

# The research on long-term clinical effects and patients' satisfaction of gabapentin combined with oxycontin in treatment of severe cancer pain

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## Abstract

Gabapentin has been used as an adjuvant for treatment of cancer pain. Previous studies showed that opioids combined with gabapentin for management of cancer pain reduced the dosage of opioids.

The objective of this study was to explore the clinical effect and patients' satisfaction of oxycontin combined with gabapentin in treatment of severe cancer pain. After titration of morphine, 60 severe cancer patients with visual analog score (VAS) more than 7 were randomly divided into trial group (n=30) and control group (n=30). The control group was administered oxycontin and placebo, and the trial group was given oxycontin and gabapentin. VAS score was recorded pre- and post-treatment; while daily dose of oxycontin, daily cost of pain relief and life quality score were observed 1 week, 1 month, 2 months, 3 months, and 6 months post-treatment. We found that daily dose of oxycontin 1 month post was comparable between the 2 groups ( $P > 0.05$ ). Three months post, compared with control group ( $58.0 \pm 15.2$  mg), average daily dose of oxycontin was significant lower in trial group ( $33.4 \pm 11$  mg) ( $P < 0.001$ ). Average daily cost of pain relief in trail group ( $34.5 \pm 10.2$  RMB) was less than the control group ( $52.4 \pm 13.7$  RMB) ( $P < 0.001$ ). Life quality score increased in all of the patients in both group post-treatment ( $P < 0.05$ ); while life quality score in trail group was greater than in control group 3 months ( $46.8 \pm 4.5$  vs  $43.5 \pm 4.6$ ,  $P = 0.007$ ) and 6 months ( $46.5 \pm 4.8$  vs  $41.4 \pm 4.3$ ,  $P < 0.001$ ) post-treatment. The incidence of drowsiness and dizziness was comparable between the 2 groups ( $P > 0.05$ ), while the incidence of nausea and vomiting ( $P = 0.038$ ), and constipation ( $P < 0.001$ ) was higher in the control group.

We concluded that oxycontin combined with gabapentin used in severe cancer pain management can control pain effectively, decreased the dose of oxycontin and the cost of cancer pain relief, and reduced the incidence of nausea and vomiting, and constipation, increased the life quality.

**Abbreviations:** NSAIDs = non-steroidal anti-inflammatory drugs, QOL = Quality of life, SD = standard deviation, VAS = visual analog score, WHO = World Health Organization.

**Keywords:** average daily cost, cancer pain, gabapentin, life quality, oxycontin

## 1. Introduction

Cancer pain, caused by the disease itself or the treatment for the cancer, is one of most fearful and most painful complications for cancer patient.<sup>[1]</sup> About 65% to 85% of cancer patients suffered from different levels of pain. Ninety percent of advanced cancer

patients suffered from agonizing pain.<sup>[2]</sup> However, most of the cancer pain can get effective treatment according to guideline on cancer pain of the World Health Organization (WHO).<sup>[3]</sup> In view of the complexity of the pathophysiology of cancer pain, it needs comprehensive evaluation and adopts the pharmacological or nonpharmacological interventions. "The three steps analgesic ladder for cancer pain management" that WHO promotes is the main means of the cancer pain treatment, and it is well known that opioids are milestones in the treatment of cancer pain.<sup>[4]</sup> However, adjuvant drugs, including antidepressants, anticonvulsants, hormone steroids, and non-steroidal anti-inflammatory drugs, etc. are also helpful and can be used in every "ladder" of pain relief. Adjuvant drugs can treat specific type of pain, improve the symptom of the accidental pain, increase the analgesic effect, and sometimes reduce side effects to some extent. Shinde et al<sup>[5]</sup> demonstrated that adjuvant drugs were used in 80% of cancer pain treatment in their retrospective study. Gabapentin, a new generation of anticonvulsant drug, was found to reduce metastatic bone cancer pain<sup>[6]</sup> and improve visceral pain.<sup>[7]</sup> It was reported that cancer pain can be well relieved by combination of oxycontin (oxycodone hydrochloride prolonged-release tablet) and gabapentin for short term.<sup>[8,9]</sup> To date, however, people seldom knew the long-term analgesic effect of such combination. Although, both opioid drug and gabapentin work on cancer pain through different mechanisms, but they may produce synergies, reduce opioids' dose and side effects, but at the same time, it may probably increase the adverse reactions of gabapentin. The objectives of the present study

Editor: Kazuo Hanaoka.

Funding: This research was supported by Natural Science Foundation of Zhejiang Province (CN) (LY15H030013) and Zhejiang Province Health Development Planning Commission research project (2016KYB197).

D-LC and Y-HL are equal contributing first authors.

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:42(e5144)

Received: 9 September 2016 / Received in final form: 22 September 2016 /

Accepted: 26 September 2016

<http://dx.doi.org/10.1097/MD.0000000000005144>

are to explore the long-term therapeutic effects and patients' satisfaction. The results of the study will provide the basis for clinical cancer pain treatment.

## 2. Materials and methods

### 2.1. Patients

Between June 2013 and October 2015, 70 patients with cancer pain who came to our hospital pain clinic were enrolled into the present study. All of the patients aged 40 to 75 years old, male or female. Inclusion criteria were the patients confirmed by histopathology for malignant tumor, and the pain visual analog score (VAS) was more than 7 points. Exclusion criteria were patients with severe liver and renal insufficiency, or if they had received opioids before the experiment, patients with intracranial hypertension, consciousness disorder or language barrier, or patients suspected or confirmed intestinal obstruction or if the patients cannot eat or drink. The study protocol was proved by the Institutional Review Board at Shaoxing People's Hospital. Each patient gave his informed consent to participate the study.

### 2.2. Study design

This was a randomized, double-blinded, parallel controlled, prospective interventional control study. Nonrepeated random integer between 1 and 70 was produced by using software of Excel, the even number assigned to the group 1, the odd number assigned to the group 2. Only the person responsible for drug dispensing knew the specific group 1 or 2 corresponded to the control group (oxycontin + placebo) or trial group (gabapentin + oxycontin). The patients who had severe side effects were revealed blind midway. They accepted corresponding treatment according to the medical regulation or guideline. The cases revealed were included in the statistical analysis and side reaction also recorded. The other cases were discovered the blind after the end of statistics. The observer who did not know the protocol assessed and recorded the data.

### 2.3. Cancer pain analgesic program

Patients in control group were administered oxycontin (Beijing Mundipharma Pharmaceutical Co., Ltd, Beijing, China; specification: 10 mg; J20140125 approved by the state) orally every 12 hours at the dosage determined according to the principle of morphine titration, and to control VAS scores less than 3. If the VAS score was more than 3, breakthrough pain was controlled by morphine hydrochloride, then titrated again to calculate the daily dosage of oxycontin. Patients in trial group were administered gabapentin (Jiansu Henrui Mundipharma Pharmaceutical Co., Ltd, Lianyungang, China, specification: 300 mg; H20030662 approved by the state) 300 mg for the first night, and 300 mg for next noon and night, respectively, and 300 mg 3 times a day as the initial dose since the third day. If VAS score was more than 3, the dosage of gabapentin was adjusted every 3 days by increment of 300 mg in the sequence of night–noon–morning. If the daily dosage of gabapentin exceeded 2700 mg, VAS was still more than 3, oxycontin was adjusted by retitration of morphine and the amount of gabapentin was reduced back to initial dosage.

### 2.4. Outcome measures

VAS was used to assess perceived pain. For this purpose, the patients were asked to write a cross on the 100 mm line to rank their pain from no pain (0 mm) to worst pain (100 mm); 1 to 3

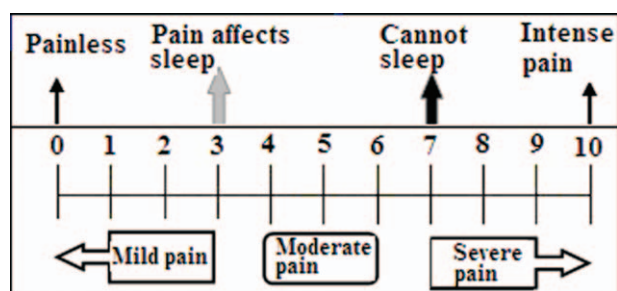


Figure 1. VAS score schematic diagram.

indicates mild pain, 4 to 6 moderate pain, and 7 to 10 severe pain. Of which, pain with VAS 4 affects sleep and patients with VAS more than 7 cannot sleep (as shown in Fig. 1). Observer in charged assessed and recorded the patients' pain VAS scores before and after taking medicine. Daily dose of oxycontin, daily cost of pain relief, and life quality score were observed 1 week, 1 month, 2 months, 3 months, and 6 months post-treatment. The daily average dose of oxycontin was calculated according to the total amount of dosage divided by the number of days, while the daily cost of cancer pain treatment, the total cost of drugs divided by the number of days. Quality of life (QOL)<sup>[10]</sup> was assessed according "cancer patients' quality of life scale" by using parameters such as appetite, spirit condition, sleep, daily life, and interpersonal relationship, each of which scaled range of 1 to 5 scores, to measure the quality of life before and after treatment. Flow chart of patient's inclusion and exclusion was shown in Fig. 2.

### 2.5. Statistical analysis and sample size estimation

Statistical analysis was performed with the use of SPSS 11.5 for Windows (SPSS, Inc., Chicago, IL) and Excel 2013. Numerical variables were presented as mean and standard deviation (SD) or median (range) where appropriate. Categorical data (incidence data) were presented as numbers or percentages. Means with normally distributed were analyzed by Student *t* test. Medians with skewness data were analyzed by Mann–Whitney *U* test. Incidence data were analyzed by Chi-square or Fisher exact test where appropriate. A *P*-value of less than 0.05 was considered statistically significant.

Sample size estimation was based on an SD of 1/3 of mean according to the trial study. Power was given at 0.85 to detect 25% difference at  $P < 0.05$  with use of G\*Power 3.0.10. It was then estimated that a minimum of 21 subjects would be necessary

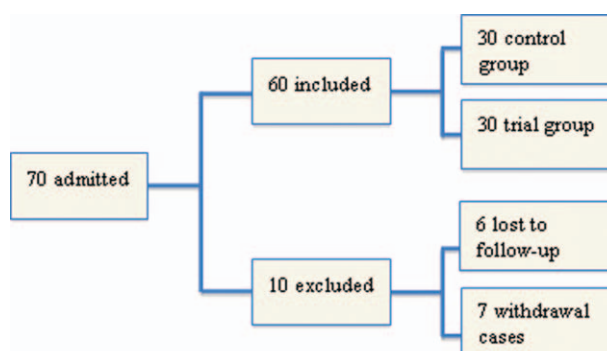


Figure 2. Flow chart of patients' inclusion and exclusion.

**Table 1**  
Patients' characteristics.

Parameters	Control group (n=30)	Trial group (n=30)	<i>t</i> / $\chi^2$	<i>P</i>
Age, y, mean $\pm$ SD	67 $\pm$ 6	65 $\pm$ 6	-1.095	0.278
Weight, kg, mean $\pm$ SD	58 $\pm$ 8	60 $\pm$ 7	0.837	0.406
Sex, male/female	19/11	17/13	0.278	0.598
Diagnosis/n				
Colorectal cancer	10	9	0.077	0.781
Lung cancer	5	7	0.417	0.519
Prostate cancer	4	3	0.162	0.688
Gastric cancer	8	6	0.373	0.542
Cervical cancer	3	5	0.567	0.451

SD=standard deviation.

for each of the 2 groups. We recruited 35 subjects in each group allowing for the possibility of the cases of "lost to follow-up" or the withdrawal cases.

### 3. Results

Seventy patients were screened for this clinical trial, among them 10 patients (5 in each group) were excluded because of 6 cases of "lost to follow-up" and 4 withdrawal cases. Therefore, 60 subjects were included in the analysis. There were no any differences in age, weight, and cancer types ( $P > 0.05$ ) (Table 1). No incidence of serious complications was observed in all patients.

There were no significant differences in daily average dosage of oxycontin ( $P > 0.05$ , Table 2), daily average cost for cancer management ( $P > 0.05$ , Table 3) between 2 groups 1 week and 1 month post-experiment. But compared with the trial group, daily average dosage of oxycontin and daily average cost for cancer management were significantly higher in control group ( $P < 0.001$ , Tables 1 and 2) 3 and 6 months post-experiment.

Where compared the incidence of side effects, we found that there was nearly similar in the incidence of drowsiness and dizziness ( $P > 0.05$ ), while the incidence of nausea and vomiting ( $P = 0.038$ ), and constipation ( $P < 0.001$ ) was significantly higher in the control group (Table 4). Life quality score increased in all of patients of both groups post-treatment ( $P < 0.05$ ); while life quality score in trail group was greater than in control group 3 months (46.8  $\pm$  4.5 vs 43.5  $\pm$  4.6,  $P = 0.007$ ) and 6 months (46.5  $\pm$  4.8 vs 41.4  $\pm$  4.3,  $P < 0.001$ ) post-treatment (Table 5).

### 4. Discussion

In the present study, we found that opioid agonist, oxycodone hydrochloride prolonged-release tablet (oxycontin), combined with the anticonvulsant (gabapentin) were used for cancer pain treatment has obvious advantages over the oxycontin alone in the

**Table 2**  
Comparison of daily average dosage of oxycontin (mg) between 2 groups.

Groups	1 wk	1 mo	3 mo	6 mo
Control group (n=30)	25.3 $\pm$ 9.0	28.7 $\pm$ 10.1	58.0 $\pm$ 15.2	72.7 $\pm$ 18.6
Trial group (n=30)	23.4 $\pm$ 7.6	27.3 $\pm$ 9.8	33.4 $\pm$ 11.0	50.7 $\pm$ 11.4
<i>T</i>	-0.931	-0.519	-7.223	-5.529
<i>P</i>	0.356	0.605	<0.001	<0.001

**Table 3**  
Comparison of daily average cost (RMB) for cancer management between 2 groups.

Groups	1 wk	1 mo	3 mo	6 mo
Control group (n=30)	22.9 $\pm$ 8.1	25.9 $\pm$ 9.1	52.4 $\pm$ 13.7	65.7 $\pm$ 16.8
Trial group (n=30)	24.7 $\pm$ 7.1	28.6 $\pm$ 9.2	34.5 $\pm$ 10.2	51.0 $\pm$ 10.5
<i>T</i>	0.898	1.121	-5.735	-4.062
<i>P</i>	0.373	0.267	<0.001	<0.001

base of long-term. The incidence of drowsiness and dizziness was comparable in 2 groups, while opioid related side adverse drug reactions such as nausea and vomiting or constipation were significantly reduced. At the same time, cost of cancer pain management reduced while life of quality of patients improved.

In the progress of tumor, there will develop all kinds of pain, resulting from malignant tumors' rapid infiltrative growth, which can produce capsular of tumor stretching that can lead to pressure on the nerve or erosion of nervous tissue. But in most cases, cancer pain is caused by the bone destruction due to cancer metastases to bone.<sup>[11,12]</sup> Drug therapy is the main method to control cancer pain and opioid drugs are the first choice for cancer pain relief, recommended by the principles of 3-step analgesic ladder for cancer pain.<sup>[13]</sup> Therefore, all of the cancer patients in this study were administered oxycodone hydrochloride prolonged-release tablet, oxycontin, which can control cancer pain effectively at the first time.

Long-term use of opioid drugs would induce opioid tolerance to analgesic action, which indicates that continuous application of opioid drugs resulting in applying the same amount of opioid with reduced analgesic effect and it needs to increase the drug dose to reach the previous potency level.<sup>[14,15]</sup> Opioid receptor desensitization is one of the main molecular mechanisms of opioid tolerance.<sup>[16]</sup> Long-term use of opioid agonist causes the decline in the number of opioid receptor or reduction of sensitivity to analgesics, which decreases sensitivity to opioid peptides and reduces analgesic effect of morphine. It needs to increase the dose of opioids to maintain analgesic effect, but the opioid induced side effects, such as constipation, is lifelong intolerance. The previous research showed that the faster increase in the dose of analgesic drugs and the greater the effective dose, the more significant the extent of drug tolerance.<sup>[17]</sup> Long-term, high dose, as well as rapid changes in concentration of opioid drug may also increase sensitivity to pain or aggravate existing pain, which is called the opioid-induced hyperalgesia that may also be another important reason for the opioid tolerance.<sup>[18]</sup> In this study, the dose of opioid drug in patients of both groups continued to increase had been presumed to be involved in drug tolerance. The current internationally accepted policy for advanced cancer patients with morphine tolerance is to increase the dose of morphine with no limitation. Clinical studies demonstrated nearly 90% of patients with cancer pain achieved satisfactory pain relief by increasing the dose of morphine after tolerance to morphine.<sup>[13]</sup> Opioids combined with the adjuvant drugs may reduce the amount of opioids, which may reduce the likelihood of the opioid tolerance. The analgesic adjuvant medications were prescribed in every ladder of WHO 3-step analgesic therapy, showing that adjuvant was important for treatment of cancer pain.<sup>[19]</sup> Shinde et al<sup>[5]</sup> found that more than 80% patients were on the 2 or more than 2 adjuvant medications along with opioid in their retrospective observational study, which reviewed the efficacy of cancer pain regimen for the

**Table 4****Comparison of side effects between the 2 groups.**

Groups	Dizziness	Nausea and vomiting		Drowsiness	Constipation
Control group (n=30)	7	18	1	29	
Trial group (n=30)	9	10	5	16	
$\chi^2$	0.341	4.286	2.914	11.02	
P	0.559	0.038	0.088	<0.001	

patients during staying in palliative cancer treatment center. But their results showed that there were not any benefits in terms of improved pain scores or opioid doses with adjuvants, but this could reflect confounding variables as a wide variety of diseases with varying severity, physician choices of combined regimen with inconsistent length of observation. Thus many factors made it difficult to draw a clear conclusion.

Gabapentin, the second-generation anticonvulsants with significant analgesic effect, is safe and reliable, which can be used to treat neuropathic, surgical, endoscopy pain. Its analgesic effect is mainly through central nervous system, spinal cord, and peripheral multichannel mediated pathway, without the impact of opioid receptor antagonist, and without tolerance after repeated doses.<sup>[20]</sup> Eckhardt et al<sup>[21]</sup> found that combined with morphine, gabapentin increased the blood concentration of morphine; therefore, the 2 drugs could be combined for the treatment of cancer pain. Keskinbora et al<sup>[22]</sup> found that combination of gabapentin with morphine for treatment of cancer neuropathic pain could reduce the pain scores in their early studies; while another study concluded that amitriptyline might be more suitable for management of neuropathic pain in cancer patients as adjuvant therapy combined with opioid because of lower cost of amitriptyline.<sup>[23]</sup> Studies showed that the effectiveness of gabapentin as an adjuvant analgesic added to opioid for cancer pain presents tissue specificity, for example, the combined program had poor beneficial effect for pain related to radiation-induced mucositis in head and neck cancer<sup>[24]</sup>; while treatment with gabapentin could be significantly effective and well tolerated in nearly all of the postmastectomy pain syndrome patients,<sup>[25]</sup> metastatic bone pain,<sup>[6]</sup> and visceral pain.<sup>[7,26]</sup> In the present study, the patients in trial group were treated with opioid drugs combined gabapentin, resulting in incensement of the analgesic effect of opioids, which might as well delay its tolerance. Daily cost of pain relief was less significantly than the patients in control group, and therefore reduced the economic burden of patients. At the same time, drowsiness induced by gabapentin

**Table 5****Comparison of life quality score between 2 groups before and after the analgesic scheme.**

Groups	Before treatment	1 mo after treatment	3 mo after treatment	6 mo after treatment
	Control group (n=30)	34.8±3.9	45.0±4.9*	43.5±4.6*
Experimental group (n=30)	33.7±4.5	47.1±3.6*	46.8±4.5*	46.5±4.8*
T	-0.979	1.941	2.797	4.367
P	0.332	0.057	0.007	<0.001

\* P&lt;0.05 vs before treatment.

after initial dose, can improve sleep in patients; while reduced the incidence of nausea and vomiting, thereby improving the quality of life.

The shortcoming of this study exists in including in 5 different cancer pain patients. Since gabapentin has a different effect on different cancer pain, further study will focus on the same kind of cancer associated pain to explore its effectiveness.

In summary, cancer pain was challenging to multidisciplinary scholars. Opioids were milestone of treatment of cancer pain, and supplementary analgesics were a basic treatment. This research showed that oxycontin combined with gabapentin could effectively control cancer pain, reducing both the dose of opioid and side effects as well, and improving quality of life. In order to achieve the desired quality of pain control, it needs to consider the specific adjuvant drug.

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