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Original Article

Efficacy and safety of titration with controlled-release oxycodone versus immediate-release morphine in patients with moderate cancer pain

Zhiyong Shi, Guangyuan Lou, Cuiping Gu, Zhengbo Song, Lan Shao, Yiping Zhang

Department of Thoracic Medical Oncology, Zhejiang Cancer Hospital, Hangzhou City, Zhejiang Province, China

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Abstract: Objective: To clarify the efficacy and safety of titration with controlled-release (CR) oxycodone tablets in comparison with immediate-release (IR) morphine tablets in analgesia of cancer patients with moderate pain. Methods: A total of 120 patients with moderate cancer pain admitted to the Zhejiang Cancer Hospital from January 2014 to December 2016 were enrolled and randomly assigned to receive CR oxycodone tablets (oxycodone group) or IR morphine formulation (morphine group). The medication for titration with CR oxycodone tablets were as follows: The patients in the oxycodone group were administered an initial dose of oral CR oxycodone tablets (10 mg) once 12 h, followed by symptomatic treatment on the basis of the pain intensity at 1 h after initial dose. In contrast, the patients in the morphine group were given an initial dose of IR morphine tablets (5-10 mg), and received symptomatic treatment on the basis of the pain intensity at 1 h whenever needed. Pain relief at h 24, d 3 and d 7 after titration, respectively, the improvements in quality of life (QOL), titration measurements and adverse events before and after were compared between the two groups. Results: The oxycodone group achieved a much higher rate of pain relief than the morphine group at hour 24 after titration (75% vs 56.7%, P=0.034), and a considerably lower rate of breakthrough pain (46.7% vs 100%, P<0.001); however, the rates were insignificant different at day 3 and 7 between the two groups. The total daily dose of the patients in the oxycodone group was 65.7±7.9 mg, strikingly lower than that (69.5±9.2; P=0.017) in the morphine group. Moreover, daily medications in the oxycodone group was considerably fewer than those of the morphine group (3.25±1.64 vs 4.20±1.79, P=0.003), and the time to achieve stable analgesia was strikingly earlier than the morphine group (3.42±0.56d vs 3.67±0.74d; P=0.039). After the completion of titration, the QOL, somatic function and emotional function of both groups were improved greatly as compared with those before titration (All P<0.05), but small differences in the improvements were seen between the two groups. All subtypes of adverse events were similar for the two formulations (All P>0.05). Conclusion: For patients with moderate cancer pain, the improvements in pain relief, QOL and adverse events in titration with CR oxycodone tablets were basically similar to those in immediate release with IR morphine tablets, for the exception of faster analgesic effect and simpler administration.

Keywords: Moderate cancer pain, controlled -release oxycodone tablet, immediate-release morphine tablet, titration

Introduction

Pain is a common complication in cancer patients. Data from a study in China suggest that 88% of cancer patients reported their pain as moderate to severe in intensity [1]. If cancer pain is untreated or poorly treated, it may adversely affect the patients' quality of life [2, 3]. However, in a multi-center survey in China, the rate of complete relief in patients was only 9.48% after analgesia, while 52.9% of cancer patients had poor pain control in another study [4, 5]. Thus, how to alleviate and control the pain of cancer patients in an effective manner remains an urgent concern.

The major principle followed in the standard management of cancer pain is the World Health Organization (WHO) three-step analgesic "ladder" approach. Opioids are the priority for treating moderate and severe cancer pain [6, 7]. The analgesic effect and safety of opioids vary greatly; hence titration is necessary for the implement of individualized doses. Repeated

medication with low-dose immediate-release (IR) morphine tablets is conducted to achieve the right dose. However, with repeated evaluation and medication, the process of titration is quite cumbersome [8]. Recently, multiple guidelines have suggested that titration with sustained-release opioids is simple, safe and effective, so it is an ideal background medication for patients with stable or moderate pain [7, 9]. Controlled-release (CR) oxycodone is a biphasic release drug with fast analgesic effect, and its sustained-release phase helps to maintain blood concentration stable [10]. Its good titration effect has been substantiated in a great number of studies [11, 12]. However, few studies have reported the comparison of effects of titration with CR oxycodone tablets versus IR morphine tablets. Therefore, the purpose of this randomized controlled study was to assess the efficacy and safety of the two titration formulations for moderate cancer pain in patients in our hospital.

Materials and methods

Participants

The eligible participants were 120 patients with moderate cancer pain hospitalized in our hospital from January 2014 to December 2016. Patients ranging from 18 to 75 years old were included in this study if they could make self-evaluation of pain symptoms, had a score on the numerical rating scale (NRS) for pain intensity of 4 to 6, no previous use of opioids but planned to administer the opioids for analgesia, no previous radiotherapy nor chemotherapy over the study period and the study protocol remained unchanged for patients with targeted therapy or long-term use of hormones, the expected survival of more than 3 months; informed, agreed and provided written informed consent. Patients were excluded if they had concomitant severe multiple organ dysfunction syndromes in the heart, the bran, the lungs, the livers or the kidneys, or an allergy to the study drugs. Scores on the NRS range from 0 to 10, with 0 indicating no pain, 1 to 3 indicating mild pain, 4 to 6 indicating moderate pain, and 7 to 10 severe pain. The data on the demographic characteristics of the patients including age and sex were collected at the initiation of the study. The study protocol got approval from the Hospital Ethics Committee.

Randomization and treatment

A total of 120 patients underwent randomization by means of a random number table, with 60 assigned to each study group. Sixty patients were assigned to receive immediate-release morphine tablets as titration (the morphine group), and the remainder patients were assigned to receive CR oxycodone tablets (the oxycodone group).

The titration formulation for the morphine group was as follows: the initial dose was 5 to 10 mg of IR morphine tablets, followed by corresponding treatment based on the pain intensity in patients at 1 h after medication whenever needed; 50 to 100% of morphine tablets were added in case of an increase in the NRS score, repeated dosing was administered in case of unchanged NRS scores, and close observation was made if the NRS score was decreased to 1 to 3; an effective dose was given at the presence of pain within 24 hours; long-acting CR oxycodone tablets were administered at 24 h after titration; 10% to 20% of the total morphine dose for the first 24 h was given at the presence of breakthrough pain (BTP, defined as pain that fails to be controlled or "breaks through" a regimen of regularly scheduled opioid may require additional doses of opioid when patients with the NRS score of greater than 4), and on the basis of the changes in pain score after medication, corresponding treatment was provided till good pain control (NRS score of 0 to 3).

In contrast, the titration formulation for the oxycodone group was as follows: the initial dose was oral CR oxycodone tablets of 10 mg per 12 h, followed by corresponding treatment based on the pain intensity in patients at 1 h after initial medication; morphine tablets (10-15 mg) were administered in case of an increase in the NRS score, morphine tablets (5-10 mg) were administered in case of unchanged NRS score and no morphine tablets were given if the NRS score was decreased to 1 to 3; an effective dose was given at the presence of pain within 24 hours; at 24 h after titration, oral CR oxycodone tablets converted from the total dose of CR oxycodone tablets and morphine tablets prescribed in the first 24 h were administered twice daily; subsequently, 10% to 20% of the total morphine dose prescribed in the first 24 h

Table 1. General data of the patients

Characteristic	OG (n=60)	MG (n=60)	x^2/t	P
Age	56.8±9.7	58.2±10.6	0.755	0.452
Sex			1.292	0.256
Male	41 (68.3)	35 (58.3)		
Female	19 (31.7)	25 (41.7)		
Tumor site			1.745	0.418
Lung	37 (61.7)	30 (50)		
Esophagus	16 (26.7)	22 (36.7)		
Other	7 (11.7)	8 (13.3)		
Pain nature			0.696	0.706
VP	27 (45.0)	29 (48.3)		
SP	18 (30.0)	14 (23.3)		
NP	15 (25.0)	17 (28.3)		
NRS score	5.3±1.4	5.1±1.6	0.729	0.468

Note: OG denotes oxycodone group, MG morphine group, VP visceral pain, SP somatic pain, NP neuropathic pain, NRS numerical rating scale.

was given at the presence of BTP, followed by corresponding treatment on the basis of the changes in pain score after medication till good pain control (NRS score of 0 to 3).

Outcome measures

Analgesic effect: The pain relief in patients was evaluated at 24 h, 3 d, and 7 d after titration, respectively, and classified into 4 grades with reference to the pain relief (PAR) system developed by the WHO. They were complete relief (CR), no pain; partial relief (PR), significantly reduced pain than that before medication, with undisturbed sleep; mild relief (MR), reduced pain than that before medication, with obvious pain and disturbed sleep; no relief (NR), no pain relief as compared with that before medication). Relief rate = Cases of (CR+PR)/Cases of patients*100%. Additionally, over the duration of titration, the number of BTP (NRS≥4) of the patients in the two groups were collected, followed by calculation of the incidence of BTP, namely, the proportion of patients with BTP in each group.

Titration measures: The measures in the titration process included titrated dose (mg/d), the time to analgesic effect (min), the times of daily medications, and the time to stable pain control (d). The titrated dose was converted to the dose of morphine tablets with the formula as follows: 10 mg of CR oxycodone tablets = 20 mg of IR morphine tablets.

Quality of life: The functional subscales and the global quality of life of the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30, version 3.0) were applied for assessments. The functional subscales contain subscales for physical, role, cognitive, emotional, and social function, with the scores of all the items categorized into 1 to 4 which indicates no change, a little, moderate, and very much, respectively. The scores of all the items for the global quality of life (QOL) range from 1 to 7, with 1 indicating poor QOL and 7 indicating perfect QOL. The actual scores were converted by the linear transformation method into standard scores of 0 to 100, with higher scores on the functional subscales indicating better functioning and higher scores on the global quality of life scale indicating higher global QOL. The patients made self-evaluation of global quality of life, physical, role, cognitive, emotional and social functions before and after titration, respectively.

Safety: The study drugs-related adverse events in patients were observed and the incidence of adverse events was calculated.

Statistical analysis

The Kolmogorov-Smirnov (K-S) test revealed all the measurement data in the study were in line with normal distribution, hence were expressed as mean ± standard deviation. The two-sample independent t-test was employed to compare the differences in the baseline data between the two groups, while the differences in categorical variables between the two groups were tested with the use of the two-tailed chi-square test or the Fisher's exact probability test. The improvements in the scores of QOL in each group before and after titration were examined using the paired t-tests, whereas the two-sample independent t-test was applied for comparison of the differences of improvements in QOL between the two groups. The level of significance was set at a two-tailed alpha of 0.05 for all tests.

Results

General data of patients

No patients in the two groups withdrew from the study over the study period. The baseline

Table 2. Pain relief of the patients in the two groups

Pain	24 h		3 d		7 d	
	OG (n=60)	MG (n=60)	OG (n=60)	MG (n=60)	OG (n=60)	MG (n=60)
PR						
CR	23	18	30	24	31	29
PR	22	16	17	22	25	26
MR	9	15	13	10	4	5
NR	6	11	0	4	0	0
RR (%)	75.0	56.7	78.3	76.7	93.3	91.0
x^2, P	4.483, 0.034*		0.048, 0.827		1.000	
BTP						
1	8	4	4	7	1	1
≥2	20	56	1	2	0	1
Rate	46.7	100.0	8.3	15.0	1.7	3.3
x^2, P	43.636, <0.001**		1.294, 0.255		1.000	

Note: *P<0.05, **P<0.001; OG denotes oxycodone group, MG morphine group, PR Pain relief, CR complete relief, PR partial relief, MR mild relief, NR no relief, RR relief rate, BTP breakthrough pain.

Table 3. Comparison of titration between the two groups

Variable	Dose titration (mg/d)	Daily medication (time)	Time to stable pain control (d)
OG (n=60)	65.7±7.9	3.25±1.64	3.42±0.56
MG (n=60)	69.5±9.2	4.20±1.79	3.67±0.74
t	2.427	3.031	2.087
P	0.017*	0.003**	0.039*

Note: *P<0.05, **P<0.01; OG denotes oxycodone group, MG morphine group.

and clinical characteristics of the patients in the two groups were shown in **Table 1**. Small differences in gender, age, tumor site, pain intensity and the NRS scores were noted between patients with oxycodone and those with morphine (P>0.05).

Pain relief

At 24 h after titration, CR, PR, MR and NR occurred in 23, 22, 9 and 6 patients in the oxycodone group, respectively, with a relief rate of 75.0%, substantially higher than 56.7% of the morphine group (P=0.034). At 3 d and 7 d after titration, the relief rates were mildly different between the two groups (78.3% vs 76.7%, 93.3% vs 91.0%; both P>0.05). Moreover, at 24 h, the rate of BTP of the patients in the oxycodone group was 46.7%, significantly lower than 100% of the morphine group (P<0.001); however, the rates differed slightly at 3 d and 7 d (8.3% vs 15%, 3.3% vs 1.7%; both P>0.05; **Table 2**).

Comparison of titration measures between the two groups

During the titration period, the total daily dose for titration with oxycodone (65.7±7.9 mg), was significantly lower than that with morphine (69.5±9.2; P=0.017). In addition, daily medications were much fewer with oxycodone than with morphine (3.25±1.64 vs 4.20±1.79; P=0.003), but the time to achieve stable pain control was significantly earlier with morphine (3.42±0.56d vs 3.67±0.74d; P=0.039; **Table 3**).

Improvements in QOL in the two groups

Before titration, the patients in the two groups were basically similar in the QOL, somatic, role, cognitive, emotional and social functions (All P>0.05). Significant improvements in the QOL, somatic function and emotional function after titration were observed in both groups as compared with those before titration (all P<0.05), though no great difference in the improvement between the two groups (P>0.05, **Table 4**).

Adverse events

Table 5 shows the adverse events in the two groups during the titration. The most common adverse event in the two groups was constipation (38.3% with oxycodone and 40% with morphine), followed by nausea and vomiting (31.7% vs 35.0%). Additional adverse events included somnolence, dizziness, urinary retention, abdominal distention, and anorexia. However, only mild difference was observed in the incidence of adverse events between the two groups (all P>0.05).

Discussion

In the WHO three-step analgesic "ladder" protocol, analgesics can be prescribed on the basis of pain intensity in patients. Patients with moderate pain received the weak opioids at step 2, while those with severe pain are administered the strong opioids at step 3. In recent years, due to poor moderate pain control of the weak opioids, the difficulties in dosage adjustment, potential sensitization of the central nervous

Table 4. Improvements in QOL in the two groups

Item	Titration	OG (n=60)	MG (n=60)	t	P
QOL	Pre-titration	61.1±20.7	62.9±20.9	0.484	0.636
	Post-titration	67.2±21.2	67.5±19.4		
	Difference	6.1±9.2	5.6±9.3	0.869	0.386
	t, P	5.135, <0.01	4.664, <0.01		
SF	Pre-titration	60.5±21.4	63.3±20.4	0.734	0.465
	Post-titration	64.2±19.2	65.8±9.4		
	Difference	4.7±5.3	3.6±4.9	1.180	0.240
	t, P	6.869, <0.01	5.691<0.01		
RF	Pre-titration	59.7±21.2	62.6±18.4	0.800	0.425
	Post-titration	60.2±19.5	63.3±18.9		
	Difference	0.5±2.1	0.7±2.8	1.708	0.090
	t, P	1.844, 0.070	1.936, 0.058		
CF	Pre-titration	64.1±22.3	67.5±25.3	0.781	0.436
	Post-titration	64.9±23.7	68.0±25.9		
	Difference	0.8±3.3	0.5±2.1	0.594	0.554
	t, P	1.878, 0.065	1.844, 0.070		
EF	Pre-titration	62.7±23.7	65.3±24.2	0.596	0.552
	Post-titration	65.1±24.0	68.6±25.5		
	Difference	2.4±4.1	3.3±4.7	1.118	0.266
	t, P	4.534, <0.01	5.439, <0.01		
SOF	Pre-titration	66.7±24.9	70.2±25.8	0.756	0.451
	Post-titration	66.9±24.8	70.8±27.1		
	Difference	0.2±0.8	0.6±2.7	1.100	0.273
	t, P	1.936, 0.058	1.721, 0.090		

Note: OG denotes oxycodone group, MG morphine group, QOL quality of life, SF somatic function, RF role function, CF cognitive function, EF emotional function, SOF social function.

Table 5. Adverse events in the two groups (n, %)

Adverse event	OG (n=60)	MG (n=60)	x^2	P
Constipation	23 (38.3)	24 (40.0)	0.035	0.852
Nausea and vomiting	19 (31.7)	21 (35.0)	0.150	0.699
Somnolence	5 (8.3)	3 (5.0)		0.717*
Dizziness	4 (6.7)	5 (8.3)		1.000*
Urinary retention	3 (5.0)	2 (3.4)		1.000*
Abdominal distention	1 (1.7)	0 (0)		1.000*
Anorexia	0 (5.0)	1 (1.7)		1.000*

Note: *The Fisher's exact test, OG denotes oxycodone group, MG morphine group.

system and other reasons, a variety of guidelines and randomized controlled studies have recommended weakening of the step 2 treatment, earlier use of strong opioids, and analgesics at step 3 (eg. morphine or oxycodone) used as options at step 2 [7, 14]. A recent randomized controlled study also demonstrated that, for patients with moderate cancer pain, low-dose morphine greatly reduced the pain intensity compared with weak opioids [15].

Dose titration of opioids whenever needed is the first step in the standard treatment of cancer pain. By titration, we can achieve adequate and fast pain control, determine the reasonable dose of analgesics, and ensure the safe drug transition and dose conversion [16]. Titration with IR morphine is a clinically common formulation for titration. However, its major flaws are cumbersome steps, complicated procedures, difficult medication and poor drug resistance. As a result, titration with sustained-release opioids has been developed recently [6, 7, 17, 18].

CR oxycodone is an opioid receptor (μ, κ) agonist. Its biphasic release feature is mainly attributed to the use of Acro Contin controlled release technology, namely, the fast analgesic effect in the release phase, with 38% of the drugs releasing rapidly and achieving pain relief within 1 hour. The commonly used CR oxycodone tablet is 10 mg per tablet, namely, the release component (38%) of the dose is equivalent to 5.7-7.6 mg of morphine tablets and within the range of the initial dose of oral morphine titration specified in the guidelines. The remaining 62% component of the drug is released slowly and maintains stable analgesia for 12 hours. Due to the above pharmacological characteristics of CR oxycodone, much attention has been attracted to the research on background titration with CR oxycodone in recent years [19, 20]. In a study in China, the use of CR oxycodone titration in 120 patients with severe cancer pain was associated with 96.7% of total pain relief, higher quality of life and fewer adverse events [21]. Salzman found no difference in the effect of titration between IR oxycodone tablets and CR oxycodone tablets, as 92% of patients with CR oxycodone and 79% of

patients with immediate-release oxycodone achieved good pain control, which is also confirmed by the results of the latest systemic evaluation [11, 20].

Both IR morphine and CR oxycodone formulations have been applied for pain titration in cancer patients, and have ideal effects. However, the available associated studies are lacking control cohorts, no uniform titration formulations, or a wide range of cancer pain intensity in target patients. Therefore, no definite evidence has found to confirm the advantages or disadvantages of the above two titration formulations. In our current study, the time to analgesic effect and the time to achieve stable pain control were markedly earlier with oxycodone than with morphine and the pain relief rate at hour 24 was also higher with oxycodone, suggesting that oxycodone titration achieves faster pain control. Nevertheless, the pain relief rates were insignificantly different at day 3 and day 7 between the two groups, similar to the results in other studies [22, 23]. In another study, the pain relief rate was strikingly higher with oxycodone than with morphine at 12 h after titration, but no significant difference at 24 h [24]. This might be associated with the diverse severity of cancer pain in the patients, with moderate cancer pain patients in our current study versus moderate to severe pain ones in the abovementioned studies.

The improvement in the QOL is also one of the major markers for evaluating the efficacy of cancer pain control. Multiple studies have demonstrated that CR oxycodone improves the QOL of patients with cancer pain with regards to symptoms, somatic function and emotional function [25, 26]. The EORTC QLQ-C30 (V3.0) is one of the questionnaires for assessments of QOL in cancer patients. It is characterized by good sensitivity, reliability and validity [27, 28]. In our current study, the QOL, somatic and emotional function improved significantly in patients of both groups after titration with either CR oxycodone or IR morphine as compared with those before titration. The two groups differed mildly in improvements in the above three items, suggesting that the two titration regimens lead to significant improvements in some aspects of the quality of life of patients. Additionally, after titration, the incidence of adverse events was basically similar between the two groups, and no severe adverse events occurred, which were similar to the results of other studies [21, 22].

In conclusion, in our current study, we assessed the efficacy of titration with CR oxycodone tablets and with IR morphine tablets regarding the titration process, pain relief, QOL and adverse events in patients with moderate cancer pain, and found the efficacy and safety of titration with CR oxycodone tablets were generally similar to those with IR morphine tablets except for faster analgesic effect. However, there are still some limitations in the current study. For example, it was a single center study and not blind; hence it could not avoid the bias from the researchers and patients. What's more, due to the small sample size of this study and only evaluation of short-term efficacy and safety, additional randomized double-blind multicenter studies with larger samples are needed to evaluate and validate the efficacy and safety of CR oxycodone background titration in patients with moderate cancer pain.

Disclosure of conflict of interest

None.

Address correspondence to: Yiping Zhang, Department of Thoracic Medical Oncology, Zhejiang Cancer Hospital, No.1 Banshan East Road, Gongshu District, Hangzhou City 310022, Zhejiang Province, China. Tel: +86-0571-88122082; E-mail: zhangyiping995@126.com

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