RESEARCH ARTICLE

Clinical Study on Fluvoxamine Combined with Oxycodone Prolonged-Release Tablets in Treating Patients with Moderate to Severe Cancer Pain

Yang Xiao[1&], Jun Liu[1&], Xin-En Huang[2*], Li-Hua Ca[1], Yi-Min Ma[1], Wei Wei[1], Rong-Xia Zhang[1], Xiao-Hong Huang[1], Juan Chang[1], Yi-Jia Wu[1]

Abstract

Objective: To observe treatment effects and safety of fluvoxamine combined with oxycodone prolonged-release tablets in treating patients with moderate to severe cancer pain. Methods: Patients confirmed pathologically with cancer and complicated with moderate to severe pain, were divided into control and experimental groups. Oxycodone prolonged-release tablets, with or without fluvoxamine, were administrated to all study patients until pain relief. Degree of pain relief, dose of oxycodone prolonged-release tablets, side effects and quality of life were compared before and after treatment. Results: In total, 120 patients were recruited. No statistically significant difference was detected regarding age, gender, types of cancer, KPS between two groups of patients ($P > 0.05$). Baseline pain score of patients with moderate pain in treatment and control group was 4.9±0.8 and 5.1±0.8, respectively; and decreased to 1.8±1.1 and 1.2±1.1 after treatment, respectively. Pain intensity was significantly reduced in the treatment group ($P = 0.028$). Average daily consumption of oxycodone prolonged-release tablets was (54.0±19.6) mg and (44.7± 18.7) mg respectively, which is lower in treatment grpup than in control group, but the difference was not statistically significant ($P=0.065$). Baseline pain score of patients with severe pain in treatment and control groups were 8.3±1.1 and 8.3±1.1, respectively; and pain intensity after treatment decreased to 2.9±1.0 and 2.3±1.0. Pain intensity was significantly reduced in the treatment group, with statistical significance ($P = 0.026$). Average daily consumption of oxycodone prolonged-release tablets was (132.0±42.2) mg and (110.7±33.9) mg, respectively, which is lower in treatment group than in control group, and the difference was statistically significant ($P=0.035$). In terms of quality of life, patients in treatment group had better performance status, daily activity, mood, and sleep than that in control group ($P < 0.05$). Patients in two groups had similar side effects, eg., constipation, nausea/vomiting, lethargy, dizziness, itchy skin, dysuria, and ataxia. Lower incidence of nausea/vomiting, lethargy, was obtained from patients in treatment than in control group, while significant low constipation was observed in treatment than in control group (35.0% vs 49.2%, $P=0.026$). Conclusion: Fluvoxamine combined with oxycodone prolonged-release tablets could be more effective in treating patients with cancer pain, and could reduce the dosage of oxycodone prolonged-release tablets and thus be associated with lower side effects, and improved quality of life.

Keywords: Cancer pain - fluvoxamine - oxycodone

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Introduction

Pain is now considered as a body status, following body temperature, pulse, respiration, and blood pressure as the fifth vital sign (Merboth et al., 2000). Pain is one of the most common symptoms associated with cancer. It is estimated that about 25% of patients new diagnosed with cancer, one third of of patients who are reciving anti-cancer medication and 3/4 of patients with advanced disease are complicated with cancer pain (Davis et al., 2004). And, cancer pain is one of the symptoms that makes patients feel discomfort, and if not controlled, will greatly affect their activities, treatment, and quality of life. The world health organization (WHO) established a principle of three ladder pain treatment guidelines that are widely accepted. This guideline recommendes that acetaminophen or non-steroidal anti-inflammatory drugs (NSAID) should be an initial therapy for patients with cancer pain. If the efficacy of treatment is not satisfactory, pain control therapy should be escalated to weak opioid, eg., codeine, and then to strong opioids eg., morphine. After guideline based treatment, if the patients still reported severe pain, suggesting insufficient analgesics and should increase dosage of these analgesics. But after repeated adjustment, some patients still reported severe pain and some patients complained significantly increased

[1]Department of Medical Oncology, The People's Hospital of Taixing City, Taixing, [2]Department of Chemotherapy, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, Nanjing, China [&]Equal contributors
**For correspondence: huangxinen06@aliyun.com*

adverse events, eg., nausea and vomiting, constipation, motor and cognitive impairment, delirium, etc. At this moment, according to WHO and NCCN pain guidelines auxiliary analgesic medications should be recommended. Auxiliary analgesics commonly used in adjuvant treatment of bone pain, neuropathy pain, visceral pain, and could reduce the dosage of opioids, especially effective when treating patients with resistant neuropathy pain. In clinical use, auxiliary analgesic medications involve a wide range of drugs, including anti-seizure drugs, antidepressants, cortical hormone and local anesthetics, etc. How to choose these auxiliary analgesic medication for treating cancer pain is still a research topic. Fluvoxamine is a serotonin reuptake inhibitors (5-HT). The mechanism of action is hypothesized to inhibit synapses cells of neurotransmitters from the reuptake of 5-HT, resulting in obvious antidepressant effect. On this background, we hypothesize that fluvoxamine combined with oxycodone prolonged-release tablets could be an effective regimen for treating patients with cancer pain.

Materials and Methods

Patient eligibility

Pathologically confirmed with malignant tumor; with moderately to severe pain; before entering into the study, all patients were graded with 0 ~ 10 pain intensity classification score (NRS) and evaluated by the quality of life and related inspection; NRS score for 4 or more points; patient was expected to survival for more than 2 months. Exclusion criteria: who has a history of drug allergy; has an opioid abuse history, severe alcoholism or severe history of mental disease; before entering into the study, has a history of treatment by antidepressants, and has an analgesia treatment, eg., surgery, radiation therapy, nerve block, etc; confirmed or suspected with paralytic ileus; complicated with moderately to severe hepatic or renal function impairment, or chronic obstructive respiratory diseases, eg., chronic asthma, etc; who is a pregnant women; with severe to adverse reactions during this study; poor compliance; with a sudden deterioration of the primary cancer; and patients who faile to be followed according to the study requirement.

Study design

During this controlled open trials, the detailed content of the this study will be explained to participant patients and informed consent will be obtained from all patients.

Treatment

Using numerical rating system (NRS), all patients with caner pain were scored (0 to 10 points). All patients, with moderate (NRS 4-6) or severe pain (NRS 7-10) were randomly divided into two groups: control group, treated with only oxycodone prolonged-release tablets, and experimental group: treated with oxycodone prolonged-release tablets and fluvoxamine. Oxycodone prolonged-release tablets, 10 mg/tablet, was made by Beijing Mengdi Pharmaceutical co., LTD. Fluvoxamine, 50 mg/ tablet, was made by Lizhu Pharmaceutical group co., LTD. Oxycodone prolonged-release tablets was used in both groups. Daily maintenance dosage of oxycodone prolonged-release tablet was estimated after two weeks. Fluvoxamine was initialed from 50 mg, qd, and increased to 50-100 mg/day, and set the daily dose below 150 mg, bid. Patients were mornitored 3 times a day, to assess pain NRS score and to adjust drug dosage. Side effects should be recorded in detail.

Observation

1. To compare pain relief in two groups: using NRS score to observe pain status before and after treatment, 0 point designates painless, 10 point means most painful.

2. To compare maintenance dosage of oxycodone prolonged-release tablets among two groups, and assessing the difference in dosage of oxycodone prolonged-release tablets between two groups after 2 weeks of treatment.

3. To observe adverse events in two groups, including constipation, nausea/ vomiting, drowsiness, headache, dizziness, respiratory depression, urinary retention, etc.

4. To compare quality of life in two groups. Quality of life will be recorded in accordance with the 2013 version of NCCN guideline, including daily activities of patient, emotion, social activity, sleep, walking ability, entertainment, etc.

5 Statistical analysis: SPSS 19.0 software is used for data processing. Count data using percentage, measurement data with mean± standard deviation. Intergroup comparison is conducted by t test. $P<0.05$ is set as statistically significant.

Results

According to the eligibility criteria, 120 patients with moderate to severa pain are recruited and randomly assigned to control group ($n = 60$), and experimental group ($n = 60$). Differences in age, gender, types of cancer, and KPS were not statistically significant between two groups of patients ($P> 0.05$).

Treatment results of cancer pain

NRS score of patients with moderate pain before

Table 1. Comparison of NRS before and after Treatment

		Before treatment		After treatment		P_3
		NRS score	P_1	NRS score	P_2	
Moderate pain	Control group	4.9±0.8	0.213	1.8±1.1	0.028	<0.01
	Experimental group	5.1±0.8		1.2±1.1		<0.01
Severe pain	Control group	8.3±1.1	0.066	2.9±1.0	0.026	<0.01
	Experimental group	8.8±1.1		2.3±1.0		<0.01

P_1, Comparison between control and experimental group before treatment; P_2, Comparison between control and experimental group after treatment; P_3, Comparison between before and after treatment.

Table 2. Comparison of Consumption of Oxycodone (mg/d)

	Moderate pain		Severe pain	
	Control group	Experimental group	Control group	Experimental group
Daily consumption of oxycodone	54.0±19.8	44.7±18.7	132.0±42.2	110.7±33.9
P	0.065		0.035	

Table 3. Incidence of Side Effects between Two Groups (%)

	Control group (*n*=120)	Experimental group (*n*=120)	χ^2	*P*
Constipation	59 (49.2)	42 (35.0)	4.941	0.026
Nausea/vomiting	28 (23.3)	18 (15.0)	2.689	0.101
Lethargy	36 (30.0)	30 (25.0)	0.752	0.386
Headache	18 (15.0)	20 (16.7)	0.125	0.724
Respiratory depression	3 (2.5)	2 (1.7)	0.204	0.651
Dysuria	5 (4.2)	7 (5.8)	0.351	0.554
Itchy skin	6 (5.0)	8 (6.7)	0.303	0.582
Ataxia	4 (3.4)	3 (2.5)	0.147	0.701

treatment in control and experimental group was 4.9 ± 0.8 and 5.1±0.8 (*P*= 0.213). NRS score of patients with severe pain before treatment in control and experimental group was 8.3±1.1 and 8.8±1.1 (*P*>0.05) (Table 1). NRS score of patients with moderate pain after treatment in control and experimental group was 1.8±1.1 and1.2±1.1, respectively. Compared with the NRS before treatment, *P* values are less than 0.01, compared between two groups after treatment, *P*=0.028. NRS score of patients with severe pain after treatment in control and experimental group was 2.9 ±1.0 and 2.3±1.0, respectively. Compared with the NRS before treatment, *P* values are less than 0.01, compared between two groups after treatment, *P*=0.026. In both moderate and severe pain group, NRS decreased significantly, the degree of pain relief was greater in experimental than in control group (*P*< 0.05) (Table 1).

Consumption of oxycodone prolonged-release tablets

In patients with moderate pain, average daily consumption of oxycodone prolonged-release tablets in control and experimental group was (54.0±19.8) mg/d and (44.7±18.7) mg/d, respectively, *P*= 0.065. The consumption of oxycodone prolonged-release tablets in experimental group is lower than that in control group, but the difference was not statistically significant. average daily consumption of oxycodone prolonged-release tablets in control and experimental group was (132.0±42.2) mg/d and (110.7±33.9) mg/d, *P*=0.035. The consumption of oxycodone prolonged-release tablets in experimental group is lower than that in control group, and the difference was statistically significant (*P*<0.05) (Table 2).

Comparison on adverse reactions

The incidence of constipation, nausea/vomiting, and lethargy was significantly lower in experimental (35.0%, 15.0%, 16.7%) than that in control group (49.2%, 23.3%, 30.0%), *P* values were 0.026, 0.101, 0.386, respectively. The incidence of constipation was statistically difference between experimental and control group. The incidence of headache, respiratory depression, dysuria, itchy skin, and ataxia in experimental group (16.7%, 1.7%, 5.8%, 6.7%, 2.5%) was similar with that in control group (15.0%, 2.5%, 4.2%, 5.0%, 3.4%), *P* values were 0.724, 0.651, 0.554, 0.582, 0.701, respectively, with no statistical difference (Table 3).

Comparison on quality of life

Quality of life before treatment in each group was compared with that after treatment, and the difference was not statistically different (*P*>0.05). However, the score of quality of life was lower after treatment than before treatment (*P*<0.01). In the experimental group, daily activities, emotions and sleep were improved (*P*< 0.05) (Table 4).

Discussion

Malignant pain is a stressful clinical status for cancer patients, especially for patients with advanced disease, and is the major factor that could influence the life quality of cancer patients so that cancer pain is of great significance for the treatment of cancer (Liang et al., 2013; Meserve et al., 2014). It is estimated that more than 50% of patients with advanced cancer are complicated with various degrees of pain, 70% cancer patients are with pain as the main symptom and 50% complain moderate tc severe pain (Meserve et al., 2014). At present, WHO guideline suggests that patients could be started on acetaminophen

Table 4. A Comparison on Quality of Life

Quality of life	Control group			Experimental group			P_3	P_4
	Before treatment	After treatment	P_1	Before treatment	After treatment	P_2		
General condition	8.0+0.8	5.2+1.0	<0.01	8.1+1.0	4.7+0.9	<0.01	0.570	0.044
Daily activity	7.2+0.9	4.2+1.0	<0.01	7.0+0.9	3.7+0.9	<0.01	0.390	0.044
Emotion	7.7+1.2	3.8+1.1	<0.01	7.5+1.1	3.1+1.1	<0.01	0.658	0.015
Walking	3.8+1.0	3.2+1.0	<0.01	4.2+1.0	2.9+0.7	<0.01	0.138	0.193
Social activity	5.2+0.9	3.0+0.9	<0.01	4.8+1.0	2.8+0.6	<0.01	0.119	0.252
Sleeping	7.5+1.1	3.7+1.4	<0.01	7.9+0.9	3.0+1.1	<0.01	0.097	0.046
Entertainment	4.9+1.1	2.8+0.9	<0.01	4.5+1.1	2.4+0.7	<0.01	0.217	0.120

P_1, Comparison between before and after treatment within control group; P_2, Comparison between before and after treatment within experimental group; P_3, Comparison between control and experimental group before treatment; P_4, Comparison between control and experimental group after treatment

or other nonsteroidal anti-inflammatory drug (NSAID). If this is not sufficient, the patients should be escalated to a step one opioid, eg., codeine, and subsequently to a second line opioid, eg., morphine. Opioids have pharmacological by binding to the opioid receptor located in central nervous system due to its inhibition on the release of substance *P* through binding with opioid receptor on shallow sensory neurons of spinal dorsal horn, and further achieving effect of pain relief. Currently 3 opioid receptors, eg., μ receptor, λ receptor and ϰ receptor are focused by researchers. The transmembrane structure and intracellular loop structure of these receptors, which are highly conserved, can be activated by endogenous opioid peptide and exogenous opioid agonist. Besides, opioids has descending inhibition effect on cerebral center of the pain to stop the pain transmitting into the brain (Mika et al., 2014). Morphine, one representative anagesics for treating patients with cancer pain, makes voltage-gated potassium channels of caudate nucleus neurons excited mainly through acting on μ receptor, which can inhibit voltage-gated calcium channel, make cytomembrane hyperpolarization and reduce the excitability of neurons which then cuts down the release of neurotransmitter of neuron axon endings, consequently blocking the transmission of nerve impulses and playing the role of nalgesic effect (Yang et al., 2014). However, the first pass effect of oral morphine is obvious, and could be low bioavailability of this medication (Shen et al., 2014).

Oxycodone prolonged-release tablet is an opioid analgesic effective for the relief of moderate to severe cancer pain (Kalso et al., 1990; Leow et al., 1992; Glare et al., 1993). And this sort of opioid analgesics is currently considered the strongest medications, without ceiling effect and hepato-or renal impairment when increased dosage is administered (Mercadante et al., 2014; Simon et al., 2014). However, after repeated dose escalate, some patients still reported severe pain and some patients complained significantly increased adverse events, eg., nausea and vomiting, constipation, motor and cognitive impairment, delirium, etc. At this moment, according to WHO and NCCN pain guidelines auxiliary analgesic medications should be recommended. Auxiliary analgesics commonly used in adjuvant treatment of bone pain, neuropathy pain, visceral pain, and could reduce the dosage of opioids, especially effective when treating patients with resistant neuropathy pain. In clinical use, auxiliary analgesic medications involve a wide range of drugs, including anti-seizure drugs, antidepressants, cortical hormone and local anesthetics, etc. How to choose these auxiliary analgesic medication for treating cancer pain is still a research topic. Fluvoxamine is a serotonin reuptake inhibitors (5-HT). The mechanism of action is hypothesized to inhibit synapses cells of neurotransmitters from the reuptake of 5-HT, resulting in obvious antidepressant effect.

In our study, after oxycodone prolonged-release tablets, with (experimental group) or without (control group) fluvoxamine was administrated to all recruited patients. Our results suggested that no statistically significant difference was detected regarding age, gender, types of cancer, KPS between two groups of patients. Baseline pain score of patients with moderate pain in treatment and control group was 4.9±0.8 and 5.1±0.8, respectively; and decreased to 1.8±1.1 and 1.2±1.1 after treatment, respectively. Pain intensity was significantly reduced in treatment group (P =0.028). Average daily consumption of oxycodone prolonged-release tablets was (54.0±19.6) mg and (44.7± 18.7) mg respectively, which is lower in treatment grpup than in control group, but the difference was no statistically significant (P=0.065). Baseline pain score of patients with severe pain in treatment and control group were 8.3±1.1 and 8.3±1.1, respectively; and pain intensity after treatment decreased to 2.9±1.0 and 2.3±1.0. Pain intensity was significantly reduced in treatment group, with statistical significance (P =0.026). Average daily consumption of oxycodone prolonged-release tablets was (132.0±42.2) mg and (110.7±33.9) mg respectively, which is lower in treatment group than in control group, and the difference was statistically significant (P=0.035). In terms of quality of life, patients in treatment group had better performance status, daily activity, mood, and sleep than that in control group ($P < 0.05$). Patients in two groups had similar side effects, eg., constipation, nausea/vomiting, lethargy, dizziness, itchy skin, dysuria, and ataxia. Lower incidence of nausea/vomiting, lethargy, was obtained from patients in treatment than in control group, but significant low constipation was observed in treatment than in control group (35.0% vs 49.2%, P=0.026).

In conclusion, we suggest that fluvoxamine combined with oxycodone prolonged-release tablets could be more effective in treating patients with cancer pain, and could reduce the dosage of oxycodone prolonged-release tablets and thus be associated with lower side effects, and improved quality of life.

References

Davis MP, Walsh D (2004). Epidemiology of cancer pain and factors influencing poor pain contro1. *Am J Hosp Palliat Care*, **21**, 137-42.

Glare PA, Walsh TD (1993). Dose-ranging study of oxycodone for chronic pain in advanced cancer. *J Clin Oncol*, **11**, 973-8.

Kalso E, Poyhia R, Onnela I' et al (1991). Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesthesiol Stand*, **35**, 642-6.

Liang SY, Chen KP, Tsay SL, et al (2013). Relationship between belief about analgesics, analgesic adherence and pain experience in Taiwanese cancer outpatients. *Asian Pac J Cancer Prev*, **14**, 713-6.

Liang SY, Wang TJ, Wu SF, et al (2013). Gender differences associated with pain characteristics and treatment in Taiwanese oncology outpatients. *Asian Pac J Cancer Prev*, **14**, 4077-82.

Leow KP, Cramond T, Smith MT (1995). Pharmacokinetics and pharmacodynamics of oxycodone when given intravenously and rectally to adult patients with cancer pain. *Anesth Analg*, **80**, 296-302.

Merboth MK, Barnason S (2000). Managing pain: the fifth vital sign (J). *Nurse Clin North AM*,,, **35**, 375-83.

Meserve J R, Kaye A D, Prabhakar A, et al (2014). The role of analgesics in cancer propagation. *Best Pract Res Clin Anaesthesiol*, **28**, 139-51.

Mika J, Popiolek-Barczyk K, Rojewska E, et al (2014). Delta-opioid receptor analgesia is independent of microglial

activation in a rat model of neuropathic pain. *PLoS One*, **9**, e104420.

Shen H, Hu X, Szymusiak M, et al (2014). Orally administered nanocurcumin to attenuate morphine tolerance: comparison between negatively charged PLGA and partially and fully PEGylated nanoparticles. *Mol Pharm*, **10**, 4556-51.

Yang J, Yang H, Du X, et al (2014). Morphine and DAMGO produce an opposite effect on presynaptic glutamate release via different downstream pathways of μ opioid receptors in the basolateral amygdala. *Neuropharmacology*, **86C**, 353-61.