Int J Clin Exp Med 2018;11(11):12592-12598
www.ijcem.com /ISSN:1940-5901/IJCEM0081967

Original Article

Effects of flurbiprofen axetil combined with different doses of butorphanol on intravenous analgesia after resection of liver cancer

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Received July 2, 2018; Accepted August 22, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: Objective: To study the effect of flurbiprofen axetil combined with different doses of butorphanol on intravenous analgesia after resection of liver cancer (LC). Methods: A retrospective analysis of 180 patients who underwent LC resection was performed. All patients were diagnosed with LC class I-II and classified into three groups A(57), B(62), and C(61) based on the use of drugs. All patients were administered midazolam 0.03-0.05 mg/kg, propofol 1-2 mg/kg, sufentanil 0.5-1 μg/kg, and atracurium 0.4-0.5 mg/kg, with continuous intravenous infusion of atracurium and propofol and sustained inhalational sevoflurane to maintain anesthesia during the operation. 6 mg, 8 mg, and 10 mg butorphanol combined with flurbiprofen axetil 100 mg + butorphanol 6 mg + 0.9% NaCl in 100 mL were administered for A, B and C respectively. Analgesia indicators were observed and the visual analog scale (VAS) scores, Ramsay sedation (RS) scores, and vital signs at 2, 4, 8, 12, 24, and 48 h after operation were recorded. Adverse reactions were observed. Results: VAS scores at each time point in group A were significantly higher than those in groups B and C ($P<0.05$). RS score in group C was significantly higher than that in groups A and B at each time point ($P<0.01$). The incidence rate of adverse reactions in group A was significantly lower than that in group C ($P<0.05$). Conclusion: Butorphanol 8 mg combined with flurbiprofen axetil 100 mg has good analgesic effect on LC patients with patient-controlled analgesia, and the incidence rate of adverse reactions is relatively lower. It is applicable to the clinic and can be widely promoted.

Keywords: Flurbiprofen axetil, butorphanol, liver cancer, analgesia

Introduction

Liver cancer (LC) is the most common primary and malignant cancer of the digestive tract. Statistics show that the incidence rate of LC ranks sixth among all cancers, but LC-related mortality is the third highest among that of malignant tumors [1]. Approximately 500,000 cases are added each year globally [2]. The treatment of LC is currently mainly based on surgical treatment. In recent years, with the development of medical science and technology, the complications and mortality of patients with LC have reduced significantly by the surgical resection of the lesion tissue, which has improved survival rate [3].

Postoperative pain is mainly due to a complex type of psychological and physiological reactions, which has a serious impact on the patient's rehabilitation and quality of life [4]. The resection of lesions in patients with LC usually causes large and deep wounds, causing severe pain. During patient-controlled analgesia (PCA), after the patient begins to feel the pain, the pre-configured analgesic is continuously and evenly infused into the body through a dedicated analgesic pump to achieve sustained analgesia [5]. However, PCA formulas for postoperative patients with LC include mainly numerous opioids. The use of large amounts of opioids can cause a variety of adverse reactions, such as vomiting, nausea, pruritus, and hyperalgesia [6].

Butorphanol belongs to a new class of synthetic opioid-specific receptor antagonists that exerts a sedative effect by acting on the κ receptor [7]. Studies have shown that the analgesic effect of butorphanol is 3.5-7 times of that of morphine, and the incidence rate of adverse reactions is more lower [7]. Therefore, butorphanol is widely

used in clinical postoperative analgesia; However, Long-term use can induce symptoms of drowsiness and dizziness [8]. Flurbiprofen axetil is a non-steroidal anti-inflammatory drug that is formulated as targeted microspheres. It inhibits peripheral and central cyclooxygenase activity, reduces prostaglandin synthesis, and relieves inflammation reaction and tissue edema in the body, thereby reducing postoperative peripheral nerve pain and achieving sedation [9].

Nowadays, flurbiprofen axetil combined with butorphanol has been widely used in a variety of postoperative analgesia protocols. However, there are few studies on flurbiprofen axetil combined with butorphanol on postoperative analgesia for LC. Non-steroidal anti-inflammatory drugs may also have certain adverse reactions, but no obvious adverse reactions were confirmed by clinical trials of flurbiprofen axetil [10, 11]. Therefore, this study explored the effect of flurbiprofen axetil combined with different doses of butorphanol on intravenous analgesia after resection of LC, providing a method for clinical analgesia.

Materials and methods

A retrospective analysis of 180 patients with LC who underwent LC resection at our hospital was performed. All patients were diagnosed as patients with LC by biopsy. They were divided into groups A, B, and C according to drug use. There were 57 patients in group A, 25 males and 22 females, with an average age of 52.8± 5.2 years; there were 62 patients in group B, 32 males and 30 females, with an average age of 53.1±4.9 years; there were 61 patients in group C, 30 males and 31 females, with an average age of 52.6±4.7 years. All patients were diagnosed with LC class I-II in accordance with the American College of Anesthesiology classification. The study was approved by the Medical Ethics Committee of the hospital. The family members of the patients and themselves were all informed and they provided signed informed consents.

Inclusion and exclusion criteria

Inclusion criteria: age >18 years; normal heart, liver, and kidney function; no congenital immunodeficiency; complete basic data available, willingness to cooperate with the treatment and follow-up; no tumor metastasis before treatment.

Exclusion criteria: autism, memory impairment, and hearing impairment; allergic to the use of the investigational drugs; gastrointestinal ulcer bleeding, history of asthma, endocrine diseases, previous use of the investigational drugs before surgery.

Anesthesia method

Food and water intake were restricted 8 and 6 h, respectively before surgery and 1 mg of phencyclidine hydrochloride was injected routinely. The patient's electrocardiogram, heart rate, arterial pressure, and oxygen saturation were recorded. All patients were administered 0.03-0.05 mg/kg midazolam (Jiangsu Enhua Pharmaceutical Co., Ltd., GYZZ H10980025), 1-2 mg/kg propofol (Sichuan Guorui Pharmaceutical Co., Ltd., GYZZ H20030115), 0.5-1 μg/kg sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., GYZZ H20054172), and 0.4-0.5 mg atracurium (Shanghai Hengrui Pharmaceutical Co., Ltd., GYZZ H20061298) to induce anesthesia. After satisfactory muscle relaxation, the endotracheal tube was inserted and connected to a ventilator (tidal volume 8-10 mL/kg, respiratory rate 10-12 times/min, respiratory ratio, 1:2) for mechanical ventilation. Continuous anesthesia was maintained intraoperatively by continuous propofol and atracurium infusion and continuous sevoflurane (Shanghai Hengrui Pharmaceutical Co., Ltd., GYZZ H20070172) inhalation. Sufentanil was administered to patients according to their intraoperative conditions.

Postoperative drug administration

All patients were intravenously injected with 5 mg tropisetron (Nanjing Real Pharmaceutical Co., Ltd., Zhunzi H20080660) after the completion of the surgery.

The specific parameters of the PCA pump were set as follows: continuous infusion rate, 2 mL/h; single dose (0.5 mL); time, 15 min. The drug concentrations in the three groups of patients were as follows: dissolved flurbiprofen axetil 100 mg + butorphanol 6 mg + 0.9% NaCl in 100 mL in group A; dissolved flurbiprofen axetil 100 mg + butorphanol 8 mg + 0.9% NaCl in 100 mL in group B; dissolved flurbiprofen axetil 100 mg + butorphanol 10 mg + 0.9% NaCl in 100 mL in group C. After the surgery was completed, a loading dose of butorphanol 1 mg was intravenously injected before the PCA pump was connected.

Table 1. Clinical data of the three groups of patients [n (%)]

Group	A group (n=57)	B group (n=62)	C group (n=61)	F/X^2	*P* value
Sex				0.915	0.178
Male	25 (43.86)	32 (51.61)	30 (49.18)		
Female	22 (38.60)	30 (48.39)	31 (50.82)		
Age (year)	52.8±5.2	53.1±4.9	52.6±4.7	0.160	0.852
BMI (kg/m^2)	22.50±1.64	22.77±1.52	22.15±1.44	2.526	0.083
Smoking history				0.348	0.840
Yes	27 (47.37)	32 (51.61)	32 (52.46)		
No	30 (52.63)	30 (48.39)	29 (47.54)		
Drinking history				0.673	0.791
Yes	10 (47.37)	15 (24.19)	13 (21.31)		
No	47 (52.63)	47 (75.81)	48 (78.69)		
History of hypertension				1.177	0.555
Yes	42 (73.68)	48 (77.42)	50 (81.97)		
No	15 (26.32)	14 (22.58)	11 (18.03)		
Blood volume in operation (mL)	412.4±213.6	429.6±232.5	420.7±262.4	0.078	0.925
Duration of operation	162.5±28.6	159.2±30.5	168.7±31.2	1.568	0.211
Postoperative recovery time (min)	16.5±9.2	18.5±9.8	16.9±8.6	0.797	0.452

Analgesia indicators

Main observation indicators included monitoring of blood pressure, heart rate, and respiratory rate at 2, 4, 8, 12, 24, and 48 h after surgery. Analgesia was assessed by the visual analog scale (VAS) and Ramsay sedation (RS) scores. The maximum score under VAS is 10; the higher the score, the more obvious is the patient's pain. A score <3 indicates that analgesia is good; 3-4 indicates that the patient is satisfied; a score >5 indicates that the analgesic effect is poor. The maximum RS score is 6; the higher the score, the more obvious is the sedative effect. A score of 1 indicates that the patient is not sedated and is restless; 2 indicates that the patient is quiet and cooperative; 3 indicates that the patient is drowsy but obeys orders; 4 indicates that the patient is asleep but can be awakened; 5 indicates that the patient is unresponsive after awakening; and 6 indicates that the patient is in deep sleep and cannot be awakened. Accordingly, a score of 2-4 indicates that the sedative effect is satisfactory, whereas a score of 5 or 6 indicates excess sedation.

Secondary observation indicators included monitoring of intraoperative blood loss, duration of surgery, and postoperative awakening time. Postoperative adverse reactions (Postoperative adverse reactions were noted and were treated symptomatically).

Statistical methods

In this study, the SPSS 20.0 software package was used to perform statistical analysis on the collected data. GraphPad Prism 7 was used to plot the data. The enumeration data were expressed as a rate (%) using the chi-square test and Fisher's exact test. The measurement data were expressed as mean ± SD, and intergroup differences consistent with normal distribution were analyzed using the *t*-test. Statistical significance was considered when $P<0.05$.

Results

Comparison of clinical data of patients

As shown in **Table 1**, we found that there was no statistical difference in gender, age, BMI, smoking history, alcohol abuse history, intraoperative blood loss, surgical duration, and postoperative recovery time among the three groups ($P>0.05$).

Postoperative blood pressure, heart rate, and respiratory rate

As shown in **Table 2**, there was no significant difference in blood pressure, heart rate, and

Table 2. Blood pressure, heart rate, and respiratory rate of the three groups of patients at different time points after operation

Time		Blood pressure	Heart rate	Breathing rate
2 h	A group	82.9±9.8	79.5±11.3	16.5±3.5
	B group	83.5±9.7	81.6±10.2	16.4±4.5
	C group	83.1±10.1	80.2±10.8	16.6±4.1
4 h	A group	83.6±9.2	80.1±11.4	16.3±4.4
	B group	84.2±10.5	80.7±10.5	16.7±4.4
	C group	84.5±9.3	80.9±10.4	16.9±4.6
6 h	A group	84.2±11.5	81.0±10.1	16.5±4.2
	B group	84.9±11.2	80.2±10.8	16.2±4.5
	C group	85.1±10.3	80.5±11.1	16.4±4.1
8 h	A group	84.6±11.4	80.4±10.9	16.4±4.2
	B group	84.4±10.8	81.5±10.5	16.6±4.5
	C group	84.1±11.8	80.6±10.2	16.3±4.1
12 h	A group	84.2±12.3	81.3±10.6	16.5±4.6
	B group	85.1±11.8	82.2±11.2	16.8±4.3
	C group	85.3±10.5	81.1±12.5	16.6±4.6
24 h	A group	84.2±11.3	81.5±12.2	16.5±3.5
	B group	85.1±10.5	81.5±12.2	16.4±4.5
	C group	84.6±11.8	81.5±13.2	16.6±4.1
48 h	A group	85.5±10.1	81.5±11.5	16.5±4.2
	B group	85.2±11.2	82.3±13.2	16.4±4.5
	C group	84.1±10.5	82.5±11.9	16.7±4.4

the respiratory rate among the three groups at 2, 4, 8, 12, 24, and 48 h (P>0.05).

Changes in VAS and RS scores

In this study, the statistical analysis of the VAS and RS scores from the three groups of patients during the treatment process showed that the VAS scores at each time point were different among the three groups (P<0.05), and the scores of groups B and C were lower than those of group A (P<0.05). As shown in **Table 3**, there was no difference in the VAS scores between groups B and C (P>0.05). There were differences in the RS scores among the three groups (P<0.05); the scores of groups A and B were lower than those of group C (P<0.05), but as shown in **Table 4**, there was no difference at each point between groups A and B (P>0.05).

Incidence of adverse reactions

We compared the incidence of adverse reactions among the three groups of patients and found that there was no difference in the incidence of adverse reactions between groups A and B (P>0.05). The incidence of adverse reactions in group A was significantly lower than that in group C (P<0.05). There was no difference between groups B and C (P>0.05) as shown in **Table 5** and **Figure 1**.

Discussion

LC is a common malignant cancer of the digestive system. With the development of society and the improvement in the quality of life, its incidence has also shown a clear upward trend [12]. In the 2016 US Cancer Statistics Report, 39,200 patients were newly diagnosed with LC and intrahepatic cholangiocarcinoma, and more than 18,200 deaths were recorded [13]. Although the five-year survival rate of patients has improved [14], the recurrence rate is as high as 70% after five years of operation. This has a serious impact on the prognosis and quality of life of patients. Early diagnosis and early treatment of LC have been the most important means in clinical practice to effectively improve the prognosis. The early stage of LC has no obvious clinical characteristics, and it needs to be roughly assessed by imaging methods. The early treatment of LC mainly improves the patient's condition by surgically removing the lesion tissue [15]. The resection of LC is an upper abdominal operation that causes extensive trauma to the patient, and the patient may experience significant stress [16]. Because traditional postoperative treatment could not effectively prevent the postoperative stress response, the concept of PCA came into being.

Micro-analgesic pumps controlled by microprocessors are used to release analgesics when the patient begins to feel the pain [17, 18]. Clinically, there are many PCA administration methods. The commonly used PCA administration methods include pure PCA, background dose + PCA, and loading dose + background dose + PCA. We used the loading dose + background dose + PCA method in this study. Compared with the other two methods, this method is simple, effective, and widely applicable. It is commonly used in clinical practice and is the main method for postoperative analgesia [19, 20]. In clinical practice, postoperative analgesia treatment mainly involves opioids and fentanyl. Although their analgesic effects are obvi-

Table 3. VAS scores in the three groups of patients

Group	2 h	4 h	8 h	12 h	24 h	48 h
A group (n=57)	3.44±0.33	3.35±0.47	3.24±0.44	2.42±0.35	2.09±0.59	1.52±0.39
B group (n=62)	2.97±0.28*	2.82±0.27*	2.61±0.26*	2.07±0.25*	1.76±0.21*	1.19±0.22*
C group (n=61)	3.05±0.34*	2.96±0.33*	2.65±0.29*	2.15±0.22*	1.85±0.17*	1.21±0.15*

Note: *indicates that there is a difference from group A (P<0.05).

Table 4. RS scores in the three groups of patients

Group	2 h	4 h	8 h	12 h	24 h	48 h
A group (n=57)	1.78±0.43*	1.89±0.46*	1.71±0.37*	1.82±0.54*	1.81±0.52*	1.85±0.47*
B group (n=62)	1.92±0.61*	2.04±0.56*	1.91±0.43*	2.01±0.52*	1.95±0.37*	2.06±0.35*
C group (n=61)	2.33±0.63	2.52±0.54	2.42±0.69	2.61±0.79	2.56±0.83	2.33±0.66

Note: *indicates that there is a difference from group C (P<0.05).

Table 5. Incidence rate of adverse reactions in the three groups of patients [n (%)]

Group	Feel like vomiting	Vomit	Dizzy	Itch of skin	Respiratory depression	Abnormal bleeding	Amount to	X^2	*P* value
A group (n=57)	0 (0.00)	1 (1.75)	1 (1.75)	1 (1.75)	0 (0.00)	0 (0.00)	3 (5.26)		
B group (n=62)	3 (4.84)	2 (3.23)	2 (3.23)	1 (1.61)	1 (1.61)	0 (0.00)	9 (14.52)	7.460	0.024
C group (n=61)	4 (6.55)	3 (4.92)	5 (8.20)	1 (1.64)	1 (1.64)	0 (0.00)	14 (22.95)	7.460	

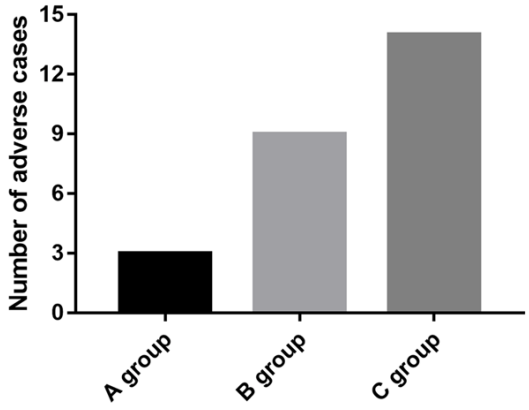

Figure 1. Number of adverse reactions in the three groups of patients. 3 patients in group A, 9 patients in group B, and 14 patients in group C.

ous, they often cause nausea, vomiting, and other adverse reactions during analgesia, which have a serious impact on the patient's quality of life [21].

Flurbiprofen axetil is a new type of synthetic non-steroidal targeted analgesic. Studies have shown that flurbiprofen axetil can reduce the pain conduction of nerve endings before surgery, and increase the pain threshold to achieve early analgesia [22]. Flurbiprofen axetil is unevenly distributed in the body, achieving analgesic effect through selective accumulation at the site of surgical incision and inflammation. It has a little adverse effect on the digestive tract, fast efficacy, and causes a low inhibitory effect on the central nervous system, and thus, has been widely used. However, flurbiprofen axetil has a capping effect on analgesia. When a capping effect occurs, the continuously increased dose will not increase the analgesic effect, but bring about more side effects [23]. Therefore, a combination of drugs is usually used in clinical practice to achieve better analgesia. Butorphanol has a long-lasting analgesic effect and a low incidence of drug dependency. The main effect of butorphanol is to stop the central nervous system from being excited before it becomes responsive to pain, and to reduce or eliminate the sensitization of the central nervous system after tissue damage, thereby achieving analgesic effects [24].

In this study, we found that the vital indicators of blood pressure, heart rate, and respiratory rate at all time points were comparable among the patients of groups A, B, and C. Subsequently, we assessed the VAS scores for the three groups of patients. According to the inter-group comparison, the scores of patients at each

time point in group A were higher than those in groups B and C, indicating that the analgesic effect of groups B and C was better than that of group A. RS scores at all time points in groups A and B were lower than those in group C, indicating that high concentrations of butorphanol have a strong stabilization effect on patients. However, by statistical analysis of the incidence of adverse reactions in the three groups of patients, we found that the incidence rate of adverse reactions in group C of high-dose butorphanol was significantly higher than that in groups A and B, and there was no difference in the incidence rate of adverse reactions between groups A and B. This shows that although the high-dose butorphanol of group C has good performance in terms of sedation and analgesia, the incidence rate of adverse effects is high. In contrast, the medium-dose butorphanol in group B also has good analgesic effect and significantly reduced the incidence rate of adverse reactions. A study by Zhang et al. [25] showed that the incidence rate of adverse reactions at 6 mg butorphanol was significantly lower than that at 8 mg butorphanol, and the analgesic effect was better than that at 4 mg butorphanol, which is similar to our study.

However, there are still some limitations of our study: small sample size, a short observation period, and a lack of long-term observation of patients. Therefore, we will increase the number of samples in the future study and lengthen our observation period to validate our conclusions.

In summary, 8 mg butorphanol combined with 100 mg flurbiprofen axetil has good analgesic effect in PCA of LC patients, and the incidence rate of adverse reactions is relatively lower, which is suitable for clinical application.

Disclosure of conflict of interest

None.

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