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ORIGINAL ARTICLE

Flurbiprofen axetil enhances analgesic effect of fentanyl associated with increase in β-endorphin levels

Zhao-Fang Liu · Xiao-Qing Chai · Kun-Zhou Chen

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Abstract
Purpose To examine the analgesic effect of preoperative administration of flurbiprofen axetil and that of postoperative administration of a combination of flurbiprofen axetil and fentanyl, as well as perioperative plasma β-endorphin (β-EP) levels in patients undergoing esophagectomy.
Methods Forty-five patients were randomly divided into three groups: group A: 100 mg flurbiprofen axetil preoperative, 10 μg/kg fentanyl + 10 ml placebo postoperative; group B: 100 mg flurbiprofen axetil preoperative, 10 μg/kg fentanyl + 100 mg flurbiprofen axetil postoperative; group C: 10 ml placebo preoperative, 10 μg/kg fentanyl + 10 ml placebo postoperative. Postoperative analgesia was achieved by intravenous infusion containing flurbiprofen axetil and/or fentanyl at 2.0 ml/h (total volume, 100 ml) using infusion pumps. The β-EP was measured at preanesthesia (T_1), the end of surgery (T_2), 24 h (T_3), and 48 h (T_4) after surgery. Visual analog scale scores (VAS) at T3, T4 (at rest), and rescue analgesic tramadol requirement was recorded.
Results The VAS of group B was significantly lower than group A and C ($P < 0.01$) at T_3 and T_4. The β-EP levels at T_2–T_4 in group A did not differ significantly from those at T_1 ($P > 0.05$); however, the β-EP levels in group B at T_3–T_4 increased significantly ($P < 0.05$), while those in group C increased at T_2 and decreased at T_4 ($P < 0.05$). The β-EP levels in group B at T_3 and T_4 were the highest as compared to its levels in groups A and C ($P < 0.01$). Tramadol consumption in group B was significantly lower than in groups A and C ($P < 0.01$).
Conclusion These results show that flurbiprofen axetil enhances the analgesic effect of fentanyl associated with increase in β-EP levels.

Keywords Flurbiprofen · Fentanyl · β-Endorphin · Analgesic

Introduction

Thoracic surgery is associated with trauma and severe sustained postoperative pain within 48 h after operation. Good postoperative analgesia helps reduce pulmonary and cardiac complications. Flurbiprofen axetil, which is incorporated in lipid microspheres that serve as the carrier, is a nonsteroidal antiinflammatory drug (NSAID) that accumulates at the site of surgical incision and the site of inflammation [1]. It has been reported that flurbiprofen axetil inhibits the biosynthesis of prostaglandins [2], reduces pain in response to the endogenous inflammatory factors, inhibits peripheral sensitization and the synthesis of prostaglandins in the spinal cord, reduces noxious perception in the peripheral afferent nerve, and alleviates central sensitization [3]. Our previous study confirmed that preoperative administration of flurbiprofen axetil in patients scheduled to undergo thoracotomy exerts marked preemptive analgesic effects [4]. Prophylactic administration of this drug before operation can effectively reduce the degree of postoperative pain and the requirement for analgesic drugs [3, 5]. NSAIDs and opioid drugs are known to possess synergistic analgesic effects. Taken together, the present and previous findings support the notion that the

Z.-F. Liu
Department of Anesthesiology, Yijishan Hospital of Wannan Medical College, Wuhu 241001, China

X.-Q. Chai (✉) · K.-Z. Chen
Department of Anesthesiology, Anhui Provincial Hospital, Hefei 230001, China
e-mail: xiaoqingchai62@yahoo.cn

contribution of the central nervous system, particularly of downstream pain-control structures, to the analgesic effects of NSAIDs involves endogenous opioidergic mechanisms [6]. Cashman [7] suggested that NSAIDs exert their analgesic effect not only through peripheral inhibition of prostaglandin synthesis but also through a central mechanism of action that augments the peripheral mechanism and that the central action may be mediated by endogenous opioid peptides. The experimental study showed that the β-EP level in the hypothalamus, medulla oblongata, and midbrain increased in a dose-dependent manner after intravenous administration of idomethacin [8]. The analgesic effect of lornoxicam can be accentuated by activating the endogenous opioid system and affecting the release of β-EP [9]. However, there have been no clinical studies to date to confirm that flurbiprofen axetil affects the level of endogenous opioid peptides. In this study, we aimed to investigate the analgesic effect of preoperative flurbiprofen axetil administration and postoperative flurbiprofen axetil and fentanyl administration on perioperative plasma β-endorphin (β-EP) level in patients scheduled to undergo radical esophagectomy under thoracotomy.

Materials and methods

After obtaining approval from the Ethics Committee of the hospital and written informed consent from the study participants, we recruited 45 American Society of Anesthesiologists (ASA) II patients (with normal lung function) who were scheduled to undergo open radical esophagectomy for cancer. The patients comprised 35 men and 10 women aged 55–64 years weighing 49–80 kg. The exclusion criteria included history of allergy to any NSAID, hepatic and renal dysfunction, and coagulopathy. Patients, nurses, and researchers involved in data collection were blinded to the use of drug. The drugs were dispensed by separate individuals and labeled using simple names. The study was randomized by drawing lots.

Forty-five ASA II patients scheduled to undergo radical esophagectomy for cancer were randomly divided into three groups ($n = 15$ in each group). Group A patients received a preoperative dose of 100 mg flurbiprofen axetil by intravenous administration and a postoperative dose of 10 μg/kg fentanyl [10] and 10 ml placebo (intralipid) and saline (total volume, 100 ml) by analgesic pump. Group B patients received a preoperative dose of 100 mg flurbiprofen axetil by intravenous administration and a postoperative dose of 10 μg/kg fentanyl and 100 mg flurbiprofen axetil and saline (total volume, 100 ml) by analgesic pump. Group C patients received a preoperative dose of 10 ml placebo and a postoperative dose of 10 μg/kg fentanyl and 10 ml placebo and saline (total volume, 100 ml) by analgesic pump. Preoperative flurbiprofen axetil/placebo was administered 15 min before the induction of anesthesia. When suturing the skin, postoperative analgesia was achieved for all patients by intravenous infusion (2.0 ml/h) using an AuBex microinfusion analgesic pump (Japan) with automatic control. In this study, we used a 50 mg/5 ml solution of flurbiprofen axetil (batch no. 5027M; Beijing Tide Pharmaceutical, China) and placebo (intralipid batch no. 061206401; Huarui Pharmaceutical, Chengdu, China). The placebo and flurbiprofen axetil solutions appeared similar.

Anesthesia methods

Diazepam (10 mg) and atropine (0.5 mg) were intramuscularly injected at 30 min before anesthesia. Next, 6% hydroxyethyl starch (130/0.4) and a mixture of sodium lactate Ringer's solution were infused at 10 ml/kg/h through a peripheral or central venous catheter. Electrocardiography (ECG) was performed, and invasive arterial blood pressure (ABP), heart rate (HR), pulse oxygen saturation (SpO_2), and central venous pressure (CVP) were monitored by standard methods. Anesthesia was induced with 0.05 mg/kg midazolam, 3.5 μg/kg fentanyl, 2 mg/kg propofol, and 1 mg/kg rocuronium, and an anesthesia machine was installed to control breathing. Subsequently, endotracheal intubation was performed with a tidal volume of 6–8 ml/kg, and ventilation was adjusted to maintain the $PETCO_2$ at 35–45 mmHg. During operation, 50–100 μg/kg/min propofol and 0.1–0.2 μg/kg/min remifentanil were intravenously infused, and 0.05 mg/kg vecuronium was intermittently injected for maintaining the effect of anesthesia. An adequate depth of anesthesia (bispectral index values, 45–55) and ABP fluctuations (±20%) in the underlying value were maintained during the operation. Before closing the chest, 1 μg/kg fentanyl was intravenously injected. An AuBex automatic microinfusion analgesic pump was used to achieve analgesia when suturing the skin. All patients were delivered to the postanesthesia recovery room (PACU) after the end of operation. The endotracheal tube was removed from patients in whom extubation was indicated. Next, 10 mg azasetron was intravenously infused to prevent postoperative nausea and vomiting. In the surgical ward, patients were administered tramadol 100 mg/times intramuscular injection to rescue analgesia.

Blood (2 ml) was collected from the central vein before the induction of anesthesia (T_1), at the end of operation (T_2), and 24 h (T_3) and 48 h (T_4) after surgery. These samples were then introduced in tubes containing 10% ethylenediaminetetraacetic acid (EDTA) and aprotinin and incubated at 4°C for 15 min. Plasma was separated by centrifugation at 3,000 rpm for 10 min. The plasma

samples were stored at −70°C until further analysis. The concentration of β-EP in plasma was measured by radioimmunoassay using commercially available standards kits (Beijing Institute of Biotechnology, Huaying, China). The pain score (at rest) was evaluated based on the visual analog scale (VAS) with a ruler (0 cm indicated no pain and 10 cm indicated worst pain) at 24 and 48 h after the operation.

Statistical analysis

All data were presented as mean ± SD. Analysis of variance (ANOVA), Q test, and chi-square test were used to analyze the repeated measured data between the groups, the data from two groups, and the enumeration data, respectively. P values less than 0.05 were considered statistically significant.

Results

There were no differences in the patients of the three groups with regard to gender, age, weight, height, operative time, dose of analgesic drug, volumes of fluid infusion, blood loss, and urine output at $P > 0.05$ (Table 1). The plasma level of β-EP (Table 2) in group A patients did not differ significantly between T_1 and T_{2-4} ($P > 0.05$). The level of β-EP in group B patients was increased at T_3 and T_4 as compared to that at T_1 ($P < 0.05$). However, the level of β-EP in group C patients increased at T_2 and decreased at T_4 as compared to its level at T_1 ($P < 0.05$).

The level of β-EP in group B patients at T_3 and T_4 was higher than that in groups C and A ($P < 0.01$). The level of β-EP in group A patients at T_4 was higher than that in group C ($P < 0.05$) (Table 2).

The VAS at rest of group A and group B patients at T_3 and T_4 decreased significantly as compared to that of group C patients ($P < 0.01$); further, the VAS score of group B patients was less than that of group A patients (T_3, $P < 0.01$; T_4, $P < 0.05$) (Table 3).

Postoperative tramadol consumption in group B was significantly lower than that in groups A and C ($P < 0.05$; $P < 0.01$) (see Table 1).

Discussion

Ohmukai [11] demonstrated that the plasma concentrations of flurbiprofen axetil peaked 5–10 min after intravenous administration of 50 mg of the drug in healthy subjects; the elimination half-life of this drug was 5.8 h. Intravenous administration of flurbiprofen axetil at a dose of 10–80 mg elevated its plasma concentrations in a linear manner. The duration of administration of 100 mg flurbiprofen axetil dose was longer than that of the 50-mg dose. In this study, we injected 100 mg flurbiprofen axetil intravenously 15 min before the induction of anesthesia; therefore, the drug had reached the effective plasma concentration at the time of skin incision. The study was performed in a randomized fashion to ensure the balance of general factors in three groups. To eliminate the effect of subjective bias on the results, we administered the drugs in a double-blinded manner.

Table 1 General data of the three groups (mean ± SD)

Items	Group A ($n = 15$)	Group B ($n = 15$)	Group C ($n = 15$)
Gender (male/female)	11/4	12/3	12/3
Age (years)	61 ± 3	61 ± 3	61 ± 2
Weight (kg)	63 ± 8	63 ± 7	62 ± 6
Height (cm)	168 ± 4	168 ± 5	167 ± 4
Operation time (min)	259 ± 37	256 ± 40	254 ± 42
Propofol dose (mg)	1,206 ± 231	1,213 ± 272	1,202 ± 214
Intraoperative remifentanil dose (mg)	2.5 ± 0.7	2.6 ± 0.7	2.5 ± 0.7
Vecuronium bromide dose (mg)	19.3 ± 3.4	19.1 ± 3.3	19.1 ± 3.9
Volumes of fluid infusion (ml)	2,527 ± 465	2,633 ± 516	2,553 ± 632
Blood loss (ml)	387 ± 136	394 ± 139	371 ± 130
Urine output (ml)	439 ± 164	424 ± 159	427 ± 149
Postoperative fentanyl (analgesic) dose (mg)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Postoperative tramadol requirement dose (mg)	180.0 ± 74.8$^{\Delta}$	100.0 ± 92.6$^{\#\blacktriangle}$	320.0 ± 86.2

$^{\Delta}$ $P < 0.01$, group A versus group C

$^{\#}$ $P < 0.05$, group B versus group A

$^{\blacktriangle}$ $P < 0.01$, group B versus group C

Table 2 Level of β-endorphin in the three groups (pg/ml) (mean ± SD)

Groups ($n = 15$)	T_1	T_2	T_3	T_4
Group A	147.21 ± 44.57	162.09 ± 38.87	146.48 ± 48.70	148.55 ± 47.41$^{\Delta\Delta}$
Group B	144.96 ± 43.04	164.57 ± 35.77	182.91 ± 46.24*$^{\#\blacktriangle}$	174.59 ± 46.47*$^{\#\blacktriangle}$
Group C	146.39 ± 51.08	174.42 ± 37.24*	127.35 ± 47.59	101.93 ± 53.24*

* $P < 0.05$ versus T_1 (preanesthesia)

$^{\Delta\Delta}$ $P < 0.05$, group A versus group C

$^{\#}$ $P < 0.01$, group B versus group A

$^{\blacktriangle}$ $P < 0.01$, group B versus group C

Table 3 Visual analog scale (VAS) scores at rest of the three groups (mean ± SD)

Groups ($n = 15$)	24 h	48 h
Group A	2.47 ± 0.64$^{\Delta\#}$	1.53 ± 0.52$^{\Delta\#\#}$
Group B	1.51 ± 0.57$^{\blacktriangle}$	1.13 ± 0.29$^{\blacktriangle}$
Group C	3.73 ± 0.39	2.73 ± 0.37

$^{\Delta}$ $P < 0.01$, group A versus group C

$^{\blacktriangle}$ $P < 0.01$, group B versus group C

$^{\#\#}$ $P < 0.05$, $^{\#}$ $P < 0.01$, group A versus group B

Postthoracotomy pain is one of the most severe types of postoperative pain. Because of the difficulty in pain control, many approaches have been suggested, but a multimodal therapeutic strategy that provides a central or peripheral block associated with NSAID and adjuvant drugs is now the cornerstone of treatment, offering the possibility of reducing opioid requirements and side effects [12]. In this study, the model in which patients received preoperative flurbiprofen axetil and postoperative flurbiprofen axetil with low doses of fentanyl combination analgesia showed the lowest pain score, lowest analgesic consumption, and highest β-EP levels, indicating that preoperative administration of flurbiprofen intravenously facilitates the analgesic effect in the early postoperative period [13], and that combination administration of low doses of fentanyl with flurbiprofen axetil results in analgesic potentiation. The combined administration of low doses of opiates with NSAIDs can produce additive or supraadditive analgesic effects [14].

Endogenous opioid systems are involved in the body's analgesic response to acute pain and stress [15]. β-EP is known to play an important role in the regulation of neural and endocrine functions and in the pain mechanism [16, 17]. Animal studies indicate that β-EP has analgesic properties; it not only mediates antinociception but also prevents the delayed hyperalgesic response [18]. Clinical studies have shown that suppression of plasma β-EP levels is associated with increased postoperative pain, and that elevation of β-EP levels results in analgesia [19, 20]. These findings suggest that pituitary β-EP release is a component of an endogenous pain inhibitory system in humans [21] and may be manipulated by pharmacological interventions [15].

In this study, with the interval of intravenous administration of flurbiprofen axetil or placebo to blood testing being 15 min before anesthesia, no significant difference in β-EP levels was seen in the three groups, indicating the flurbiprofen axetil did not alter basal β-EP release. The pretreatment of intravenous administration of flurbiprofen axetil was combined with a general anesthetic, thereby minimizing any influence of nociceptive stress on the elevated endorphin levels observed; thus, the β-EP levels had no statistically significant increase at the end of surgery in groups A and B. The increase of plasma β-EP levels at the end of surgery in group C could have been caused by surgery stress-induced pituitary manipulation with massive release into the peripheral blood [22]. NSAID pretreatment did not alter basal endorphin release from pituitary, but enhanced pituitary β-EP release was caused by a variety of stimuli in the presence of NSAIDs [23]. The β-EP levels in group B at T_3 and T_4 was the highest as compared to its levels in groups A and C; the interaction between flurbiprofen axetil and elevated β-EP levels can likely be attributed to potentiation of stress-induced release. This result supports the study in which ibuprofen enhanced the pituitary release of β-EP by corticotroph cells in response to stress [23].

Animal and clinical studies showed that central and peripheral prostaglandin E_2 (PGE_2) levels were increased during and after surgery, which can be attenuated by NSAIDs [24–26]. The central effects of NSAIDs might involve interaction with the opioid receptor system through indirect mechanisms [27]. PGE_2 inhibits release of β-EP and corticotropin from pituitary corticotroph cells, suggesting that suppression of prostaglandin levels can increase β-EP release [23, 28]. PGE_2 did not alter the release of basal β-endorphin-like immunoreactive substances (β-EI); however, stimulation with arginine–vasopressin (AVP) or corticotropin-releasing factor (CRF) elevated PGE_2 concentration and inhibited the release of β-EI by 60%. Similarly, flurbiprofen had no effect on the basal release of

ACTH-like substances or β-EI, but it enhanced ACTH-immunoreactivity/β-EI release upon stimulation by AVP or synthetic ovine CRF [29]. Therefore, we consider that the elevated levels of β-EP are related to the inhibition of PGE_2 production by flurbiprofen axetil, as reported in our previous study in which flurbiprofen axetil significantly decreased the plasma concentration of PGE_2 [4]. In this study, the β-EP level in group B patients was significantly elevated, indicating that flurbiprofen axetil regulated the release of endogenous β-EP by inhibiting PGE_2 production.

The elevated β-EP levels observed in this study were related to pain stress at the end of operation in group C patients. An equal amount of fentanyl was administered to the patients of all three groups after the operation. However, the plasma level of β-EP in group C patients decreased after the operation and was significantly lower than its preoperative level at 48 h after surgery; further, the group C patients had the lowest level of β-EP over the same period. These results suggested that the exogenous opioid analgesics inhibit the release of endogenous opioid peptides by a feedback mechanism [30, 31]; alternatively, PGE_2 inhibits the release of β-EP and promotes the extravasation of the immune cells containing opioid peptides in circulation and the migration of these cells to the tissue of inflammation, which participated in immunogenicity opioid peptide analgesic mechanisms in the impaired site [32].

In conclusion, the results of this study show that flurbiprofen axetil enhances the analgesic effect of fentanyl associated with increase in β-EP levels. However, the detailed mechanisms by which the flurbiprofen axetil increase β-EP release remain to be elucidated.

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Conflict of interest The authors declare that they have no competing interests.

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