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Excessive amount of sufentanil can increase the postoperative ileus of patients with laparoscopic colorectal cancer surgery

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Abstract

Background: Colorectal cancer is one of the common tumors that seriously threaten human health worldwide. As a commonly used opioid pain medication, sufentanil is widely used in laparoscopic anesthesia for colorectal cancer. Opioids have the effect of inhibiting gastrointestinal activity, however, there is few research on the effect of sufentanil on gastrointestinal tract inhibition. Therefore, we hope to clarify the relationship between the dosage of sufentanil and the time of postoperative obstruction of laparoscopic colorectal cancer by analyzing the correlation between the two and find the standard for the use of sufentanil in anesthesia of these patients. **Methods:** We retrospectively analyzed 217 patients with colorectal cancer included in this study, collected their doses of sufentanil, postoperative ileus time, clinical data and grouped them. The above data were statistically analyzed. **Results:** The average age of the sample patients was 62.02 years old and the average weight was 67.87 kg, including 79 cases of colon cancers and 138 cases of rectal cancers. Among them, 81 patients received laparoscopic surgery with ostomy. The average dose of sufentanil and that distributed by weight was 35.58ug and 0.54ug/kg, meanwhile the average time of ileus was 2.27 days. It was found that the longer duration of intestinal obstruction occurred in elderly patients and patients without ostomy or colon cancers ($P<0.05$). Patients given high dose of sufentanil to per kg weight were more likely to develop long-term ileus (4.200 days $P<0.05$), which was more pronounced in non-ostomy cohorts. **Conclusion:** Higher doses of sufentanil on average body weight lead to poor intestinal activity and long ileus time in patients undergoing laparoscopic colorectal cancer surgery, especially in patients without ostomy.

Key Words: sufentanil, colorectal cancer, postoperative ileus

Introduction

The rate of colorectal cancer (CRC) is increasing per year worldwide, accounting for the third place in the world in malignant tumors. More than 1 million new cases of colorectal cancer are diagnosed every year and the mortality rate is close to 33%[1, 2]. Laparoscopic surgery for colorectal cancer has become the main surgical intervention means for the treatment of colorectal cancer due to its advantages of small trauma and quick recovery in clinical work[2, 3]. However, moderate or severe postoperative pain can still occur in patients after laparoscopic surgery, so it is particularly significant to provide sufficient analgesic effect with minimal side-effects in the evaluation criteria and indicators of intraoperative and postoperative pain management drugs[4, 5]. Opioids are commonly used as auxiliary analgesics for surgical anesthesia. In addition to sedation, tolerance, dependence and respiratory depression, side-effects of opioids also include gastrointestinal adverse reactions, such as nausea, constipation and vomiting, which are collectively referred to as OIBD (intestinal dysfunction caused by opioids) [6, 7]. It has been reported that up to 81% of patients with opioids treatment got constipation, as well as vomiting, abdominal cramps and distension, and even gastrointestinal bleeding [8, 9]. In severe cases opioids have been shown to increase the risk of ileus, leading to hospitalization and even death. Therefore, when opioids are applied to patients undergoing gastrointestinal surgery, gastrointestinal adverse reactions should be paid enough attention. Sufentanil is a kind of highly selective opioid receptor agonist and has many advantages: a long elimination half-life, can provide reliable analgesic effect, stable hemodynamics, and has been widely used in clinical postoperative analgesia as one of the classic opioids. But the doses are often given based on experience and simple assessments of a patient's height and weight cause there are no strict guidelines and regulations. Thus it can be seen drug overdose could happen easily and obviously increased the risk of relevant side-effects. Previous studies on the adverse effects of sufentanil on digestive tract activity have mostly focused on basic experiments or constipation symptom in cancer patients, however, there are few reports on side-effects about postoperative gastrointestinal function and fewer literatures on the gastrointestinal side-effects of sufentanil from the perspective

of drug dose weight distribution [10, 11].

Patients after digestive tract surgery are likely to show ileus symptoms of stopping expelling gas and defecation, and the recovery of intestinal activity is a significant clinical indicator to evaluate the postoperative status of patients[12, 13]. Therefore, our study intended to take the average body weight dose and the time of postoperative ileus as the main research objects to determine the poor influence of the weight distribution of sufentanil on the postoperative digestive tract activity after laparoscopic colorectal cancer surgery. We retrospectively studied 217 patients who accepted laparoscopic colorectal cancer surgery in the department of anorectal surgery of First Affiliated Hospital of China Medical University and observed the postoperative ileus state. Combined with the statistical analysis of the intraoperative drug dose received by patients, the correlation was studied and the guiding significance of the standard use of sufentanil in the pain management of these patients was expected to be generated.

Materials and Methods

Patients and Methods

Study Population: From January to July 2018, 217 patients who received laparoscopic surgery for colorectal cancer in the department of anorectal surgery of the First Affiliated Hospital of China Medical University were collected and selected according to the following criteria. Exclusion criteria were as follows: 1.Complete clinical case data could not be obtained or follow-up was lost; 2.Patients with postoperative intestinal fistula and other serious postoperative complications; 3.Patients with preoperative intestinal obstruction symptoms; 4. Patients with perioperative colitis, hemorrhagic bowel disease and other digestive diseases; 5. Patients who received liver, ovary or other organ surgery at the same time. The final patient samples included 79 cases of colon cancer and 138 cases of rectal cancer.

(Figure.1)

Data Collection: All the patients was operated in laparoscopic surgery by the experienced Chengzhong Xing, M.D. The same parenteral nutrition, antibiotics and other adjuvant drugs were used for postoperative treatment, none of which contained ingredients such as somatostatin that might cause inhibition of gastrointestinal activity.

Anesthesia was induced using midazolam, sufentanil (Yichang Humanwell pharmaceutical co.,LTD, Drug Batch No.81A09071), cis-atracurium and etomidate, intravenously injected. Anesthesia was maintained with the end-tidal sevoflurane concentration at 1-1.5 minimum alveolar concentration (MAC) in anoxygen flow of 2L/min and propofol intravenously injected at a speed of 4mg/kg/h. No other opioid analgesics except sufentanil were given during the perioperative period. All patients were temporarily given parenteral nutrition by intravenous injection after surgery during periods of fasting and water deprivation. The absence of abdominal distension and the presence of at least three times daily expelling gas or the first time defecation was considered to recovery of intestinal activity and improvement of ileus. The ileus time was calculated and accurate to days and the dose of sufentanil were retrospectively counted through the anesthesia records of the patients. Meanwhile, the clinical data of the patients were collected and statistically analyzed.

Statistical analysis

Statistical analysis was conducted by SPSS 24.0 (Chicago, IL, USA) and Graphpad Prism 7.0 (Graphpad Software, CA, USA). The classification data were analyzed using the Pearson chi-square test, continuous variables were tested by spearman two-variable correlation test and the linearity was analyzed by the log-rank test. A *P* value of less than 0.05 ($P < 0.05$) was considered statistically significant.

Result

Baseline characteristics

A total of 217 patients were included in the study sample with an average age of 62.02 years, including 139 males and 78 females respectively, an average weight of 67.87kg, 79 patients with colon cancer and 138 others with rectal cancer. The laparoscopic surgery received in 81 cases of patients with fistula and 136 cases of patients without fistula, and in 91 cases, the operation time exceeded the average level (116.53h). The average postoperative recovery ileus time of these patients was 2.23 days, meanwhile 144 patients had postoperative expelling gas or defecation within 1-2 days and the remaining 73 patients had intestinal obstruction for 3 days or more. Intraoperative use of sufentanil: the average dose per person was 35.58ug, and 85

patients received sufentanil exceeding 35ug, while the other patients did not exceed the average dosage. Sufentanil was given at an average of 0.5398ug/kg per kg of body weight, with 121 patients receiving less than 0.54ug/kg and 96 others exceeding this dose. **(Table.1)**

Correlation between characteristics and postoperative ileus time

2-sided chi-square test and multivariate logistic regression analysis adjusted for age, gender and operation duration as covariate reference factors were used to test the correlation between various clinical indicators and postoperative ileus time. The results showed that there was a positive statistical correlation between the time of ileus and age ($P<0.05$) while the long-term postoperative intestinal obstruction was more likely to occur in patients with colon cancer or without ostomy ($P<0.05$), but no statistical significance between the time of ileus and gender or operation time was found ($P>0.05$). In terms of medication dose, the time of ileus was not related to the total amount of sufentanil ($P>0.05$), but patients with high doses per kg of body weight were more likely to have long-term postoperative intestinal obstruction ($P<0.05$). **(Table.2)**

Based on the above results, we hoped to study whether this correlation existed in different groups of people in a more detailed way. The sample patients were divided into groups according to age, primary organ and ostomy. The results showed that: A higher sufentanil of mean body weight was associated with a longer postoperative duration of ileus in patients with younger age or without ostomy ($P<0.05$). No statistical significance was found in the other patient groups. **(Table.3)**

Correlation between postoperative ileus time and sufentanil per kg of body weight

Therefore, we speculated that higher sufentanil dosages in mean body weight may be associated with longer postoperative ileus time in colorectal cancer patients after laparoscopic surgery, which may be more obvious in young patients and patients with ostomy. Kaplan-Meier curves for the time of ileus related to the mean body weight dose of sufentanil were prepared **(Figure.2)**: There was a statistically significant difference in ileus time between patients with low and high mean weight medications ($P<0.05$). The intestinal obstruction time of low-dose patients was 3.485 days (3.213-3.756) after surgery expectedly, while that of high-dose patients was 4.200 days

(3.761-4.639). High doses per kg of body weight also resulted in prolonged intestinal obstruction time in the non-ostomy group: The average time of ileus in patients with low dose of per kg sufentanil in non-ostomy patients was 3.542 days (3.208-3.875) after surgery, while that in patients with high dose was 4.414 days (3.868-4.960) after surgery. But the association above was not found in the younger age group ($P>0.05$). Based on COX multivariate analysis results, we could infer that the sufentanil dose of average weight is an independent influencing factor to postoperative ileus time in patients after laparoscopic colorectal cancer surgery ($P<0.05$). (**Table.4**)

Discussion

Opioids have been shown to be safe for general anesthesia and perioperative analgesia, but the accompanying digestive tract side effects cannot be ignored. The recovery of postoperative gastrointestinal activity is significant especially for patients undergoing colorectal surgery. Therefore it is necessary to intervene actively in the management of pain in opioids during anesthesia. Opioid receptors are widely present in the central nervous system and the smooth muscle of peripheral organs including the colorectum. Previous studies have suggested that opioids inhibit intestinal function primarily by activating presynaptic alpha receptors in the central nervous system [14, 15]. In the peripheral gastrointestinal system, opioid drugs could increase smooth muscle tone and reduce smooth muscle contraction, intestinal peristalsis, bowel channel secretion by combining opioid receptors, which even cause hard stools due to the dry intestine [16-18].

As a typical opioid agonist, sufentanil has been widely used in surgical analgesia on account of strong analgesic effect and short plasma half-life [19]. Due to the simple assessment based on patient weight and hemodynamics before administration of anesthesiologists during surgery with lack of accurate pain and blood concentration monitoring, overdose is inevitable. In a abdominal operation using target-controlled infusion sufentanil combined with sevoflurane anesthesia, it was found that sufentanil target concentration in the range of 0.8 ng/ml is suitable for maintaining anesthesia during abdominal surgery and leading to better postoperative surgery, and the recovery time in the recovery room extended as sufentanil dose increased [20].

However, the relationship between sufentanil dose and recovery of postoperative gastrointestinal function has not been reported yet. As a representative opioids drug sufentanil has a corresponding response to gastrointestinal suppression, thus we retrospectively studied 217 patients undergoing laparoscopic colorectal cancer surgery. Statistical analysis was performed on the doses of sufentanil, relevant clinical parameters and postoperative intestinal obstruction but no direct correlation between sufentanil and the postoperative ileus time was found. However, after we calculated the patient's dose of sufentanil by weight distribution, it was found that there was a positive correlation between the dose of sufentanil measured by per kilogram of body weight and the long-term obstruction. That is, when the patient received sufentanil at dose of exceeding 0.54 ug/kg, it is more prone to ileus without expelling gas or defecation for 3 days or more after surgery, which means worse recovery of postoperative gastrointestinal activity. It was reported that the incidence and severity of adverse reactions increased with the increasing dose of opioids, which shows concentrations and doses are important factors in the adverse effects for opioids [21]. It was found that the drug inhibited neural transmission of motor neurons in the annular smooth muscle layer in a concentration-dependent manner when opioids were used in vitro in human and baboon jejunal tissues [22]. During healthy volunteers using opioid oxycodone, MRI scan revealed increased volume of segmental colorectal in the cecum/ascending colon, decreased bowel movement and constipation add [23]. Sufentanil could dose-dependently increase the contractile tension and contractility of isolated rat small intestinal smooth muscle, affecting the small intestine propulsion propulsion [10]. Above reports confirmed that the inhibition effect on digestive tract of opioids including sufentanil could become severe with increasing drug concentrations, which supported and explained our findings. We supposed that the excessive dose of sufentanil with average body weight would lead to adverse postoperative effect on poor recovery of digestive tract activity in patients undergoing laparoscopic colorectal cancer surgery.

Interestingly, we found that this correlation was particularly significant in patients received non-ostomy surgery. Compared with traditional open surgery, laparoscopic

surgery has the advantages of quick recovery, less trauma and short operation time, but the difference between surgical procedures is still not negligible. Whether the artificial ostomy is included in the surgical procedure is an important factor that may affect the recovery of postoperative intestinal activity in patients. For instance, the patient's intestinal contents are directly excreted through the artificial ostomy anus after surgery of Miles, Hartmann, etc, so that the length of the digestive tract is further shortened. However, Dixon surgery and colon cancer cure intraoperative procedures require surgical resection of the intestines and anastomized subsequently. The presence of anastomotic stoma in these surgery procedures and longer retention of digestive tract make postoperative reconstruction of digestive system in non-ostomy patients more dependent on the peristaltic activity of intestinal tract, which may be the cause of the significant digestive tract inhibition by sufentanil in these patients. In addition, we also found that the average weight of high-dose sufentanil caused long-term postoperative obstruction was not reflected in the elderly population by stratified statistics. In elderly people, due to poor intestinal peristalsis and slow recovery of digestive tract, it was easy to produce delayed expelling gas or defecation, which was confirmed by our research results. This could misdirect the statistical results about the inhibition of intestinal activity by sufentanil in the elderly population and more in-depth studies of larger samples are necessary.

In conclusion, based on the findings of this report, we believed that older age and the average weight of sufentanil over 0.54 ug/kg can have a significant effect on intestinal activity in patients undergoing laparoscopic colorectal cancer surgery and lead to long postoperative ileus time. It was suggest that the dose should be controlled in accordance with the principle of weight related in order to obtain a better postoperative intestinal recovery. Therefore, we recommend that sufentanil should be administered no more than 0.54 ug/kg depending on the patient's weight in general anesthesia laparoscopic surgery for colorectal cancer, especially in non-ostomy surgery procedures.

Conclusion

Higher doses of sufentanil on average body weight lead to poor intestinal activity

and long ileus time in patients with laparoscopic surgery for colorectal cancer. Sufentanil should be given carefully according to the patient's weight for patients with such surgery, especially those who receive non-ostomy procedures.

Figure legends

Figure.1 Screening process of sample patients

Figure.2 Kaplan-Meier curves of mean weight sufentanil and ileus time in different groups

(a) All patients (b) Young patients (c) Non-ostomy patients

Declarations

Ethics statement

The First Hospital of China Medical University and the Medical Ethics Committee of China Medical University approved this study. Due to the retrospective nature of the study, the First Hospital of China Medical University and the Medical Ethics Committee of China Medical University waived the need of written informed consent by the patients. All the samples were anonymous.

Consent for publication

Not applicable.

Availability of data and material

The datasets used during the present study are available from the corresponding author upon reasonable request.

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Conflicts of interest

All authors declared that they have no conflict of interest.

Authors' contributions

Y.L and H.J participated in literature search, study design, data collection, data analysis, data interpretation, and wrote the manuscript. C.X, H.M participated in study design and provided the critical revision. Zhuang.L, Zhe.L, G.S and C.Y carried out the data collection and data analysis, and provided the critical revision. All authors read and approved the final manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figures

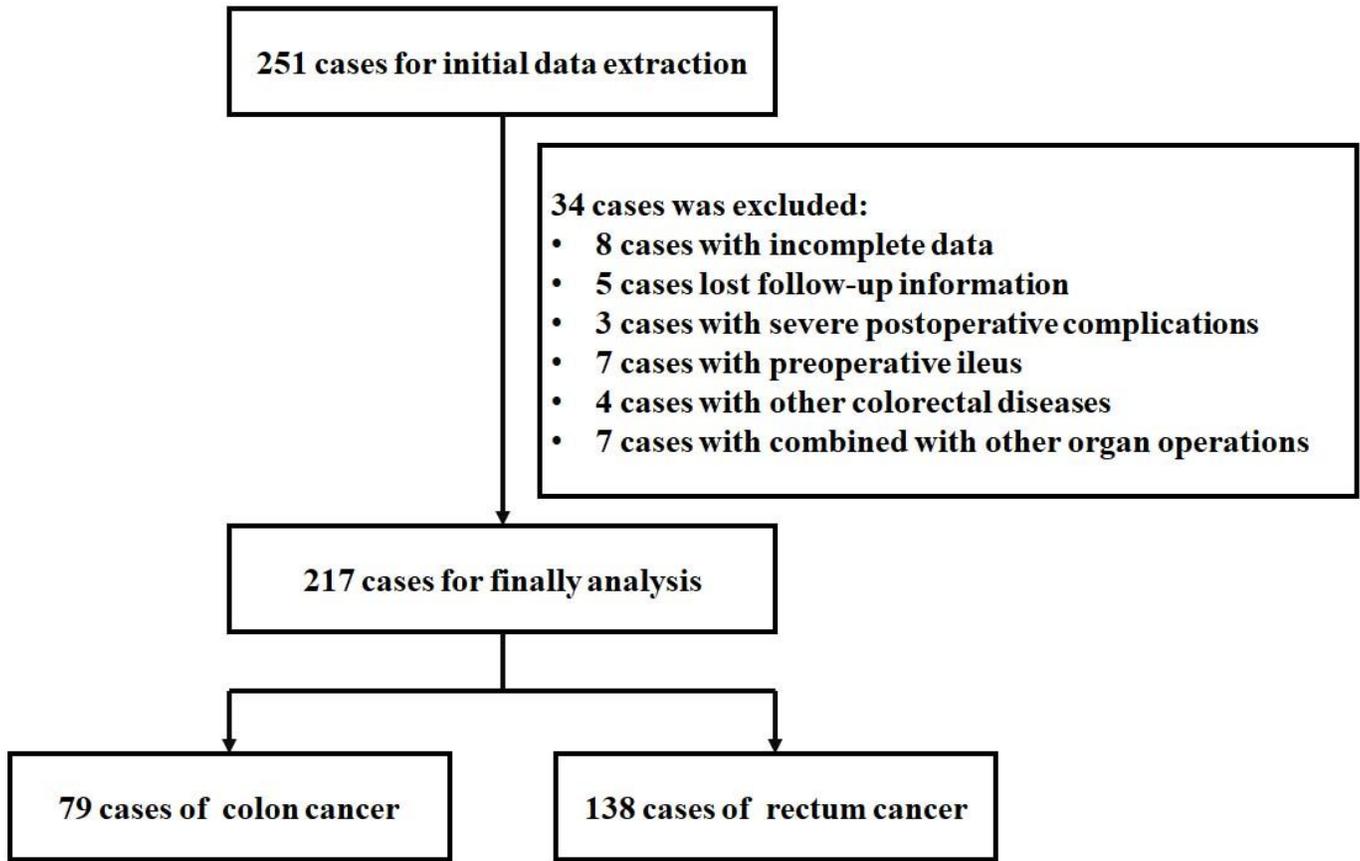


Figure 1

Screening process of sample patients

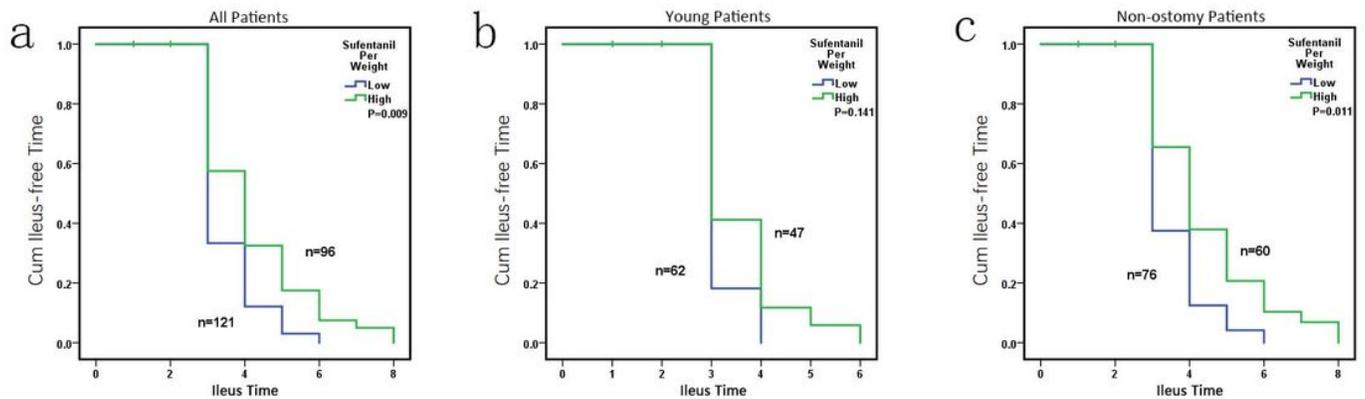


Figure 2

Kaplan-Meier curves of mean weight sufentanil and ileus time in different groups. (a) All patients (b) Young patients (c) Non-ostomy patients