

# Butorphanol tartrate is better than fentanyl for postoperative analgesia after intestinal surgery: A prospective cohort study

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## Research article

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## Abstract

**Background** Traditional opioid analgesics act on the  $\mu_2$  receptors and lead to delayed gastric emptying and weakening of the peristalsis. Butorphanol is an opioid analgesic that has strong excitatory effect on  $\kappa$  receptors, weak  $\mu$  receptor agonistic and antagonistic activity. This study aimed to compare the effects of butorphanol tartrate and fentanyl on the analgesia and the gastrointestinal motility after intestinal surgery. **Method** This prospective cohort study was conducted in Zhongnan Hospital of Wuhan University, Wuhan, China from May to September 2017. One hundred and forty six patients admitted to ICU after intestinal surgeries, were divided into fentanyl group and butorphanol group. The fentanyl group continually infused fentanyl with 1ug/kg/h and the butorphanol group continually infused butorphanol with 20ug/kg/h. The analgesics were used until the patients were transfer out of ICU or up to 24 hours. The primary outcome was the time required for the first passage of flatus. The second outcomes included the pain and sedation scores, the incidence of nausea and vomiting, serum motilin concentrations, and the incidence rate of adverse reactions. **Results** There were 69 patients in butorphanol group and 77patients in fentanyl group. Compared with the fentanyl group, the time required for the first passage of flatus was shorter ( $69.82 \pm 18.84$  h vs.  $79.34 \pm 15.69$  h,  $p= 0.0012$ ) and the incidence of nausea (14.9% vs. 29.3%,  $P=0.013$ ) and vomiting (11.7% vs. 27.3%,  $P=0.031$ ) was significantly lower in the butorphanol group without any significant difference in analgesic score and sedation score. The serum motilin increase level was significantly higher in butorphanol group [21.36(6.17, 28.47) ng/L vs. 5.56(3.04, 9.81) ng/L,  $P = 0.034$ ]. **Conclusion:** In patients undergoing intestinal surgery, butorphanol tartrate allows faster recovery of gastrointestinal function and similar analgesia compared to fentanyl. TRIAL REGISTRATION Chinese Clinical Trial Register (ChiCTR-INR-17011031). Registered on Mar 31th 2017.

## Background

Continuous intravenous analgesia is an effective method for relieving pain, antagonizing stress and reducing oxygen consumption. It has become one of the preferred methods for providing postoperative analgesia ADDIN EN.CITE [1, 2] . However, one of the major concerns with these analgesics is their side effects, especially inhibition of intestinal motility. Traditional opioid analgesics act on the  $\mu_2$  receptors and lead to delayed gastric emptying and weakening of the peristalsis. The most commonly reported gastrointestinal side-effects include nausea, vomiting and abdominal distention ADDIN EN.CITE [3-5] .

Butorphanol is a lipid soluble opioid analgesic which can be used intravenously, intrathecally as well as for epidural analgesia. It has strong excitatory effect on  $\kappa$  receptors, weak  $\mu$  receptor agonistic and antagonistic activity, and minimal effect on the  $\sigma$  receptors ADDIN EN.CITE [6, 7] . Due to the mild  $\mu_2$  receptor agonist activity, the gastrointestinal side-effects of butorphanol are believed to be lesser than that of the traditional opioids ADDIN EN.CITE [8] . It has been used alone ADDIN EN.CITE [9] , in combination with dexmedetomidine ADDIN EN.CITE [10] , dezocine ADDIN EN.CITE [9] ] for patient-controlled analgesia in the postoperative period after laparoscopic surgeries. It has also been used preoperatively in combination with flurbiprofen axetil to attenuate remifentanyl-induced hyperalgesia ADDIN EN.CITE [11] . Some researchers have also used butorphanol in combination with ropivacaine or bupivacaine via thoracic epidural catheter for postoperative analgesia after abdominal surgeries ADDIN EN.CITE [12, 13] . In this context, butorphanol was found to have lesser gastrointestinal side-effects compared to fentanyl [14]. However, there is little data on the effect of intravenous butorphanol infusion of the gastrointestinal motility. Hence, we conducted this study to compare the effects of butorphanol tartrate and the traditional opioid analgesics (fentanyl) on the gastrointestinal motility after intestinal surgery.

## Methods

### *Patient selection*

This prospective study was conducted in the Intensive Care Unit (ICU), Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China from May 2017 to September 2017. Inclusion criteria were: (1) patients admitted to ICU after elective intestinal surgery; (2) under general anesthesia and transferred into ICU with intubation, expected to stay in ICU at least 12 hours; (3) age 18-85 years; (4) weight 45-80 kg; (5) ASA I – II. Exclusion criteria were: 1) patients with known allergies to butorphanol or other drugs used in this study; 2) long-term use of narcotic analgesics, sedatives, antidepressants, non-steroidal anti-inflammatory drugs; 3) persistent systemic hypotension and poor tissue perfusion despite the use of vasopressors; 4) acute severe brain injury; 5) severe cardiac, respiratory, liver and kidney dysfunction; 6) patients who participated or are participating in other drug trials in last 3 months.

This study conforms to the standards of medical ethics and has been approved by the ethics committee of Zhongnan Hospital of Wuhan University (ethical approval number – 2017026). This study was registered in Chinese Clinical Trial Register (ChiCTR-INR-17011031), registered on Mar 31th 2017. Written informed consent was obtained from each patient or his/her family member.

### *Process*

Patients after intestinal surgery who satisfied the above criteria were included in the study and given intravenous analgesia postoperatively in the ICU. The patients were divided into fentanyl group and butorphanol tartrate group based on the initial analgesic drug used by the clinicians. In the fentanyl group, 500ug of fentanyl was diluted with 50ml of normal saline, started at 1ug/kg/h and maintained at 0.5-2ug/kg/h. In the butorphanol tartrate group, butorphanol tartrate injection 20mg was diluted with normal saline 50ml, started at 20ug/kg/h and maintained at 10-30ug/kg/h. In both groups, continuous intravenous analgesia was administered using micro-pump until the patients were transferred out of ICU or up to 24 hours. The degree of patients' analgesia was judged using the Critical Care Pain Observation Tool (COPT) score. The target score was set at 0-1. If the score was more than 1, the infusion rate was accordingly adjusted.

Sedation protocol: No sedation was used initially. The Richmond Agitation-Sedation Scale (RASS) score used to assess sedation. The ideal target score was set between -2 to 0 point. If RASS score above 1 point (including 1 point), sedation was given. The choice of sedative drugs was based on clinician's experience.

### *Variables*

Primary outcome: time of first passage of flatus after operation (from ICU admission after surgery to first passage of flatus). To ensure the accuracy for timing the first passage of flatus, we educated the patients how to record the time both at extubation and transferring out of ICU. The study investigators visited the patients every 12h (7am, 7pm) to record the time (measured at hours) until the first passage of flatus had occurred.

Secondary outcomes:

- (1) The pain scores (CPOT score) and sedation scores (RASS score) at 1h, 6h, 12h and 24h after surgery
- (2) The total amount of analgesic drugs and sedative drugs used in the postoperative period.
- (3) The incidence and severity of postoperative nausea and vomiting. Nausea was evaluated as follows: 0 point for no nausea, 1 point for a mild nausea at rest and 2 for severe nausea at rest. Vomiting was assessed as follows: 0 for no vomiting, 1 for mild vomiting (1~2 times a day), and 2 for severe vomiting (more than 3 times a day).
- (4) Intestinal barrier function and serum motilin concentration before the use of analgesic drugs and 12 hours after their use.
- (5) Recovery of oral feeding after operation (from ICU to the first time of oral feeding).
- (6) The incidence rate of cardiorespiratory adverse reactions. It included hypertension (systolic pressure >140 mmHg or diastolic pressure >90 mmHg or higher than normal level of 20%); hypotension (systolic pressure <90 mmHg or diastolic <60 mmHg or decreased by 20% more than normal level); respiratory depression (respiratory frequency less than 10 times per minute); tachycardia (heart rate more than 110 times per minute); bradycardia (heart rate less than 50 times per minute).

### *Measurement*

Three milliliters of venous blood samples were collected from patients before the use of analgesic drugs and at 12 hours after their use, and 1ml was directly used to detect the Intestinal barrier function biochemical indicators (D-lactic acid, diamine oxidase, endotoxin) by the JY-DLT intestinal barrier function biochemical index analysis system (Zhongsheng Jinyu, Beijing, China); The other 2ml were centrifuged at 2,000 g for 20 minutes and the serum fraction was frozen and stored at -80°C until analyzed. The serum motilin concentrations were measured using enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (Huamei, Wuhan, China).

### *Statistical analysis*

For the primary outcome, we hypothesized that butorphanol tartrate group would be noninferior to fentanyl group for analgesia based on a normal distribution for the difference in proportions between groups. The trial would have at least 80% power to detect a between-group difference of 10-flatus recovery-hour and to declare noninferiority on the basis of a predefined noninferiority margin of 10 percentage points, with an overall alpha of 0.05. We initially determined that with 63 patients in each group, with an estimate of 10% loss, the sample size would be 70 for each group and approximately 140 for sum.

All the data were analyzed using SPSS version 22.0. The categorical data were assessed using chi-square test. The continuous data were compared by rank sum test or T test. All the statistical tests were conducted using bilateral tests. The P value of less than or equal to 0.05 was considered to be statistically significant. t-test or chi-square test was used to compare demographic data and other basic value indicators to determine the two groups of equilibrium levels. T test or rank sum test were used to evaluate the validity index. Safety analysis, such as the time, frequency of adverse events, and the incidence of adverse reactions in the both groups were analyzed by chi-square test.

## Results

### *Comparison of patient characteristics*

In this study, 216 patients were recruited and 146 patients were finally included (Fig 1). All patients were under general anesthesia and transferred into ICU with intubation. The number of butorphanol tartrate group was 69 and fentanyl group was 77. There were no significant differences in gender, age, height, weight, past medical history, acute physiology chronic health status score system II (APACHE II) score, surgical site, surgical technique and time course of ventilation between the two groups ( $P > 0.05$ ) (Table 1).

### *Comparison of the time required for first passage of flatus and for resumption of oral feeding*

The duration from ICU admission to the first passage of flatus was significantly shorter in butorphanol group ( $69.82 \pm 18.84$  h vs.  $79.34 \pm 15.69$  h,  $p = 0.0012$ ). The time required for resumption of oral feeding of liquid diet was also shorter in butorphanol group ( $108.64 \pm 18.82$  h vs  $94.40 \pm 20.46$  h,  $p < 0.001$ ).

### *Comparison of the analgesic effect*

Compared with the fentanyl group, the CPOT score before starting medication was significantly higher in the butorphanol group ( $P < 0.05$ ). There was no significant difference in the COPT score between the two groups at 1h, 6h, 12h and 24h after the initiation of the medication ( $P > 0.05$ ) (Table 2). However, the CPOT scores at different time points in both groups were significantly lower than those before starting the medications ( $P < 0.05$ ) (Table 2). The dosage of analgesic drugs in two groups was shown in Table 4.

### *Comparison of the sedation score (RASS score)*

Due to good analgesia and smooth removal of the tracheal intubation, sedative drugs were only used in one patient in butorphanol group (propofol -1) and two patients in fentanyl group (midazolam -2) (Table 4). The comparison of RASS score between two groups was shown in table 3.

### *Comparison of intestinal barrier function and serum motilin levels*

The D-lactic acid, diamine oxidase, endotoxin and serum motilin concentrations before starting the medications were similar in the two groups (Table 5). There was statistically significant difference between diamine oxidase concentration 12h after starting the medication in butorphanol group and fentanyl group ( $P < 0.05$ ). The other indexes, such as the D-lactic acid, endotoxin before and 12h after medication were similar ( $P > 0.05$ ). The serum motilin concentration 12h after medication in two groups was significantly higher than that before medication. There was no significant difference in serum motilin concentration before and 12h after medication in the two groups (Table 5). However, the level of increase in serum motilin in the butorphanol group was significantly higher than that in the fentanyl group [ $21.36(6.17, 28.47)$  vs.  $5.56(3.04, 9.81)$ , ( $P = 0.034$ )].

### *Comparison of the incidence of nausea and vomiting*

Most of the patients had no nausea before the start of medication. There was significant increase in the incidence of nausea at 6h and 12h after starting medications in both groups. The proportion of patients at 6h (6.0% vs. 20.0%,  $P = 0.006$ ) and 12h (14.9% vs.

29.3%,  $P=0.013$ ) with nausea was significantly higher in the fentanyl group as shown in Table 6. The incidence of vomiting in the butorphanol group was significantly lower than that in fentanyl group at 24h after starting medications (11.7% vs. 27.3%,  $P=0.031$ ) (Table 7).

#### *Comparison of the adverse reactions after analgesic medications*

Compared with the fentanyl group, there was no significant difference in the incidence of hypertension, hypotension, tachycardia and bradycardia in the butorphanol group ( $P>0.05$ ). The incidence of respiratory depression was lower in the butorphanol group but failed to reach statistical significance (10.1% vs. 22.1%,  $P=0.052$ ). (Table 8).

## **Discussion**

In this study, we found that use of butorphanol tartrate infusion in the immediate postoperative period after intestinal surgery was associated with lesser time for the passage of flatus, lower incidence of nausea and vomiting with similar analgesic effects compared to fentanyl infusion.

Traditionally used opioid drugs (such as morphine and fentanyl) stimulate the  $\mu_1$  receptors which has the analgesic effect as well as the  $\mu_2$  receptors which are widely distributed throughout the gastrointestinal tract, resulting in adverse reactions including nausea, vomiting, abdominal distention, and delayed transit time. On the other hand, butorphanol tartrate is different from traditional opioids, has both agonistic and antagonistic effects on opioid receptors; it has an exciting effect on kappa receptors, both agonistic and antagonistic action on the  $\mu$  receptors, and low binding force with  $\sigma$  receptors ADDIN EN.CITE [6]. Its binding force with  $\kappa:\mu:\sigma$  receptor is 25: 4: 1 [7]. Due to its minimal effect on the  $\mu_2$  receptors, butorphanol tartrate has lesser impact on the gastrointestinal motility compared to the traditional opioids.

After any intestinal surgery, there is gastrointestinal dysfunction in the postoperative period due to general anesthesia, altered intestinal barrier and structural changes, the incidence of which can reach up to 40% ADDIN EN.CITE [4]. In ICU, concurrent gastrointestinal dysfunction can significantly prolong the duration of mechanical ventilation and ICU stay ADDIN EN.CITE [15]. Therefore, patients undergoing intestinal surgery should have recovery of their gastrointestinal functions as soon as possible. In this study, we found that, compared with the traditional opioid fentanyl, butorphanol tartrate can shorten the time required for first passage of flatus, hasten the feeding process, and reduce the proportion and severity of vomiting. These effects might be related to the increased levels of serum motilin by butorphanol tartrate.

Fentanyl predominantly activates  $\mu$  receptors and is 100 times more effective than morphine. On the other hand, butorphanol tartrate mainly acts on  $\kappa$  receptor, and has double inhibitory effect on  $\mu$  receptor. Its analgesic effect is 5 times that of morphine [16]. In this study, we found both fentanyl and butorphanol to have good analgesic effect as suggested by significant decrease in the CPOT score after starting the medications (Table 2). Moreover, there was no significant difference in the CPOT score at any time of the treatment between the two groups, indicating that the analgesic effect of the two drugs was similar.

With regards to the dose of analgesic drugs used, in the fentanyl group, the mean dosage was 1.05 mg per person, equivalent to the use of 105.0 mg morphine while in the butorphanol group, the mean dosage was 24.58 mg per person, equivalent to the use of 122.9 mg morphine. This shows that the analgesic activity of butorphanol tartrate is no less than that of fentanyl for postoperative analgesia in patients undergoing gastrointestinal surgery.

Based on the iPad guidelines ADDIN EN.CITE [17], the use of sedative drugs in the postoperative period can be reduced by providing good analgesia. In our study, due to good analgesic effect of both fentanyl and butorphanol, there was almost no need of sedative in the two groups, and the RASS score of the two groups at any time were in the ideal range from -1 to 0.

Opioid analgesics have multiple adverse effects including inhibition of intestinal motility leading to nausea, vomiting, constipation, cardiac dysfunction affecting heart rate, blood pressure and respiratory depression. Our study found that no significant difference in the effect of fentanyl and butorphanol infusion on blood pressure and heart rate of the patients (Table 8). However, the incidence of respiratory depression was higher in the fentanyl group though not statistically significant due to small sample size (Table 8). Fentanyl activates the  $\mu_2$  receptors, and acts on the ventrolateral medulla to suppress respiratory impulses and slow down the respiratory rhythm ADDIN EN.CITE [18, 19]. Additionally, the traditional opioids can also induce respiratory inhibition by causing

chest wall muscle stiffness [20]. Conversely, butorphanol predominantly acts on  $\kappa$  receptor which has little influence on respiration. Hence, the inhibition of respiration by butorphanol was less than fentanyl.

Our study has some limitations. First, it was a prospective cohort study and not a randomized controlled study leading to possibility of selection bias. Second, the sample size was small and it was a single center study. Future multicenter studies with larger sample size are required to validate our findings. Third, the effect of intraoperative anesthetic drugs on the postoperative analgesia was not analyzed and excluded. Moreover, most of the variables to evaluate the primary outcome were from the patients' subjective descriptions although serum motilin was also very useful to explain the phenomenon. Further research should aim at improving the above limitations in order to get more convincing results.

## **Conclusion**

Butorphanol tartrate has good postoperative analgesic effect after gastrointestinal surgery similar to that of fentanyl with shorter time for recovery of bowel motility and lower incidence of nausea and vomiting.

## **Abbreviations List**

ICU: Intensive Care Unit

CPOT: Critical Care Pain Observation Tool

RASS: Richmond Agitation-Sedation Scale

ELISA: enzyme-linked immunosorbent assay

APACHE II: acute physiology chronic health status score system II

## **Declarations**

### **Ethics approval and consent to participate**

This study conforms to the standards of medical ethics and has been approved by the ethics committee of Zhongnan Hospital of Wuhan University (ethical approval number – 2017026). This study was registered in Chinese Clinical Trial Register (ChiCTR-INR-17011031), registered on Mar 31th 2017. Written informed consent was obtained from each patient or his/her family member.

### **Consent for publication**

Not applicable

### **Availability of Data and Materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing Interests**

The authors declare that they have no competing interests

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### **Authors' contributions**

BH and ZP designed this study and protocol development: ZW, JW, HX, and YZ were responsible for patient recruitment, data extraction and analysis. BH & ZP conducted the manuscript writing. All authors read and gave their approval for the final version of

the manuscript.

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## Tables

Table 1. Comparison of patient characteristics

	Butorphanol (n=69)	Fentanyl (n=77)	Test statistics	P value
Sex (M/F, n)	40/29	42/35	0.173	0.677
Age (y, $\bar{x} \pm s$ )	61.29 $\pm$ 13.02	62.18 $\pm$ 11.54	-0.439	0.661
Height(cm, $\bar{x} \pm s$ )	165.91 $\pm$ 9.10	165.74 $\pm$ 8.05	0.122	0.903
Weight (kg, $\bar{x} \pm s$ )	65.09 $\pm$ 7.22	63.78 $\pm$ 5.61	1.212	0.227
APACHE II score( $\bar{x} \pm s$ )	5.54 $\pm$ 1.82	5.22 $\pm$ 2.25	0.936	0.936
Hypertension(Y/N, n)	19 / 50	27 / 50	0.956	0.328
Coronary artery disease(Y/N, n)	5 / 64	3 / 74	0.023	0.476
Diabetes(Y/N, n)	6 / 63	8 / 69	0.120	0.728
Smoking(Y/N, n)	16 / 53	12 / 65	1.357	0.244
Alcohol(Y/N, n)	3 / 66	6 / 71	0.165	0.500
Surgical site (n)				
duodenum and small bowel	8	10	0.065	0.798
Colon	33	38	0.034	0.854
Rectum	28	29	0.130	0.718
Surgical technique(open/lap, n)	42 / 27	42 / 35	0.364	0.545
Time course of ventilation(hour, $\bar{x} \pm s$ )	7.32 $\pm$ 3.37	7.13 $\pm$ 2.30	0.391	0.696

APACHE II score: acute physiology and chronic health score II;

Table 2. Comparison of analgesic effect

	N	CPOT score ( $\bar{x} \pm s$ )				
		Before medication	1h after medication	6h after medication	12h after medication	24h after medication or out of ICU
Butorphanol	69	1.33±1.76	<sup>a</sup> 0.48±0.90	<sup>a</sup> 0.14±0.39	<sup>a</sup> 0.01±0.12	<sup>a</sup> 0.00±0.00
Fentanyl	77	0.77±1.21	<sup>a</sup> 0.44±0.72	<sup>a</sup> 0.13±0.41	<sup>a</sup> 0.10±0.55	<sup>a</sup> 0.05±0.36
Test statistics		2.239	0.270	0.226	-1.385	-1.270
<i>P</i>		0.027	0.787	0.822	0.170	0.208

Compared with the COPT score before administering medications, <sup>a</sup>P<0.05

Table 3. Comparison of RASS score

	N	RASS Score ( $\bar{x} \pm s$ )				
		Before medication	1h after medication	6h after medication	12h after medication	24h after medication or out of ICU
Butorphanol	69	-1.38±2.28	-0.48±1.35	-0.23±0.81	-0.10±0.55	-0.10±0.46
Fentanyl	77	-1.69±1.97	-0.78±1.44	-0.16±0.71	0.00±0.28	-0.01±0.20
Test statistics		0.887	1.301	-0.606	-1.387	-1.483
<i>P value</i>		0.377	0.195	0.545	0.169	0.141

Table 4. Dosage of analgesic and sedative drugs

	n	Total dose (mg)	Dose adjusted [n (%)]	Addition of sedative drugs [n (%)]	Sedative drugs	
					Propofol (mg)	Midazolam (mg)
Butorphanol	69	24.58±8.26	11(15.9%)	1 (1.4%)	320	NA
Fentanyl	77	1.05±0.22	7 (9.1%)	2 (2.6%)	NA	5

Table 5 Comparison of intestinal barrier function and plasma motilin level after medication

	D-lactic acid(mg/L)		Diamine oxidase(U/L)		Endotoxin(U/L)		Serum motilin(pg/L)	
	Before medication	12h after medication	Before medication	12h after medication	Before medication	12h after medication	Before medication	12h after medication
Butorphanol	35.74± 13.82	28.86± 14.77	26.06± 17.92	19.75± 14.39	9.67± 8.32	4.74± 5.55	49.93± 23.28	70.78± 36.78 <sup>a</sup>
Fentanyl	32.48± 11.75	30.72± 13.87	28.33± 16.46	25.84± 15.55	9.39± 5.79	7.08± 6.04	48.43± 21.01	54.44± 27.14 <sup>a</sup>
Test statistics	1.527	-0.778	-0.792	-2.432	0.227	-2.045	-0.121	-1.827
<i>P value</i>	0.129	0.438	0.429	0.016	0.802	0.172	0.903	0.067

Compared with Before medications<sup>a</sup> P<0.05

Table 6 Comparison of nausea between the groups

	N	Before medication [n(%)]		1h after medication and before medication [n(%)]		6h after medication and before medication [n(%)]		12h after medication and before medication [n(%)]	
		0 point	1 point	1 point ↓	1 point ↑	1 point ↓	1 point ↑	1 point ↓	1 point ↑
Butorphanol	67	64(95.5%)	3(4.5%)	0(0%)	1(1.5%)	2(3.0%)	4(6.0%)	2(3.0%)	10(14.9%)
Fentanyl	75	74(98.6%)	1(1.4%)	0(0%)	6(8.0%)	0(0%)	15(20.0%)	0(0%)	22(29.3%)
Test statistics	/	1.278		3.198		7.499		6.098	
<i>P value</i>	/	0.258		0.073		0.006		0.013	

1. Some patients were intubated before and 1h after medication, unable to evaluate nausea status.

2. Nausea score: 0 No nausea, 1 Mild nausea at rest, 2 Severe nausea at rest

Table 7 Comparison of vomiting between the groups

	N	Before medication		24h after medication			24h after medication and before medication		
		[n (%)]		[n (%)]			[n (%)]		
		0 point	1 point	0 point	1 point	2 points	1 point ↓	1 point ↑	2 points ↑
Butorphanol	68	67(98.6%)	1(1.4%)	61(88.4%)	6(8.7%)	2(2.9%)	0(0%)	7(10.3%)	1(1.4%)
Fentanyl	77	75(97.4%)	2(2.6%)	56(72.7%)	18(23.4%)	3(3.9%)	2(2.6%)	18(23.4%)	3(3.9%)
Test statistics	/	0.226		5.305			3.725		
P value	/	0.634		0.021			0.054		

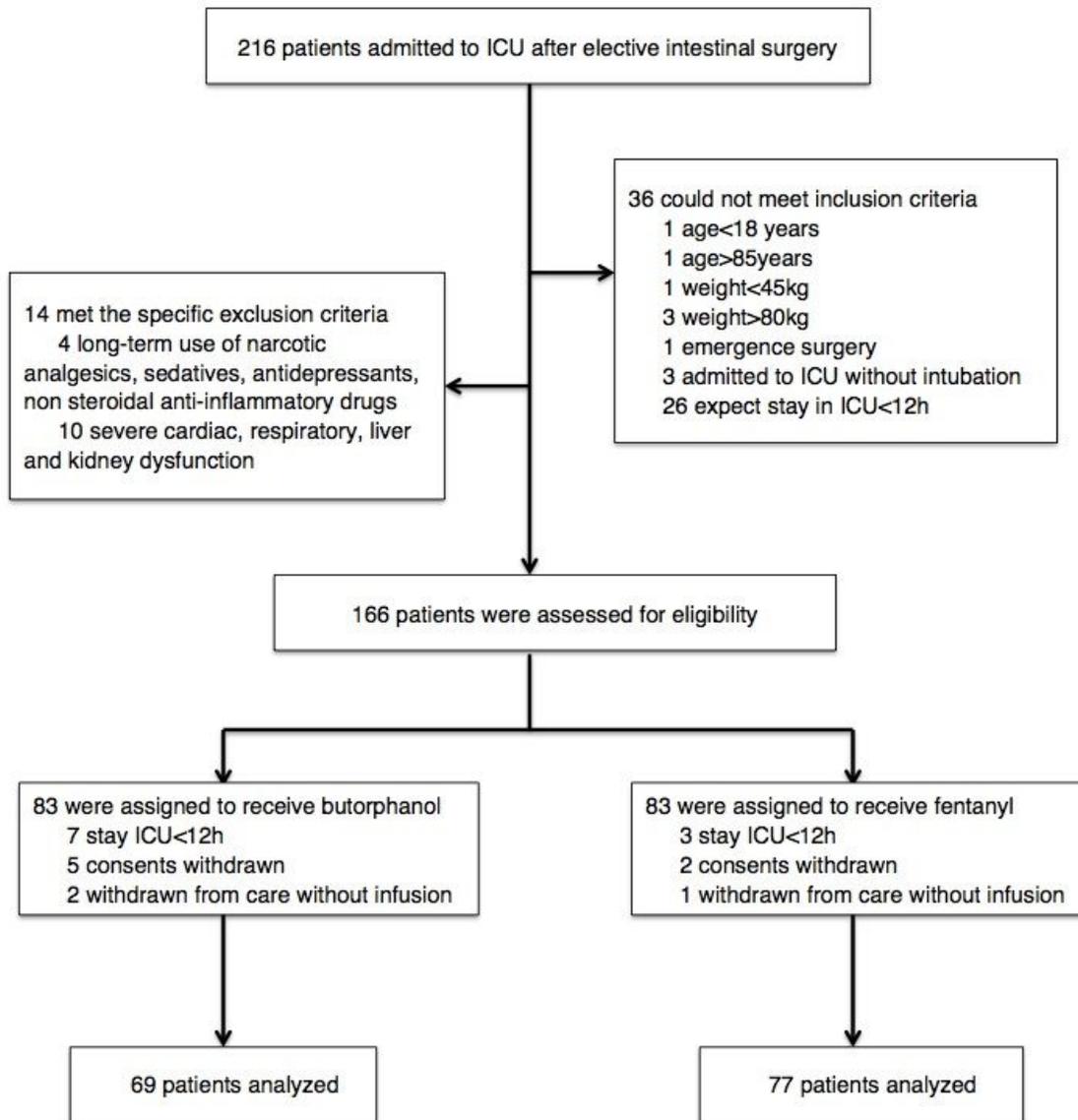
1. Some patients were intubated before and 1h after medication, unable to evaluate vomiting status.

2. Vomiting score: 0 No vomiting, 1 Mild vomiting (1-2 times per day), 2 Severe vomiting (more than 3 times per day)

Table 8 Comparison of adverse reactions after medications

	hypotension (n,%)	hypertension (n,%)	respiratory depression (n,%)	bradycardia (n,%)	tachycardia (n,%)
Butorphanol(n=69)	6(8.7%)	2(2.9%)	7(10.14%)	4(5.80%)	9(13.04%)
Fentanyl (n=77)	2(2.6%)	4(5.19%)	17(22.08%)	7(9.09%)	10(12.99%)
<i>P value</i>	0.149	0.684	0.052	0.452	0.992

## Figures



**Figure 1**

The CONSORT flow diagram of patient enrollment. Abbreviation: ICU intensive care unit