

# Analysis of Optimizing Effects of Dexmedetomidine and Oxycodone on Cytokine Levels in Patients with Laparoscopic Radical Gastrectomy

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**Liu *et al.*: Analysis of optimizing effects of dexmedetomidine and oxycodone on cytokine**

**This study was designed to analyze the effects of dexmedetomidine combined with oxycodone in patients underwent laparoscopic radical gastrectomy for stomach carcinomas. A total of one hundred and twenty (120) patients were recruited and divided into A, B and C groups, using a random number table method,**

**40 cases in each group. After surgery patients in group A received oxycodone alone, patients in group B received dexmedetomidine combined with oxycodone and patients in group C received dexmedetomidine alone respectively. The Visual Analog Scale score and Ramsay sedative score at 2h, 6h, 24h and 48h after surgery were observed and the effective compressions number of controlled intravenous analgesia was documented. The incidence of side effects was recorded. TNF- $\alpha$ , CRP and IL-6 were evaluated by enzyme-linked immunosorbent assay on the day before surgery and in the morning of 1<sup>st</sup> and 3<sup>rd</sup> d after surgery. 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 occurrence of adverse reactions in group B was lower than group A and group C. The postoperative levels of TNF- $\alpha$ , CRP and IL-6 at 72h in group B were lower than group A and C. Dexmedetomidine combined with oxycodone showed improve sedative and analgesic effects with fewer adverse reactions. It can lessen the release of inflammatory cytokines of TNF- $\alpha$ , CRP and IL-6 in the body and has certain clinical application value**

**Key words: Dexmedetomidin, oxycodone, gastrectomy, analgesia, inflammatory factor**

Previous study reported that nearly one million cases of gastric carcinoma diagnosed annually worldwide<sup>[1,2]</sup>. With advancement in medical field, laparoscopic-assisted gastrectomy (LAG) has become the standard treatment for early gastric cancer<sup>[3]</sup>. In spite of various advantages, laparoscopic resection of gastric carcinoma has the characteristics of long operation time, large incision and large intra-abdominal organ interference. After surgery the patient experiences sever pain, so advanced techniques are required to perform lymph-node dissection along the splenic artery as well as reconstruction by esophagojejunostomy<sup>[4]</sup>. The flexibility of the damage information processing system is reduced, and the time required for functional repair of tissue damage is prolonged<sup>[5,6]</sup>. The patient's mood is seriously affected by Postoperative pain which causes oversensitivity, irritability, anxiety, behavioral changes even mental disorder. Therefore to improve the quality of life of patients and postoperative recovery, the choice of appropriate analgesic measures should be given a prime importance as it can reduce the patient's pain and give early rehabilitation training. It has been reported by previous clinical studies that patients prefer intravenous pain controlled analgesia as compare to traditional dosage form. It is mostly believed that intravenous PCA offers better analgesia than other opioid analgesic regimens. An enhanced analgesic effect can be attained by applying multimodal analgesia<sup>[5-6]</sup>. The aim of this study was to evaluate the clinical effect of dexmedetomidine combined with oxycodone injection on postoperative analgesic effect of laparoscopic radical resection of gastrectomy, and its effect on the inflammatory cytokine's levels in patients with gastric cancer. A total of 120 patients (American Society of Anesthesiologists class 1 or 2, 45-75 y old)

with gastric cancer were recruited, undergoing laparoscopic radical resection surgery for gastric cancer in Jinan Third People's Hospital, Shandong China, from June 2015 to December 2017. The patients were divided into groups according to random number table method as A, B and C groups, 40 cases in each group. Postoperatively; group A patients received oxycodone (O) alone, patients in group B were given dexmedetomidine combined with oxycodone (DO) and dexmedetomidine (D) alone was given to group C patients. All patients included in the study went through laparoscopic radical gastrectomy. Experienced clinicians headed all surgical procedures in our hospital and duly signed informed consent. A history of schizophrenia or preoperative cognitive impairment; severe history of hypertension, ischemic heart disease and heart block; liver and renal dysfunction; using analgesics, sedatives and antidepressants recently; patients had a history of anaphylaxis; patients had a history of drug addiction and long-term use of opioids or antipsychotic drugs. In all patients, venous access was obtained. Propofol plus remifentanyl was used for anesthesia and induction. The maintenance of anesthesia induction and intraoperative were 3-5 mg/l and 4-8 ng/ml, respectively. Flucuronium 0.15 mg/kg was administered intravenously. After the disappearance of consciousness, the mechanical ventilation was applied to assist respiration. During the surgery, according to the situation the target concentrations of propofol and

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remifentanyl were adjusted. Muscles were relaxed by using Cisatracurium and maintained the BIS value between 40~60. The muscle relaxant was stopped half an hour before the end of the operation. According to the surgical situation, intravenous anesthesia was stopped. If needed, the effect of muscle relaxants was antagonized prior to extubation by using neostigmine 1 mg + atropine 0.5 mg. in case of low heart rate, Atropine was administered intravenously and low mean arterial pressure was treated by administration of vasopressor. All patients go through invasive brachial artery manometry and central venipuncture. Intraoperative monitoring involved blood pressure (BP), heart rate (HR), electrocardiogram (ECG), partial pressure of carbon dioxide at end-tidal (PetCO<sub>2</sub>), pulse oxygen saturation (SpO<sub>2</sub>), and bispectral index (BIS). Patient-controlled intravenous analgesia (PCIA) pumps were used for all three groups. 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 2.5 µg/kg + oxycodone 50 mg, diluted in 100ml normal saline. The parameters used for the postoperative analgesia pump included: continuous background infusion dose of 1 ml/h, single press dose of 2 ml, locking time of 15 minutes. It was recommended that when the patients felt pain then presses an analgesic pump first and pethidine (50mg) was given intramuscularly as the analgesia rescue if analgesic pump was not effective. Patients were evaluated, after 48 h of postoperative analgesic pump removal for their satisfaction with pain control. Heart rate (HR), Mean arterial pressure (MAP),

and SPO<sub>2</sub> were recorded at different time points: before extubation (T1); extubate (T2); reach PACU (T3); 1 d postoperatively (T4); and 2 d postoperatively (T5). Ramsay sedation score, Visual Analog Scale (VAS) score and the effective compressions number of CIA at 4h, 6h, 24h, and 48h were evaluated postoperatively. The incidence of side effects comprising nausea, vomiting, fever, dizziness, drowsiness, respiratory depression, itchy skin, and other adverse reactions were observed. Inflammatory cytokines CRP, TNF- $\alpha$ , and IL-6 were evaluated by ELISA on the day before surgery and on the morning of the 1st and 2nd d after surgery, respectively. Data was analyzed statistically by using SPSS 19.0 statistical software. Categorical variables were presented as numbers and percentages, and they were analyzed by pearson's chi-squared test ( $\chi^2$ ). Continuous and categorical variables were reported as means and standard deviations ( $\bar{x}\pm s$ ), independent samples between three groups were compared by using t test, the analysis of variance of repeated measures design was used for comparison of two groups of multiple time points, and the comparison between groups was done by using LSD method of variance analysis. Pairwise t-test was used to compare pairs of two time points, and corrected the inspection level. 5% p value ( $p < 0.05$ ) was considered statistically significant. This study was approved from the institutional ethical review board of Jinan Third People's Hospital, Shandong, China. The Reference No. is 1022-JPH/2015. The hospital protocols and Helsinki's declaration were followed during the study. Table 1 indicated that clinical data showed no significant difference such as in age, height, weight, anesthesia time, and operation time between the three groups, and the clinical data are comparable ( $p = 0.086$ ). The VAS score of group A and group C ( $p = 0.02$ ) was same, while score of group B was lower than both groups A and C. Table 2 showed that no statistical difference was exist between group A and group C ( $p = 0.073$ ). Ramsay

**TABLE 1: GENERAL INFORMATION OF THREE GROUPS OF PATIENTS (N=30)**

Group	A	B	C
Age	61.2 $\pm$ 8.7	63.1 $\pm$ 8.4	64.2 $\pm$ 6.8
Height	165.5 $\pm$ 7.0	166.5 $\pm$ 6.8	167.5 $\pm$ 6.0
Weight	69.3 $\pm$ 8.2	66.1 $\pm$ 8.7	65.2 $\pm$ 8.1
Anesthesia time	203.7 $\pm$ 20.1	212.1 $\pm$ 24.4	217.2 $\pm$ 21.5
Operation time	180.4 $\pm$ 15.5	183.4 $\pm$ 16.6	189.2 $\pm$ 18.3

**TABLE 2: POSTOPERATIVE VAS SCORE OF PATIENTS**

Group	Postoperative 2h	Postoperative 6h	Postoperative 24h	Postoperative 48h
A	4.3 $\pm$ 0.8	3.5 $\pm$ 0.5	2.5 $\pm$ 0.5	2.4 $\pm$ 0.4
B	3.5 $\pm$ 0.6	2.7 $\pm$ 0.4	1.7 $\pm$ 0.3	1.6 $\pm$ 0.2
C	4.4 $\pm$ 0.7	3.8 $\pm$ 0.6	2.7 $\pm$ 0.4	2.6 $\pm$ 0.5

Ramsay sedative score at different time points

**TABLE 3: RAMSAY SEDATIVE SCORE OF PATIENTS AFTER OPERATION**

Group	Postoperative 2h	Postoperative 6h	Postoperative 24h	Postoperative 48h
A	2.22 $\pm$ 0.40	2.10 $\pm$ 0.36	2.03 $\pm$ 0.29	1.96 $\pm$ 0.15
B	2.11 $\pm$ 0.33	2.06 $\pm$ 0.25	1.99 $\pm$ 0.28	1.88 $\pm$ 0.17
C	2.30 $\pm$ 0.39	2.19 $\pm$ 0.33	2.11 $\pm$ 0.32	2.04 $\pm$ 0.25

Comparison of the effective compressions number of CIA

sedative score of patients was evaluated at different time points which showed no significant difference among the three groups ( $p=0.058$ ) given in Table 3. The effective compressions number of CIA in group A and group C ( $p=0.032$ ) was greater than group B. Group A and group C ( $p>0.9$ ) showed no statistical difference, and no invalid compression times were recorded. (Table 4). In group B The number of adverse reactions was lower than in group A and group C ( $p=0.04$ ). Table 5 showed that statistical difference between group A and group C ( $p=0.7$ ) was negligible. Table (6) indicated that group A, B and C showed no statistical difference in the levels of inflammatory cytokine before surgery ( $p=0.63$ ). After surgery within 24 h, the levels of TNF- $\alpha$ , CRP and IL-6 in group B were lower than those in group A and C. But Table 6 indicated that there was no statistical differences among three groups ( $p=0.71$ ). Within 72 h after surgery, TNF- $\alpha$ , CRP and IL-6 in group B were lower than those in group A and C ( $p=0.32$ ) given in (Table 6). Previous study indicated that surgical resection of gastric cancer and regional lymphadenectomy are the only options for treatment in the patients of early gastric cancer. As it has many advantages over conventional open gastrectomy, but it is occasionally linked with significant morbidity that may be affect the quality of life such as postoperative pain<sup>[3]</sup>. Therefore, postoperative anesthesia for sedation in patients is required in laparoscopic radical resection. Now a day's ideal analgesic affect can be achieved by applying multimodal analgesia method in which the pain can be controlled by using different methods or through the combination of analgesic drugs with different mechanisms of action. It can make the internal environment stable and decline the complications, by reducing the effects of pain and drugs on nerves, immunity and endocrine system. In present scenario, there are two most commonly used methods are; continuous epidural patient-controlled analgesia (PCEA) and intravenous patient-controlled analgesia (PCIA). Main drawback of above mentioned methods is that there is no specific provision for the current specific requirements<sup>[9]</sup>. Hence, PCEA and PCIA both have parallel analgesic effects, but PCEA is susceptible to a sequence of side effects included; puncture sites, and catheter breakage, infections lead to limit its clinical use. While PCIA has a remarkable analgesic effect with minor adverse reactions and is widely used at present in clinical applications<sup>[10]</sup>. Still Opioids are extensively used as postoperative analgesic drugs. Though, most commonly used opioids are  $\mu$  receptor agonists, while their analgesic effect is specific, but due to huge

gastrointestinal side effects are not favorable to the recovery of postoperative gastrointestinal function, and their treatment is less effective for nerve pain and distracted visceral pain<sup>[11]</sup>. For patients of gastric carcinoma, the selection of analgesic method with remarkable analgesic effect and fewer adverse reactions is still need to be explored. Oxycodone is synthesized from an alkaloid the baine extract; act as an opioid central nerve analgesic, which has agonistic effect on the K receptor and also agonize the  $\kappa$  receptor. Therefore, it is believed that the curative effect of oxycodone is better in visceral pain as compared to  $\mu$  receptor agonist used alone. Furthermore, Oxycodone possesses different characteristics such as high bioavailability, good analgesic effect, fewer adverse reactions and it has long duration of drug efficacy while its peak time is just 5 minutes. Its analgesic effect is parallel to morphine and mainly used in moderate to severe pain<sup>[12]</sup>. Oxycodone produce batter curative effect on incision pain and visceral pain and it also cause slight inhibition in gastrointestinal function. Therefore it is considered suitable for gastrointestinal surgery. Its onset of action is rapid and affects slightly on immunosuppression, which is favorable for rehabilitation in the elder patients<sup>[13]</sup>. Dexmedetomidine hydrochloride acts mainly on the locus coeruleus and adrenergic receptors in the spinal cord. It is highly selective  $\alpha 2$  receptor agonist and causes sedative effect, myocardial protection, pain-suppressing inflammatory response and alleviation of cognitive dysfunction. It is very helpful for patient's postoperative recovery as it can inhibit inflammatory reactions and cytokines release effectively<sup>[14]</sup>. As it has weak sedative effect therefore should be given in combination with opioids. Dexmedetomidine has selective effect on the locus coeruleus and peripheral  $\alpha 2$  receptors of the central nervous system so lessen the activity of the sympathetic nervous system and diminish the sensitivity of stress response. it is also more favorable in the maintenance of hemodynamic stability<sup>[15]</sup>. It was observed in the present study that TNF- $\alpha$ , CRP and IL-6 in group B were lower than those in group A and C ( $P<0.05$ ) within 72 d after surgery which indicated that body's stress response can be reduced when dexmedetomidine and oxycodone given in combination, it also inhibit the release of inflammatory cytokines in patients. It was confirmed from clinical data that combination of oxycodone and dexmedetomidine hydrochloride have no significant effect on the time of evacuation after surgery which shows that there is no significant effect on the gastrointestinal function of the patient, and clinical

application is relatively safe<sup>[16]</sup>. Clinical studies showed that oxycodone and dexmedetomidine hydrochloride usage, lead to decrease the dosage of oxycodone and dexmedetomidine in patients, but the effective compressions number of CIA and VSA score of the patient were reduced. Study indicated that there was no significant reduction in Ramsay sedative score therefore oxycodone and dexmedetomidine have good analgesic effects and satisfactory sedative effects can be achieved in patients with gastric cancer. The patient's good analgesic effect can lead to promote the patient's functional exercise which is favorable for gastrointestinal function recovery in patients, and additionally it will reduce the inflammatory cytokines release in patients. Postoperative observation of adverse reactions indicated that the dexmedetomidine combined with oxycodone group showed higher occurrence of nausea and dizziness as compare to dexmedetomidine and oxycodone groups while there was no difference in the occurrence of other adverse reactions. Results of the present study revealed that the incidence of nausea, vomiting and dizziness increased can be increased with increase oxycodone dose and all three groups no patient faced respiratory depression, indicated that dexmedetomidine combined with oxycodone have minor side effects. Additionally not only this combination, improve the analgesic effect but also reduce the dosage of drugs. Therefore incidence of adverse reactions is reduced, especially for postoperative analgesia in elderly patients with gastric cancer. This study revealed the use of dexmedetomidine combined with oxycodone in patients with gastric cancer. Though, the dose and ratio of dexmedetomidine in combination with oxycodone is still unknown, and their effects on hemodynamics and the metabolic mechanism in patients are still not clear, and its efficacy difference for patients of different ages is not clear and needs more research to confirm. It was concluded from present research study that Dexmedetomidine combined with oxycodone has improved sedative and analgesic effects, a reduced amount of adverse reactions, and can decrease the release of inflammatory cytokines of TNF- $\alpha$ , CRP and IL-6 in the body and has certain clinical application value.

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