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ORIGINAL ARTICLE

Correlations of cancer pain degree with levels of β-EP, CGRP and PGE2 and the effects of oxycontin on them

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Summary

Purpose: *To analyze the effects of Oxycontin on β-endorphin (β-EP), calcitonin gene-related peptide (CGRP) and prostaglandin E2 (PGE2) in treating patients with cancer pain, and to investigate and discuss the role and value of Oxycontin in treating cancer pain.*

Methods: *A total of 95 patients (60 male and 35 female) were enrolled in the study, who were diagnosed in our hospital with malignant tumors complicated with pain from May 2016 to July 2017. All received Oxycontin for pain relief in addition to conventional treatment. The role of Oxycontin was analyzed by collecting the patients' general information, age, gender, Karnofsky performance status (KPS) score, site of pain and degree of pain, and by detecting the remission rates of clinical symptoms, average analgesic time, number of pain outbreak per day, levels of β-EP, CGRP and PGE2, as well as changes of KPS score, Zubrod performance status (ZPS) score and quality of life (QoL) score of the enrolled patients before treatment and at 1 week after treatment.*

Results: *(1) After treatment with Oxycontin, the remission rate of clinical symptoms was significantly increased, the average analgesic time was extended remarkably and the number of pain outbreaks per day was decreased notably. All the differences were statistically significant ($p<0.05$). (2) For patients with cancer pain receiving Oxycontin, the main adverse reactions were nausea and vomiting (15.37%), followed by constipation, abdominal distension and anorexia. (3) At 1 week after Oxycontin therapy, the KPS score and QoL score of the enrolled patients were increased, while the ZPS score was decreased, and the differences were statistically significant ($p<0.05$). (4) At 1 week after treatment with Oxycontin, the levels of β-EP, CGRP and PGE2 of the enrolled patients were significantly lowered ($p<0.05$). (5) The levels of β-EP, CGRP and PGE2 with regard to the average analgesic time were negatively correlated with β-EP ($r=-0.765$, $p<0.01$), CGRP ($r=-0.673$, $p<0.01$) and PGE2 ($r=-0.801$, $p<0.01$).*

Conclusions: *On treating patients with cancer pain, Oxycontin can significantly decrease the β-EP, CGRP and PGE2 levels, ameliorate the clinical symptoms, effectively relieve the pain and improve the QoL to some extent.*

Key words: *calcitonin gene-related peptide, cancer pain, β-endorphin, Oxycontin, prostaglandin E2*

Introduction

Nowadays, with the constant changes in lifestyle and environment, the incidence rates of malignant tumors become higher and higher. The most common clinical manifestation of advanced tumors is chronic pain all over the body, seriously affecting the patient QoL [1]. In most cases, the pain caused by advanced tumors is controlled by drugs, dominated by opioids [2]. Correct drug therapies for cancer pain can alleviate most pain problems of the patients. Therefore, it is extremely important to

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choose analgesic drugs rationally [3]. Relevant data show that millions of patients are newly diagnosed with tumors in China every year, and the disease becomes the direct cause of rising death rate. Most of the patients with late-stage malignant tumors cannot receive effective treatment protocols [4]. In the late stage of malignant tumors, pain is the most prominent problem leading to decreased QoL [5]. As a result, clinical workers should regard cancer pain relief as the major part of the treatment protocols for patients with advanced tumors [6]. Oxycontin (oxycodone hydrochloride) prolonged-release tablet, is a kind of opioid receptor agonist. It has the advantages of unlimited dose and analgesic effect in addition to good analgesic efficacy [7]. Oxycontin has similar analgesic efficacy to morphine, but its bioavailability is higher than that of morphine [8]. For patients with advanced tumors, since the compression of surrounding tissues and nerves by primary and secondary masses of tumors leads to excessive release of calcitonin gene-related peptide (CGRP), it further results in overexpression of β-endorphin (β-EP) and induces hyperalgesia [8]. At the same time, the tumor tissue cells themselves can also release prostaglandin E2 (PGE2), tumor necrosis factor (TNF) and other substances [9]. However, there has been no definite conclusion yet on whether Oxycontin will influence the levels of β-EP, CGRP and PGE2 in the patient's body when it is used to treat cancer pain.

Methods

General data

A total of 95 patients who were diagnosed in our hospital from May 2016 to July 2017 with malignant tumors complicated with pain were enrolled. There were 60 males and 35 females, aged 30-78 years (mean±SD 48.31±5.39). The KPS score of all the enrolled patients was 60 or higher, and the detailed general clinical data of the enrolled patients are shown in Table 1. The diagnostic criteria for all malignant tumors were based on the pathology and imaging. Among the enrolled patients, there were 23 cases of gastric cancer, 20 cases of lung cancer, 15 cases of colon cancer, 10 cases of esophageal cancer, 13 cases of breast cancer, 7 cases of ovarian cancer and 5 cases of other cancers. This study was approved by the ethics committee of Jining No.1 People Hospital. Signed informed consents were obtained from all participants before the study. Exclusion criteria: patients who used other morphine analgesics before treatment, patients who received radiotherapy or chemotherapy before and during Oxycontin therapy, patients with pain caused by their non-cancerous diseases, patients who could not undergo Oxycontin therapy according to the course of treatment, or patients with severe heart, liver or renal comorbidities.

Cancer pain grading

Grade 0 (no pain), Grade 1 (mild and tolerable pain, for which medicine intervention was not needed), Grade 2 (moderate pain influencing sleep, etc., for which analgesic treatment was needed), and Grade 3 (severe pain seriously influencing the patients' life, for which analgesics were needed).

Therapeutic methods

All the enrolled patients took Oxycontin (10 mg per tablet) provided by Mundipharma Pharmaceutical Co., Ltd. Beijing, China. Oxycontin was administered when the patient expressed obvious pain, with an initial dose of 10 mg/12 hrs. The drug was prohibited to be broken, ground or chewed. If the pain was not relieved 24 hrs after the patient took the drug orally, the dose could be increased to 20 mg/12 hrs the next day, and so on, to the maximum dose of 60 mg/12 hrs. Close attention was paid to the pain improvement conditions of the patients during treatment, so the dose of Oxycontin could be adjusted at any time. The treatment course was 2 weeks.

Detection of serum indexes

A total of 15 mL peripheral blood was drawn from each enrolled patient 1 day before treatment and 2 weeks after treatment, after fasting and water deprivation for 10 hrs overnight. The serum was taken to measure the levels of β-EP, CGRP and PGE2 before and after treatment using enzyme-linked immunoassay.

Table 1. General clinical data of the enrolled patients with liver cancer

General data	*n (%)*
Age (years)	
≥60	44 (46.32)
<60	51 (53.68)
Gender	
Male	60 (63.16)
Female	35 (36.84)
KPS score	
60	18 (18.95)
70	30 (31.58)
80	31 (32.63)
90	16 (16.84)
Site of pain	
Visceral pain	39 (41.05)
Bone pain	25 (26.32)
Nerve pain	9 (9.47)
Visceral pain + bone pain	4 (4.21)
Soft tissue pain	7 (7.37)
Visceral pain + nerve pain	6 (6.32)
Others	5 (5.26)
Degree of pain	
Moderate	23 (24.21)
Severe	72 (75.79)

Assessment of therapeutic effects

Assessment of pain relief effects: Complete remission (CR): There was no pain after treatment. Partial remission (PR): The pain was alleviated significantly after treatment, and the patients had a basically normal life. Mild remission (MR): The pain was alleviated slightly after treatment, but there was still obvious pain that affected the patients' life. No remission (NR): The pain was not alleviated at all after treatment.

Assessment of adverse reactions: Mild: There were generally mild adverse reactions, which did not affect the patients' life. Moderate: there were relatively remarkable subjective symptoms which affected the patients' life and needed intervention with medical methods, but the patients could undergo the Oxycontin therapy still. Severe: The patients could not live a normal life, the adverse reactions could not be relieved through clinical treatment, and the Oxycontin therapy needed to be stopped at once.

KPS score: 60 points: The patients were mostly independent in their daily life, but they needed help occasionally; 70 points: The patients could live independently, but they could not maintain normal life and work; 80 points: The patients could barely participate in normal activities, but there were some symptoms and signs; 90 points: The patients could conduct normal activities, but there were mild symptoms and signs; 100 points: There were no symptoms and signs. ZPS grading: Grades 0-1 (normal to mild symptoms which did not affect the patients' life); Grades 2-3 (symptoms which seriously influenced the patients' life); and Grades 4-5 (severe bed rest or death). QoL score: 0-20 points (extremely poor); 21-30 points (poor); 31-40 points (fair); 41-50 points (relatively good) and 51-60 points (good).

Statistics

SPSS 19.0 software (Armonk, NY, USA) was applied to process the data. The collected data were expressed as mean ± standard deviation. The quantitative data were compared using *t*-test, and the qualitative data were compared using x^2 test. $P<0.05$ suggested that the difference was statistically significant.

Table 2. Comparison of analgesic efficacy before and after Oxycontin therapy

Time	*n*	*Effective rate (%)*	*Average analgesic time (h)*	*Number of pain outbreaks per day (n)*
Before treatment	95	39.16	13.06±3.71	3.57±0.16
After treatment	95	85.43	20.93±0.58	0.95±0.06
p value		0.000	0.001	0.001

Table 3. Adverse reactions after Oxycontin therapy

Adverse reaction	*n*	*Severity*			*Proportion (%)*
		Mild	*Moderate*	*Severe*	
Nausea and vomiting	15	11	3	1	15.37
Constipation	10	7	3	0	10.96
Abdominal distension	8	6	2	0	8.71
Anorexia	6	4	2	0	6.32
Dizziness	4	2	2	0	4.46
Lethargy	3	3	0	0	3.08

Table 4. Comparison of scores related to QoL before and after Oxycontin therapy

Time	*n*	*KPS score (mean±SD)*	*ZPS grading (mean±SD)*	*QoL score (mean±SD)*
Before treatment	95	60.37±8.56	3.77±0.68	40.03±5.13
After treatment	95	81.38±5.17	2.03±0.09	58.76±3.23
p value		0.016	0.037	0.029

Table 5. Comparisons of β-EP, CGRP and PGE2 levels before and after Oxycontin therapy (ng/L)

Time	*n*	*β-EP (mean±SD)*	*CGRP (mean±SD)*	*PGE2 (mean±SD)*
Before treatment	95	241.78±43.91	47.63±4.21	5.79±1.31
After treatment	95	188.53±40.27	21.05±3.73	2.13±0.70
p value		0.002	0.001	0.001

Results

Comparison of analgesic efficacy before and after Oxycontin therapy

After the treatment with Oxycontin, the remission rate of clinical symptoms increased, the average analgesic time prolonged remarkably and the number of pain outbreaks per day decreased notably. All the differences were statistically significant (p<0.05) (Table 2).

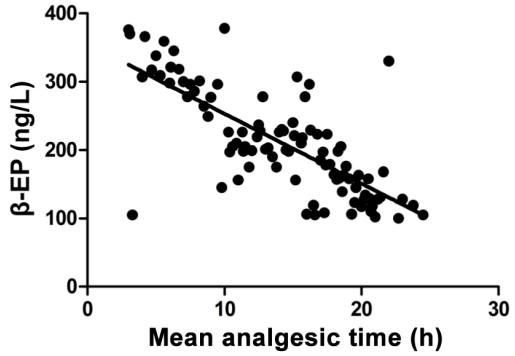

Figure 1. Correlation of mean analgesic time with β-EP. The mean analgesic time was negatively correlated with β-EP (r=-0.765, p<0.001).

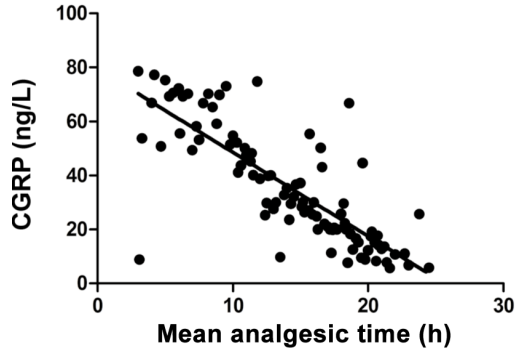

Figure 2. Correlation of mean analgesic time with CGRP. The mean analgesic time was negatively correlated with β-EP (r=-0.673, p<0.001).

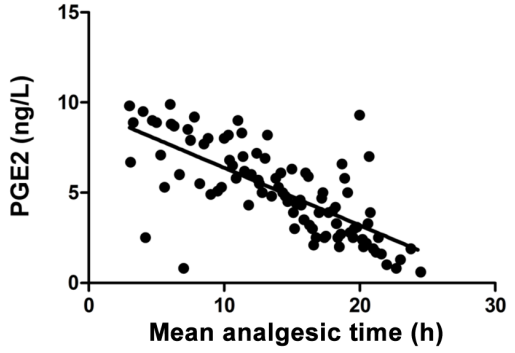

Figure 3. Correlation of mean analgesic time with PGE2. The mean analgesic time was negatively correlated with β-EP (r=-0.801, p<0.001).

Adverse reactions after Oxycontin therapy

For patients with cancer pain receiving Oxycontin therapy, the main adverse reactions were nausea and vomiting, accounting for 15.37%, followed by constipation (10.96%), abdominal distension, anorexia, etc. (Table 3).

Comparisons of scores related to QoL before and after Oxycontin therapy

At 1 week after Oxycontin therapy, the KPS and QoL scores of the enrolled patients increased, while the ZPS score decreased remarkably, with statistically significant differences (p<0.05) (Table 4).

Comparisons of β-EP, CGRP and PGE2 levels before and after Oxycontin therapy

At 1 week after treatment with Oxycontin, the levels of β-EP, CGRP and PGE2 of the enrolled patients were significantly lowered (p<0.05) (Table 5).

Analyses on the correlations of cancer pain degree with the levels of β-EP, CGRP and PGE2

The average analgesic time was negatively correlated with β-EP (r=-0.765, p<0.01), CGRP (r=-0.673, p<0.01) and PGE2 (r=-0.801, p<0.01), which had statistical significance (Figures 1-3).

Discussion

Among patients with late-stage malignant tumors, the most common clinical manifestation is pain at different parts of the body, seriously influencing their QoL. At the same time, cancer pain is a serious health problem related to public safety that attracts concerns of the whole society [10]. The leading therapeutic method for cancer pain is control through drugs. Relevant data have shown that the pain relief rate can be as high as nearly 95% if the drugs treating pain are selected and used appropriately [11]. For patients with pain, the World Health Organization has specifically proposed a helping tool that provides references for clinical medication using three-ladder medical treatment methods [12]. Opioids are the most commonly used and most important analgesia-related drugs. Similar to opioids, Oxycontin belongs to the third ladder of the three-ladder medical treatment, and it is mainly used to patients with moderate to severe cancer pain [13]. Oxycontin, also known as oxycodone hydrochloride controlled-release tablet, is a kind of semisynthetic opioid receptor agonist [14]. There are many advantages using Oxycontin to treat patients with cancer pain, such as short onset time, prolonged analgesic time and decreased number of pain outbreaks [15]. Relevant studies

have indicated that Oxycontin can exert the analgesic effect within 1 hr in most of the patients with pain who take the drug, and the average analgesic time is about 12 hrs [16]. In addition to the rapid onset, Oxycontin has relatively stable analgesic efficacy. This is because the controlled release rate of Oxycontin is 62%, Oxycontin itself has no ceiling effect, and generally it takes about 24 to 36 hrs to reach a relatively stable status [17]. On the other hand, Oxycontin has high bioavailability and good analgesic efficacy. It can be administered orally, so it is convenient for treatment. Moreover, it has fewer and milder adverse reactions than other analgesics, and its utilization is not affected by age [16]. The impact of Oxycontin on renal functions is relatively small, and the amount of metabolic products has no reference value, so long-term use of Oxycontin rarely leads to aggregation of metabolic products [17]. Reactions of the digestive system are the major adverse reactions, including nausea, vomiting and constipation. If the patients receive morphine for analgesia routinely, Oxycontin can be used cooperatively, and it will not cause incompatibility [18]. In this research it was found that among patients with cancer pain, after the treatment with Oxycontin, the remission rate of pain was increased obviously, the average analgesic time was prolonged, the number of pain outbreaks per day was decreased, and the QoL was improved. All the differences were statistically significant ($p<0.05$). Furthermore, fewer and milder adverse reactions occurred. All the results are consistent with the above conclusions.

The major mechanism of pain in patients with malignant tumors is that the tumor itself affects or directly compresses surrounding or distant sensory nerves, inducing excessive synthesis and release of CRRP and directly increasing the expression of β-EP, thus enhancing the sensitivity to pain [19]. The tumor tissue cells themselves can secret various factors at different amounts, including TNF and PGE2. Relevant studies have revealed the patients with cancer pain can be alleviated with morphine. However, if they have severe intractable pain, the analgesic efficacy of morphine is not satisfactory. The reason is that breakthrough pain can reduce the patient QoL to a large extent via the excessive psychological stress and impaired motor function caused by pain [19]. Oxycontin is significantly resistant to the levels of β-EP, CGRP and PGE2 of the patients, and it alleviates pain by resisting allergy and inhibiting immuno-inflammatory responses of the body, decreasing the content of mucus and increasing the absorption and decomposition of proteins [20].

Conclusions

In this research, it was found that the levels of β-EP, CGRP and PGE2 of the patients with cancer pain were lowered remarkably after treatment with Oxycontin. Moreover, the analgesic efficacy had negative correlations with the levels of β-EP, CGRP and PGE2, indicating the more severe the cancer pain, the higher the levels of β-EP, CGRP and PGE2 will be. When Oxycontin decreases the β-EP, CGRP and PGE2 levels of the patient, it can effectively relieve the pain.

Conflict of interests

The authors declare no conflict of interests.

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