adverse reactions were noted. CRP, TNF-α, and IL-6 were detected by ELISA prior to surgery and on the morning of the 1st and the 3rd day after surgery, respectively. VAS scores in group B were lower than group A and C, the effective compressions number of CIA in group B was less than group A and C, the incidence of adverse reactions in group B was lower than group A and group C. The levels of CRP, TNF-α and IL-6 at 72h after surgery in group B were lower than group A and C. Dexmedetomidine combined with oxycodone has better sedative and analgesic effects with less adverse reactions, it can reduce the release of inflammatory cytokines of CRP, TNF-α and IL-6 in the body and has certain clinical application value.

Keyword: Dexmedetomidin, oxycodone, radical resection.

INTRODUCTION

Compared with common laparoscopic surgery, laparoscopic resection of rectal cancer has the characteristics of large incision, long operation time, and large intra-abdominal organ interference. The postoperative pain in patients not only included the incision pain, but also included severe visceral pain caused by the pulling organs. Some patients were older, and the central nervous system was vulnerable to over excitation caused by noxious stimulation. The malleability of the damage information processing system is reduced, and the time required for functional repair of tissue damage is prolonged (Gatti *et al.*, 2011; Yan, 2014). Moreover, the pain-transmitting fibers and the receptors for painful substances in the elderly are significantly altered, making them more sensitive to drugs (Friedman *et al.*, 2015). Postoperative pain seriously affects the patient's mood and causes irritability, anxiety, oversensitivity, and even mental disorder and behavioral changes. Therefore, for the patient to choose the appropriate analgesic measures to achieve satisfactory results, not only can reduce the patient's pain and early rehabilitation training, but also improve the quality of life of patients and promote postoperative recovery. Clinical application studies have shown that patients prefer intravenous patient-controlled analgesia compared to traditional regimens. It is generally accepted that intravenous PCA provides better analgesia than other opioid analgesic regimens. A better analgesic effect can be obtained by applying multimodal analgesia (Gottlieb & Njie, 2016; Carpenter, 2016). This study was to investigate the clinical effect of oxymetholone hydrochloride injection combined with dexmedetomidine on postoperative analgesic effect of laparoscopic radical resection of rectal cancer, and its effect on the levels of inflammatory cytokine in patients with rectal cancer, providing the reference for promoting the postoperative analgesia of patients with rectal cancer.

*Corresponding author: e-mail: unknc537@aliyun.com

MATERIALS AND METHODS

Clinical data

A total of 90 patients (American Society of Anesthesiologists class 1 or 2, 40-75 years old) with rectal cancer undergoing laparoscopic radical resection surgery for rectal cancer in the First Hospital of Jilin University from June 2014 to December 2016 were selected. The patients were divided into A, B and C group using a random number table method, 30 cases in each group. Patients in group A received oxycodone (O) alone postoperatively; patients in group B received dexmedetomidine combined with oxycodone (DO) postoperatively and patients in group C received

dexmedetomidine (D) alone postoperatively. All patients underwent laparoscopic radical surgery for rectal cancer. The surgery was led by experienced clinicians in our hospital and informed consent was signed.

Exclusion criteria

Preoperative cognitive impairment or a history of schizophrenia; severe history of hypertension, ischemic heart disease and heart block; liver and kidney function was not complete; taking antidepressants, sedatives and analgesics recently; patients had a history of anaphylaxis; patients had a history of drug addiction and long-term use of opioids or antipsychotic drugs.

Methodology

The venous access was obtained in all patients. Both anesthesia and induction were conducted with propofol plus remifentanil. The anesthesia induction and intraoperative maintenance were 3-5mg/L and 4-8ng/ml, respectively. When unconsciousness was induced then, flucuronium 0.15 mg/kg was administered intravenously and assisted respiration with mechanical ventilation was applied. The target concentrations of propofol and remifentanil were adjusted according to the situation during the surgery. Cisatracurium was used to maintain muscle relaxation, maintaining the bispectral index (BIS) value between 40~60. The muscle relaxant was stopped half an hour before the end of the operation, and the intravenous anesthesia was stopped according to the surgical situation. Prior to extubation, if needed, neostigmine 1 mg + atropine 0.5 mg were used to antagonize the effects of muscle relaxants. Atropine was administered intravenously to treat low heart rate, and vasopressor was administered to treat low mean arterial pressure. All patients underwent central venipuncture and invasive brachial artery manometry. Intraoperative monitoring included electrocardiogram (ECG), blood pressure (BP), heart rate (HR), pulse oxygen saturation (SpO2), partial pressure of carbon dioxide at end-tidal (PetCO2) and BIS. All three groups used patient-controlled intravenous analgesia (PCIA) pumps. The oxycodone group was given 50 mg oxycodone and diluted in 100 ml normal saline; the dexmedetomidine combined oxycodone group was given the dose of dexmedetomidine 2.5μg/kg + oxycodone 50 mg, diluted in 100ml normal saline. The parameters for the postoperative analgesia pump were as follows: continuous background infusion dose of 1 ml/h, single press dose of 2 ml, locking time of 15 minutes. It was recommended to press an analgesic pump first when the patients felt pain, and if it was not effective, 50mg of pethidine was given intramuscularly as the rescue analgesia. After 48 hours of postoperative analgesic pump removal, patients were evaluated for their satisfaction with pain control.

Measured indexes

Mean arterial pressure (MAP), heart rate (HR) and SPO2 at different time points: before extubation (T1); extubate (T2); reach PACU (T3); 1 day postoperatively (T4); and 2 days postoperatively (T5) were recorded. Visual Analog Scale (VAS) score, Ramsay sedation score and the effective compressions number of CIA at 4h, 6h, 24h, and 48h after surgery were evaluated. The occurrence of side effects including fever, nausea, vomiting, drowsiness, dizziness, itchy skin, respiratory depression and other adverse reactions were noted. Inflammatory cytokines CRP, TNF-α, and IL-6 were detected by ELISA on the day before surgery and on the morning of the 1st and 2nd day after operation, respectively.

Ethical approval

The ethical approval of this study was given by the institutional ethical committee of Jilin University, Changchun, PR China. The reference No. 765/IRB/JU/2014.

STATISTICAL ANALYSIS

SPSS 19.0 statistical software was used for data analysis. Measured data were expressed as mean ± standard deviatio, t test was used for comparison of independent samples between three groups, the analysis of variance of repeated measures design was used for comparison of two groups of multiple time points, the LSD method of variance analysis was used for comparison between groups. Pair wise t-test was used to compare pairs of two time points, and corrected the inspection level. $P<0.05$ was considered statistically significant.

RESULTS

Comparison of general information of three groups of patients

table 1 shows that there was no significant difference in clinical data such as age, weight, height, anesthesia time, and operation time between the three groups, and the clinical data are comparable ($P>0.05$).

Postoperative VAS score of patients

The VAS score of group B was lower than that of group A and group C ($P<0.05$). There was no statistical difference between group A and group C ($P>0.05$). (table 2)

Ramsay sedative score of patients at different time points

There was no significant difference in Ramsay sedative score among the three groups ($P>0.05$) as shown in table 3.

Comparison of the effective compressions number of CIA

The effective compressions number of CIA in group B was lower than that in group A and group C ($P<0.05$). There was no statistical difference between group A and group C ($P>0.05$), and no invalid compression times were recorded. The data is presented in table 4.

Table 1: General information of three groups of patients（n=30）

Group	A	B	C
Age	62.±8.9	63.1±8.5	62.3±6.9
Weight	68.1±8.3	65.1±8.9	67.1±8.2
Height	166.5±8.0	167.5±6.9	168.5±6.1
Anesthesia time	202.8±20.3	214.2±24.3	218.4±21.6
Operation time	178.4±16.5	181.6±18.6	186.3±20.3

Table 2: Postoperative VAS score of patients in all three groups

Group	Postoperative 2h	Postoperative 6h	Postoperative 24h	Postoperative 48h
A	4.2±0.9	3.6±0.6	2.6±0.6	2.3±0.3
B	3.4±0.6	2.8±0.4	1.9±0.3	1.4±0.2
C	4.5±0.8	3.9±0.7	2.8±0.5	2.5±0.4

Table 3: Ramsay sedative score of patients after operation

Group	Postoperative 2h	Postoperative 6h	Postoperative 24h	Postoperative 48h
A	2.25±0.46	2.12±0.37	2.01±0.28	1.94±0.16
B	2.15±0.37	2.08±0.27	1.98±0.24	1.86±0.18
C	2.32±0.41	2.21±0.31	2.08±0.31	2.01±0.27

Table 4: Comparison of the effective compressions number of CIA between the three groups

Group	A	B	C
the effective compressions number of CIA	24±4	14±1	29±5

Table 5: The occurrence of adverse reactions

Group	Headache	Nausea	Fever	Dizziness	Itchy skin	Drowsiness
A	3	12	2	5	5	3
B	2	6	1	2	2	1
C	3	8	1	4	1	2

Table 6: The levels of inflammatory cytokine of patients after surgery

Group	A	B	C
Preoperative			
CRP	12.46±2.01	11.51±1.86	13.2±2.05
TNF-α	2.48±0.19	2.63±0.51	2.52±0.35
IL-6	17.23±2.67	16.42±1.61	15.36±2.01
postoperative 24h			
CRP	32.58±3.67	29.42±2.94	30.24±3.03
TNF-α	4.31±0.67	4.01±0.54	4.24±0.82
IL-6	31.82±9.45	30.46±8.92	32.04±7.96
postoperative 72h			
CRP	28.37±3.26	21.04±2.75	26.45±2.96
TNF-α	3.97±0.59	2.86±0.37	3.46±0.51
IL-6	27.82±7.89	19.34±3.63	21.45±4.01

The occurrence of adverse reactions

The number of adverse reactions in group B was lower than that in group A and group C ($P<0.05$). There was no statistical difference between group A and group C ($P>0.05$) as shown in table 5.

The levels of inflammatory cytokine in patients with different groups

There was no significant difference in the levels of inflammatory cytokine between the three groups before surgery ($P>0.05$). Within 24 hours after operation, the

levels of CRP, TNF-α and IL-6 in group B were lower than those in group A and C, but there were no statistical differences (P>0.05). Within 72 hours after operation, CRP, TNF-α and IL-6 in group B were lower than those in group A and C (P<0.05). The data is presented in table 6.

DISCUSSION

Laparoscopic colorectal cancer technology has been applied in the treatment of colorectal cancer because of its advantages of less trauma, higher safety, radical tumor and rapid postoperative recovery. In addition, because of the wide range of operations involved in radical resection of colorectal cancer, the involvement of innervation is complex, and acute pain including incision pain and visceral pain may occur early in the postoperative period (Hartley *et al*., 2000). Therefore, laparoscopic radical resection for colorectal cancer requires postoperative anesthesia for sedation. In order to achieve ideal analgesia, multimodal analgesia is currently advocated in the clinical, through the combination of analgesic drugs with different mechanisms of action or various analgesic methods to control pain. It can reduce the effects of pain and drugs on nerves, immunity, and endocrine system, maintain the internal environment relatively stable, and reduce complications. At present, the most commonly used postoperative analgesic methods are mainly the following two: continuous epidural patient-controlled analgesia (PCEA) and intravenous patient-controlled analgesia (PCIA), but there is no uniform provision for the current specific requirements (Hartley *et al.,* 2000). Therefore, PCEA and PCIA have similar analgesic effects, but PCEA is prone to a series of side effects such as puncture sites, infections, and catheter breakage, which limits its clinical application. PCIA has a definite analgesic effect with few adverse reactions and is currently widely used in clinical applications (Lazzari *et al.,* 2014). Opioids are still widely used as postoperative analgesic drugs. However, most of the traditional opioids are μ receptor agonists, although the analgesic effect is definite, but the large gastrointestinal side effects are not conducive to the recovery of postoperative gastrointestinal function, and their treatment of distracted visceral pain and neuropathic pain is less effective. Elderly patients have increased drug sensitivity and are prone to a series of adverse reactions such as gastrointestinal dysfunction, respiratory depression, and drowsiness (Lee *et al.,* 2016). For rectal cancer patients, how to choose an analgesic method with good analgesia and less adverse reactions requires further exploration.

Oxycodone is an opioid central nerve analgesic synthesized from an alkaloid thebaine extract, which mainly agonizes the K receptor, and also has an agonistic effect on the κ receptor. Therefore, it is considered that oxycodone has a better curative effect on visceral pain than a single u receptor agonist. Oxycodone has the characteristics of high bioavailability, good analgesic effect and small adverse reaction, its peak time is 5 minutes and has long duration of drug efficacy. It is mainly used for the treatment of moderate to severe pain in clinical and has an equivalent analgesic effect with morphine (King *et al.,* 2011). Oxycodone has curative effect on incision pain and visceral pain and slight inhibition of gastrointestinal function. It is especially suitable for gastrointestinal surgery. It has a rapid onset of action and is light on immunosuppression, which is conducive to rehabilitation in the elderly (Toshiaki *et al.,* 2013). Dexmedetomidine hydrochloride is a highly selective α 2 receptor agonist, mainly acting on the locus coeruleus and adrenergic receptors in the spinal cord. It has the effects of sedation, pain-suppressing inflammatory response, myocardial protection, and alleviation of cognitive dysfunction. It can effectively inhibit inflammatory reactions and inflammatory cytokines release, and it is more beneficial to patients' postoperative recovery however, its sedative effect is weak and needs to be combined with opioids (Koizumi *et al.,* 2014). Dexmedetomidine can selectively activate the locus coeruleus and peripheral α2 receptors of the central nervous system, reduce the activity of the sympathetic nervous system, reduce the sensitivity of stress response, and is more conducive to the maintenance of hemodynamic stability (Mo & Zimmermann, 2013). The results of this study also showed that CRP, TNF-α, and IL-6 in group B were lower than those in group A and C (P<0.05) within 72 days after operation, indicating that dexmedetomidine combined with oxycodone can reduce the body's stress response and inhibit the release of inflammatory cytokines in patients. Clinical studies have confirmed that oxycodone combined with dexmedetomidine hydrochloride have no significant effect on the time of postoperative evacuation, indicating that there is no significant effect on the patient's gastrointestinal function, and clinical application is relatively safe (Fujita *et al.,* 2013).

From the perspective of clinical application, the use of oxycodone and dexmedetomidine hydrochloride decreased the dosage of oxycodone and dexmedetomidine in patients, but the patient's VSA score and the effective compressions number of CIA were reduced. The Ramsay sedative score was not significantly reduced, indicating that oxycodone and dexmedetomidine have good analgesic effects and can achieve satisfactory sedation in patients with rectal cancer. We speculate that the patient's good analgesic effect can also promote the patient's early exercise and functional exercise, promote rapid recovery of gastrointestinal function in patients, and further reduce the release of inflammatory cytokines in patients.

By comparing the occurrence of adverse reactions after surgery, the incidence of nausea and dizziness in dexmedetomidine combined with oxycodone group was

higher than that in dexmedetomidine and oxycodone group, and there was no difference in the incidence of other adverse reactions. This result suggests that with the increase of oxycodone dose, the incidence of nausea, vomiting and dizziness increased, and all patients in the three groups did not experience respiratory depression, indicating that the side effects of dexmedetomidine combined with oxycodone were relatively small. This combination could not only improve the analgesic effects, but also reduce the dosage of drugs, thereby reducing the occurrence of adverse reactions, especially for postoperative analgesia in elderly patients with rectal cancer.

This study only preliminary explored the use of dexmedetomidine combined with oxycodone in patients with rectal cancer. However, the dose and ratio of dexmedetomidine combined with oxycodone are not yet known and their effects on hemodynamics and the metabolic mechanism in patients are not yet clear, and its difference in efficacy for patients of different ages is unclear and needs further research to confirm.

CONCLUSION

In conclusion, Dexmedetomidine combined with oxycodone has better sedative and analgesic effects, less adverse reactions, and can reduce the release of inflammatory cytokines of CRP, TNF-α and IL-6 in the body and has certain clinical application value.

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