RESEARCH ARTICLE

Intravenous Flurbiprofen Axetil Enhances Analgesic Effect of Opioids in Patients with Refractory Cancer Pain by Increasing Plasma β-Endorphin

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Abstract

Background: The study aimed to investigate the analgesic effect of a combination of intravenous flurbiprofen axetil and opioids, and evaluate the relationship between refractory pain relief and plasma β-endorphin levels in cancer patients. Materials and Methods: A total of 120 cancer patients was randomly divided into two groups, 60 patients took orally morphine sulfate sustained-release tablets in group A, and another 60 patients receiving the combination treatment of intravenous flurbiprofen axetil and opioid drugs in group B. After 7 days, pain relief, quality of life improvement and side effects were evaluated. Furthermore, plasma β-endorphin levels were measured by radioimmunoassay. Results: With the combination treatment of intravenous intravenous flurbiprofen axetil and opioids, the total effective rate of pain relief rose to 91.4%, as compared to 82.1% when morphine sulfate sustained-release tablet was used alone. Compared with that of group A, the analgesic effect increased in group B (p=0.031). Moreover, satisfactory pain relief was associated with a significant increase in plasma β-endorphin levels. After the treatment, plasma β-endorphin level in group B was 62.4±13.5 pg/ml, which was higher than that in group A (45.8±11.2 pg/ml) (p<0.05). Conclusions: Our results suggest the combination of intravenous flurbiprofen axetil and opioids can enhance the analgesic effect of opioid drugs by increasing plasma β-endorphin levels, which would offer a selected and reliable strategy for refractory cancer pain treatment.

Keywords: Flurbiprofen axetil - morphine - refractory cancer pain - analgesic effects - β-endorphin

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Introduction

Refractory cancer pain is defined as failure to achieve adequate analgesia despite maximal opioids escalation and rotation, and development of analgesic-related toxicities or intolerant to opioid-related side effects (Lin et al., 2012). The treatment of refractory cancer pain is more difficult and may be managed as the following methods. First, secondary opioids rotation is the most common and available therapeutic choice (Indelicato et al., 2002). Second, an implantable intrathecal drug delivery system may provide sustained pain control, less drug-related toxicity, and possibly better survival (Smith et al., 2005). Third, bilateral open thoracic cordotomy is not a technique widely used in all the medical facilities, though various neurosurgerical options are often presented in some refractory cases (Atkin et al., 2010). Fourth, single use of new drugs, such as Nabiximols (Portenoy et al., 2012), Flurbiprofen axetil (Wu et al., 2009), Ketamine (Robinson et al., 2012), Ziconotide (Alicino et al., 2012), Methadone (Shaiova et al., 2002), etc, or the combined use of these drugs and opioids, can provide new opportunities for the refractory cancer pain.

Flurbiprofen is a new type of non-selective cyclooxygenase (COX) inhibitors used as non-steroidal anti-inflammatory drugs (NSAIDs) in clinical practice (Roszkowski et al., 1997). Flurbiprofen axetil is a prodrug prepared by esterification of flurbiprofen, which makes the compound lipophilic and soluble in soybean oil in the lipid microsphere. Lipid microsphere is a targeted drug delivery carrier which can congregate selectively in the site such as inflammation or injured blood vessel, and change the distribution of drugs *in vivo* (Zhang et al., 2011). Flurbiprofen axetil injection is composed of lipid microspheres and flurbiprofen axetil (Fujii et al., 2009). Essentially, tumor microenvironment is an inflammatory area presenting abundant neovascularization (Fujii et al., 2011), so flurbiprofen axetil injection is easy to congregate in tumor and relieve cancer-related pain by reducing inflammatory mediator production, inhibiting

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prostaglandin synthesis and decreasing pain threshold (Su et al., 2012). The half-life time of flurbiprofen axetil is 5.8 hours. After being used post-operation, flurbiprofen axetil can exert its effects about 15 minutes later, and last this role for about 3 hours. When flurbiprofen axetil is used in cancer patients, it begins to work quickly about in 30 minutes, and the duration of action is about 9 hours (Yamashita et al., 2006). So it is especially suitable for the patients with breakthrough pain (Fujimoto et al., 2012). As an endogenous peptide opioid derived from proopiomelanocortin, β-endorphin is a neurohormone secreted by the anterior pituitary into the systemic circulation. Although the role of β-endorphin in pain regulation remains unclear, plasma β-endorphin level has been reported to correlate with pain intensity in chronic daily headache (Facchinetti et al., 1981), perioperative pain (Liu et al., 2011) and cancer pain (El-Sheikh et al., 2004).

In this study, our results show that intravenous flurbiprofen axetil can provide few side effects and enhance the analgesic effect of opioid drugs such as morphine sulfate sustained-release tablets by the increased plasma β-endorphin levels in refractory cancer pain, which would be a selected and reliable strategy for refractory pain treatment.

Materials and Methods

Ethics statement

This study protocol was approved by the Ethics Committees of Wuhan General Hospital of Guangzhou Command, People's Liberation Army; Hubei Cancer Hospital; and General Hospital of Jinan Command, People's Liberation Army. Written informed consent was obtained from all patients.

Patients

A total of 120 patients with refractory cancer pain at Wuhan General Hospital of Guangzhou Command, People's Liberation Army; Hubei Cancer Hospital; and General Hospital of Jinan Command, People's Liberation Army from January to November of 2013, was included in this study. Each cancer diagnosis was confirmed by histopathology or cytopathology. Although the patients had been treated by several cycles of chemotherapy or radiotherapy in the past, palliative therapy was the main treatment without other adjuvant treatments currently. These patients had received opioid drugs for at least two weeks and experienced at least one time of opioids rotation, but their cancer-related pain was relieved unsatisfactorily and above moderate pain by visual analogue scale score (VAS score >7). Before the treatment, all the cases had no obvious dysfunction in heart, liver and kidney, etc, and no history of peptic ulcer, hemorrhage, hypertension, or asthma caused by aspirin. In the past four weeks, they did not receive chemotherapy, radiotherapy, nuclide or diphosphonate treatment. Before the treatment, leukocytes count was $>4\times10^9$/L, and platelets count was $>90\times10^9$/L in each patient. The expected survival time was more than one month. Exclusion criteria included serious peptic ulcer disease, blood diseases, abnormal kidney or liver function, hypertension, or difficulty communication, as well as a history of adverse response to flubiprofen axetil.

Usage of flurbiprofen axetil and opioids

Flurbiprofen axetil injection (50mg/5ml/day) was supported by Beijing Tide Pharmaceutical. Co., Ltd, Beijing, China. 50mg flurbiprofen axetil added in 100ml of 0.9% isotonic saline was injected every time through vein within 30 minutes. Morphine sulfate sustained-release tablet (MS Contin) was supported by Mundipharma Pharmaceutical Co., Ltd, Beijing, China. 60 patients enrolled in group A were only treated with the MS Contin (240mg/day or more), and the other 60 patients received the combination of flurbiprofen axetil (50mg/5ml/day) and MS Contin (240mg/day or more) in group B. 7 days later, pain relief, quality of life improvement and side effects were evaluated. If breakthrough pain occurred in the treatment period, intravenous flurbiprofen axetil (50mg/time, l-2 times/day) or oral morphine hydrochloride (10mg/time, l-4 times/day) can be used for rescue medication. The patients with breakthrough pain were excluded in the statistics of total remission rate and plasma β-endorphin assay, but included in the evaluation of quality of life and side effects.

Pain relief evaluation criteria

Cancer pain intensity was evaluated by VAS (0-10), and the three grades were as the followed: mild pain (1-3 score), moderate pain (4-6 score) or severe pain (7-10 score). Pain relief was recorded based on four-scale criteria (Takada et al., 2001): Complete relief (CR): The pain disappeared completely, or was alleviated significantly. The sleep was good or was improved obviously. Partial relief (PR): The pain was alleviated significantly than before. The sleep was not disturbed by and large. Patient could live in normal or use a few anesthetic drugs. Minimal relief (MR): The pain was alleviated than before, but was still felt obviously. The sleep was still disturbed by the pain, and the dosage of anesthetic drugs was not reduced significantly than before. No effect (NR): The pain was not alleviated significantly than before, or the dosage of anesthetic drugs was not reduced than before. CR and PR were regarded as total effective response to cancer pain treatment.

Quality of life evaluation

The EORTC QLQ-C30 quality of life scale (Chinese version) was applied in our study. The EORTC QLQ-C30 questionnaire is a tool used to measure quality of life and consists of 30 items rated on a 1 to 4 scale (two questions are rated between 1 and 7) (Meuser et al., 2001). This instrument has been translated in many countries and adapted for use transculturally. The items in Chinese version comprise 15 domains, including 5 functional domains (physical function, role function, cognitive function, emotional function and social function), 3 symptom domains (fatigue, nausea/vomiting, pain), 1 general health status/quality of life domain and 6 single items (each item is one domain). The higher scores in functional domain and general health status suggest the better functional status and quality of life, meanwhile,

Table 1. Clinical Characteristics of 120 Patients with Refractory Cancer Pain (n)

Characteristic	Group A	Group B	*p* value
Sex			
Male/Female	30/30	32/28	
Average Age (Years)	52.8±4.1	50.2±3.7	
Mean Daily Opioid Dose (Mg)	290.51±43.6	280.48±40.2	
Primary Cancer			*p* =0.715
Gastric (Cardia)	8	10	
Oesophageal	5	6	
Rectal	6	5	
Lung	13	12	
Breast	8	7	
Prostate	4	5	
Nasopharyngeal	6	5	
Hepatic	8	9	
Unknown Primary	2	1	
Pathological Stage			*p* =0.456
III	26	22	
IV	34	38	
Pain Type			*p* =0.710
Nociceptive	12	9	
Neuropathic	8	7	
Mixed	40	44	

Group A: MS Contin; Group B: A combination of intravenous flurbiprofen axetil and MS Contin

the higher scores in symptom domain suggest the more severe symptom and the poorer quality of life. A research assistant guided each patient to complete the investigation. Before and after the treatment, each patient received one time of questionnaire survey.

Side effects

All side effects were assessed and graded according to the National Cancer Institute common terminology criteria for adverse events. Some symptoms such as swirl, nausea/vomiting, abdominal pain, diarrhea, constipation, urine retention and drowsiness were observed. In addition, the changes of blood routine, kidney function and liver function were noticed especially in the treatment period.

Plasma β-endorphin assay

For β-endorphin detection, blood samples (2 ml) were collected from the peripheral vein before and after the analgesic treatment, respectively. Then, the samples were shifted in tubes containing 10% ethylenediaminetetraacetic acid (EDTA) and aprotinin, and incubated at 4°C for 15min. Plasma was separated by centrifugation at 3, 000 rpm for 10min. The plasma samples were stored at -70°C for further analysis. β-endorphin concentration in plasma was measured by radioimmunoassay using commercially available standards kits (Beijing Institute of Biotechnology, Huaying, China).

Statistical analysis

The raw scores of the QLQ-C30 for each domain and single item were transformed to give a value between 0-100. For the five functional scales and the global health status, item responses were recorded so that a higher score represented a better level of functioning. For the symptom-oriented scales and items, a higher score corresponded to a severe level of symptoms. The EORTC QLQ-C30 quality of life scale and plasma β-endorphin levels were expressed as means±SD. Statistical differences between the means were analyzed by Independent-Samples t-test. Rates and quality of life scores were compared by χ^2 test. A *P* value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Table 2. Results of Analgesic Effects in the Two Groups (n)

Characteristic	Group A	Group B	*p* value
Enrolled cases	60	60	
Evaluated cases	56	58	
Pain relief			*p*=0.031
NR	2	1	
MR	8	4	
PR	34	31	
CR	12	22	
Total effective rate (%)	82.14%	91.38%	

*Group A: MS Contin; Group B: A combination of Intravenous flurbiprofen axetil and MS Contin; Total effective rate (%) = (CR + PR) cases / evaluated cases %

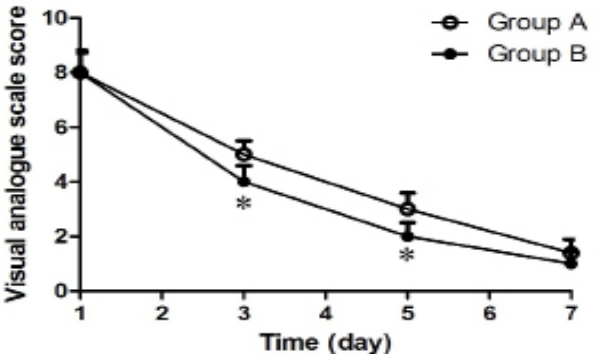

Figure 1. Comparison of Visual Analogue Scale Score Between Flurbiprofen Axetil/Opioids Combination Group and Opioids Single-Use Group. The mean VAS pain score decreased more in the combination group of flurbiprofen axetil and MS Contin (Group B) than the MS Contin single-use group (Group A) from day 3 to day 7. *p<0.05, showed statistically significant

Results

Efficacy of pain relief

A total of 120 patients with refractory cancer pain was enrolled (Table 1), and was randomly divided into the MS Contin group (group A) and flurbiprofen axetil combined with MS Contin group (group B). Because of breakthrough pain, 56 patients in the group A and 58 patients in the group B remained in the final analysis for total remission rate.

After one week of treatment, the total effective responses of the above two groups were 82.14% and 91.38%, respectively. Between them, the total effective responses of group B was higher than that of group A (p=0.031) (Table 2).

Assessment of pain relief

Before analgesic administration, all the patients in two groups suffered refractory cancer and had VAS pain

Table 3. Quality of Life Scores of Patients Before and After Treatment in the Two Groups (Mean±SD)

Characteristic	Group A		Group B	
	Before treatment	After treatment	Before treatment	After treatment
Physical function	53.72±11.13	65.21±10.0*	55.72±9.43	70.16±10.2*
Role function	75.04±9.32	77.16±8.93	76.28±7.96	78.31±10.17
Emotional function	56.28±0.25	69.45±12.0*	60.12±10.73	73.5±10.63#
Cognitive function	68.11±10.27	71.66±10.34	70.98±10.39	74.18±9.33
Social function	62.08±11.15	72.85±12.7*	65.57±11.46	79.26±12.2#
General health status	64.42±9.13	80.66±10.2#	64.35±10.67	83.19±11.4#
Languor	42.68±8.07	38.24±7.89	44.68±10.49	38.09±8.62
Nausea/vomiting	17.78±5.63	14.56±6.75	18.87±5.36	13.79±7.62
Pain	38.76±4.06	29.06±4.12*	38.16±4.35	25.97±6.11#
Anhelation	14.15±4.31	12.68±4.07	13.88±5.81	10.25±4.79
Insomnia	30.42±5.16	27.02±4.62	30.68±6.74	26.49±4.56
Appetite	21.78±4.88	11.24±3.46*	23.35±3.16	12.17±5.28*
Constipation	20.24±1.22	18.46±3.25	19.83±3.08	20.06±1.19
Diarrhea	13.53±3.17	12.66±2.81	12.04±4.19	13.36±3.02
Financial straits	38.72±8.92	40.73±10.06	40.04±6.26	38.67±9.36

Group A: MS Contin; Group B: A combination of Intravenous flurbiprofen axetil and MS Contin; *p<0.05, #p<0.01, the score after treatment compared with that before treatment

Table 4. Side Effects of the Patients in the Two Groups (n)

Characteristic	Group A	Group B
Epigastric discomfort	3	5
Abdominal pain	3	2
Diarrhea	2	0
Nausea	4	3
Vomiting	1	1
Constipation	1	3
Dizziness	2	2
Drowsiness	0	2
Uroschesis	1	0
Excessive sweating	2	0

*Group A: MS Contin; Group B: A combination of Intravenous flurbiprofen axetil and MS Contin

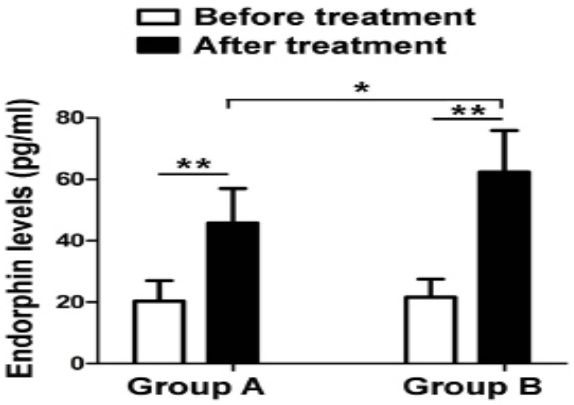

Figure 2. Intravenous Flurbiprofen Axetil Enhances Analgesic Effect of Opioids for Refractory Cancer Pain by the Increased Plasma β-Endorphin Levels. Following different treatment, plasma β-endorphin levels were assayed in the morphine sulfate sustained-release tablet group (Group A) and in the flurbiprofen axetil /opioids combination group (Group B). *p<0.05 and *p<0.01, showed statistically significant

scores of 7 or higher. At day 3, the mean VAS pain score decreased in group B than that in group A (p<0.05). Furthermore, the mean VAS pain score was significantly lower in the flurbiprofen axetil/opioids combination group than that in the MS Contin single-use group at day 5 (p<0.05) (Figure 1).

Quality of life assessment

Quality of life of most of the enrolled patients improved obviously, including physical function, emotional function, social function, general health status, pain, appetite, etc (Table 3). The score rose more higher both in the combination group and in MS Contin group, including physical function (p<0.05), emotional function (p<0.05), social function (p<0.05) and general health status (p<0.01). Meanwhile, pain and appetite scores were significantly different between the patients before treatment and after treatment (p<0.05). But there was no obvious difference for the above six items after the treatment between the two groups.

Side effects

No serious adverse events were observed in all the patients. Gastrointestinal toxicities, including epigastric discomfort, abdominal pain, diarrhea, constipation, nausea and vomiting, were found in the two groups. But there was no significant difference between them. The other symptoms such as dizziness, drowsiness, urine retentionor excessive sweating, were also observed in the cases, which can be endured without any treatment. No patient had grade 3 or 4 acute hematologic toxicities, and liver or renal dysfunction during treatment (Table 4). Gastrointestinal toxicity such as alimentary tract ulcers and bleeding which were usually found in NSAIDs did not be found in all of the cancer pain cases.

Plasma β-endorphin levels

According to the standard procedure, the concentration of β-endorphin in plasma was measured by radioimmunoassay. As shown in Figure 2, after the treatment, plasma β-endorphin levels increased significantly both in the group A (before treatment *vs* after treatment: 20.3±6.7 *vs* 45.8±11.2 pg/ml) (p<0.01) and in the group B (before treatment *vs* after treatment: 21.6±5.9 *vs* 62.4±13.5 pg/ml) (p<0.01), which showed that

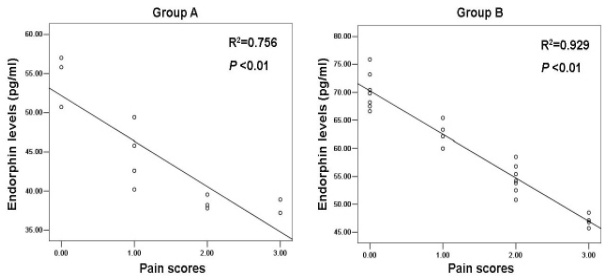

Figure 3. Plasma β-Endorphin Levels were Negatively Correlated with Pain Scores for CR Patients in Both of the Two Groups. A negative correlation between plasma β-endorphin levels and pain scores was observed using curve estimation and linear regression analyses for CR patients in the group A (morphine sulfate sustained-release tablet) and the group B (flurbiprofen axetil /opioids combination). Correlation coefficients and *p* values are shown for each analysis. $p<0.01$ showed statistically significant

satisfactory analgesia was associated with a significant increase in plasma β-endorphin levels. Moreover, plasma β-endorphin level in the combination group was 62.4±13.5 pg/ml, which was higher than that in morphine single-use group (45.8±11.2 pg/ml) ($p<0.05$). Figure 3 showed that higher plasma β-endorphin levels negatively correlated with lower pain scores for CR patients in both of the two groups (Group A: $R^2=0.756$, $p<0.01$. Group B: $R^2=0.929$, $p<0.01$).

Discussion

Flurbiprofen axetil is a new type of non-selective COX inhibitors, which has been widely used for preemptive analgesia (Sánchez et al., 2012), the prevention of propofol injection pain (Mizushima et al., 1986; Park et al., 1999), and the reduction of postoperative pain (Xu et al., 2008; Vendramini-Costa et al., 2012) and cancer pain (Davies et al., 1995; Hao et al., 2013), including metastatic bone pain and multiple breakthrough pain. Wu et al reported that intravenous flurbiprofen axetil can provide better analgesic effect and few side effects for the patients with refractory cancer pain (Wu et al., 2009). In this study, our results show that the combination of flurbiprofen axetil and opioids can provide few side effects, and intravenous flurbiprofen axetil can enhance the analgesic effectof MS Contin in refractory cancer pain, which would provide a selected and reliable strategy for refractory pain treatment.

Potent opioids have fast and slow release preparations for the treatment of cancer pain. Morphine, hydromorphine, buprenorphine, methadone, fentanyl, and alfentanyl are the most used potent opioids. Morphine can make voltage-gated potassium channels excited mainly through acting on μ receptor, which inhibits voltage-gated calcium channel and cuts down the release of neurotransmitter (Arslan et al., 2014). Recently, a study has analyzed cost-effectiveness of morphine, MS Contin and oxycodone in the treatment of cancer pain. The results showed that morphine, MS Contin and oxycodone give similar pain relief and adverse reaction rates but of all (Zhang et al., 2014). In our study, when treated with flurbiprofen axetil and opioids combination, the majority of the patients reached complete painless status. These facts suggest that drug combination not only can surpass the analgesic effects of MS Contin single-use, but also accomplish painless survival in the patients with refractory cancer pain. After the drug combination, the pain of the patients was alleviated satisfactorily, sothat the physical function, emotional function, social function, general health status and appetite improved. At the same time, our data showed that by the treatment of flurbiprofen axetil/opioids combination, adverse events did not increase in most of the patients, even decreased in a few cases. After the one week of observation, most of the cases continued to receive the effective analgesic proposal, some patients adjusted the dosage of analgesia because of the development of diseases or drugs tolerance. However, part of the patients reduced gradually the dosage of opioids for the satisfactory analgesic effects (data not shown).

Moreover, our data showed that satisfactory analgesia was associated with a significant increase in plasma β-endorphin levels in cancer patients with refractory pain. β-endorphin is known to play an important role in the regulation of neural and endocrine functions and in the pain mechanism (Hargreaves et al., 1990). In patients undergoing esophagectomy, the flurbiprofen axetil enhances the analgesic effect of fentanyl associated with increased perioperative β-endorphin levels (Liu et al., 2011). Thus, flurbiprofen axetil may enhance the effects of opioids in refractory cancer pain through a similar mechanism. In the previous reports, lower plasma β-endorphin levels in patients with breast, lung and visceral cancer were associated with poorly controlled pain, and plasma β-endorphin levels increased after pain reduction (Lopez et al., 1985; Mystakidou et al., 1999). In addition, plasma β-endorphin levels increased after pain relief by continuous subcutaneous octreotide in gastrointestinal cancer patients (Befon et al., 2000). In our study, cancer patients received the combination of intravenous flurbiprofen axetil and opioids not only had better pain relief, but also had higher plasma β-endorphin level. Moreover, an inverse relationship existed in the pain relief and plasma β-endorphin level. Although the role of plasma β-endorphin in pain pathophysiology remains unclear, some literature reported that endorphin system is a parallel analgesic system, and in some manner plasma endorphin levels reflect the current levels of pain or analgesia, but detailed mechanisms needs to be investigated (Tseng et al., 2001).

In conclusions, intravenous flurbiprofen axetil can enhance the analgesic effect of morphine in refractory cancer pain by the increased plasma β-endorphin levels. But for the inadequate cases and the short time of observation, the best dosage in single-use and combined use, the usage time, the effects on the patients' immune function, side effects after the long-term use of flurbiprofen axetil, and the mechanisms by which flurbiprofen axetil/opioids increase β-endorphin are not involved in this study. And, the results of our study need to be confirmed by large-scale, prospective and randomized studies. Nonetheless, the combination of flurbiprofen axetil/opioids is an effective method to relieve refractory cancer pain.

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