Clinical Trial/Experimental Study

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Efficacy and safety of sustained-release oxycodone compared with immediate-release morphine for pain titration in cancer patients

A multicenter, open-label, randomized controlled trial (SOCIAL)

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Abstract

Background: The study aims to investigate the effect and safety of sustained-release oxycodone hydrochloride as background dose on pain titration in patients with moderate-to-severe cancer pain.

Material and methods: Adult patients scheduled with a regular strong opioid for cancer-related pain were recruited and randomly assigned to sustained-release oxycodone group (tablets, 12 hourly) and immediate-release morphine group (5 mg initially, hourly). All patients were hourly reassessed for efficacy and dose titration.

Results: The primary end point was the number of titration cycles required to achieve adequate pain relief (numerical rating scale, NRS $\leq$ 3). Secondary end points included the proportion of patients achieving adequate pain relief during each cycle, potential predictive factors for titration performance, and side effects. Ninety (94.7%) patients in oxycodone group and 78 (86.7%) patients in morphine group achieved adequate pain control during 1 to 4 cycles of titration. Patients in oxycodone group reached adequate pain control within the first 2 cycles of titration, which was significantly shorter than morphine group wherein the number of titration cycles ranged from 1 to 4 (P = .034). Oxycodone prescription significantly increased the response rate of patients to morphine titration during the first cycle of titration (P = .010). The initial NRS score and oxycodone administration were significantly associated with titration performance. The mild or moderate adverse effects were similar in 2 groups, while severe adverse effects were only identified in morphine group (P = .001).

Conclusion: Use of background sustained-release oxycodone is more efficient and better tolerated on dose titration than immediate-release morphine.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events v 4.0, EAPC = European Association of Palliative Care, GEE = generalized estimating equations, IR = immediate-release, NRS = numerical rating scale, ULN = upper limit of normal.

Keywords: cancer-related pain, dose titration, immediate-release (IR) morphine, side effects, sustained-release oxycodone, titration cycle

Editor: Miao Liu.

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The present study was supported by Mundipharma (China) Pharmaceutical Co., Ltd.

The authors report no conflicts of interest.

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Medicine (2019) 98:24(e15505)

Received: 29 January 2018 / Received in final form: 28 February 2019 / Accepted: 10 April 2019

http://dx.doi.org/10.1097/MD.0000000000015505

1. Introduction

Chronic cancer-related pain is a common clinical problem affecting the quality of life and survival of patients with advanced stages of cancer,[1] accounting for 60% to 90% of patients with advanced cancer.[2] Treatment with strong opioids, following the World Health Organization (WHO) analgesic ladder, can be considered the mainstay of cancer pain therapy. Morphine is well-established as the gold standard opioid for treating moderate-to-severe cancer pain.[3] However, the dosage of morphine required for proper pain relief varies with individual patients and disease progression, and it is difficult to predict the correct dose for each patient,[4] which may cause inadequate pain management and create a great challenge for clinical health providers. It has been reported that up to 50% of cancer pain did not receive adequate treatment and 30% of patients received inappropriate drugs for treating cancer pain.[5] A dose titration procedure using immediate-release (IR) morphine has been recommended to ease the analgesia assessment during the start of pain management.[6] It has been well documented that morphine titration is adequate to find the appropriate dose with acceptable adverse effects.[7] However, for frail and elderly patients, the 4-hourly scheduled procedure of the clinical pain management is cumbersome and inevitably causes problems of compliance of patients and physicians.[8,9] Meanwhile, the increased dose of morphine may expose patients to a high incidence of adverse effects.[7] A modified approach for dose titration is of great significance for dose titration and therefore simplifying the procedure and improving life quality of the cancer pain patients.

Oxycodone sustained-release, a semi-synthetic opioid analgesic, is an alternative to morphine for moderate-to-severe cancer pain. It has no ceiling effect for analgesia and the total daily dose can be titrated until the proper pain control.[10] Increasing studies have proved that controlled-released oxycodone could be as a rational alternative for moderate-to-severe cancer-related pain.[11–13] It has a better oral bioavailability than morphine, with less interindividual variation and more predictable plasma concentration. The titration schedules using oral formulations of immediate- or slow-release morphine, oxycodone, and hydromorphone has been suggested for dose titration.[14] Dose titration of oral sustained and IR oxycodone has been reported to achieve the same goal in patients with chronic moderate-to-severe pain.[15] However, it was still considered as a new 'old' drug with the pharmacology and clinical potential needing fully exploit.[16] Few studies have focused on the effect of background treatment with sustained-release oxycodone on dose titration during the start of pain management. Therefore, this randomized control study is aimed to investigate the effect of sustained-release oxycodone as background dose on initial dose titration of morphine to achieve adequate pain relief in patients with moderate-to-severe cancer pain.

2. Materials and methods

2.1. Trial design

This was a multicenter, open-label, randomized controlled trial. The study was approved by the ethics committee of the Sir Run Run Shaw Hospital, Zhejiang University, and the protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This trial was registered in the Chinese Clinical Trial Registry (No.ChiCTR-ORC-13003351), the primary registry of WHO International Clinical Trials Registry Platform. All patients gave the written informed consent.

The study consisted of a screening period of 3 days before randomization, followed by a dose titration phase of up to 8 days, and a no less than 3 days of dose maintenance phase. Patients with chronic cancer-related pain were randomly assigned to either oxycodone group or morphine group using stratified block randomization based on age, gender, and initial numerical rating scale (NRS) score of the patients. Patients in oxycodone group were prescribed with 10 mg of oxycodone hydrochloride sustained-release tablets (OxyContin Tablets, Bard Pharmaceuticals Limited, UK) every 12 hour and IR morphine as needed. Patients in morphine group were titrated with IR morphine alone 4 hourly at the initial dose of 5 mg. All patients were reassessed for efficacy and dose titration every 60 minutes. Nonresponders to the first cycle of titration were titrated with IR morphine again until adequate pain control (NRS $\leq$ 3) or intolerable adverse effects. Doses of morphine were retitrated according to response of the patients (Fig. 1). Patients nonresponsive to the fourth cycle of morphine titration were defined as titration failure.

2.2. Participants

The study included adult patients scheduled for a regular strong opioid for cancer-related pain (NRS $\geq$ 4) during August 2013 to

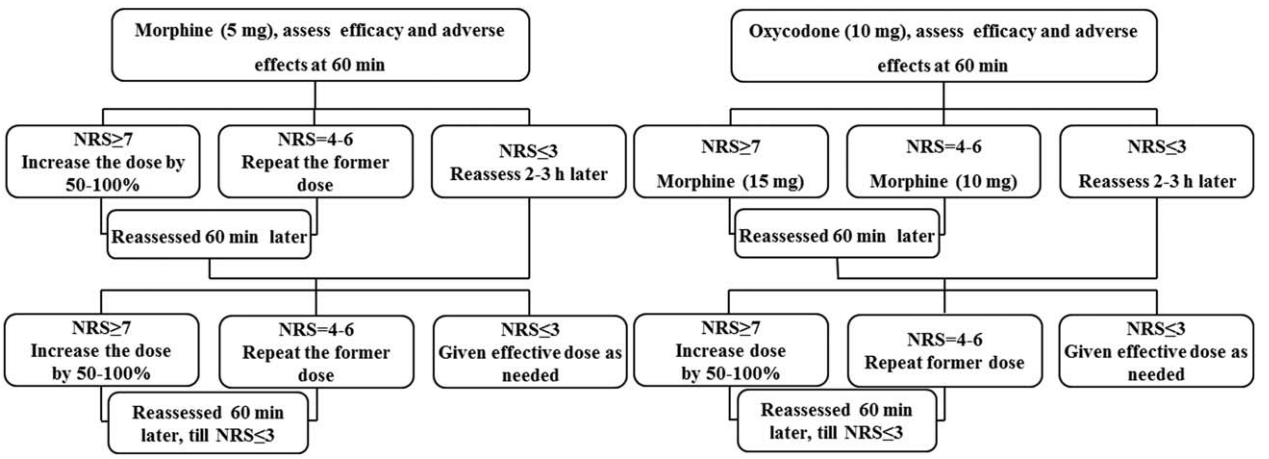

Figure 1. The general titration procedures with or without sustained-release oxycodone as background dose for cancer pain management.

Table 1

Clinical data of the patients.

	Oxycodone group ($n=95$)	Morphine group ($n=90$)	P
Age (y)	60.1 ± 13.3	59.8 ± 11.5	.854*
Gender (n, %)			.877†
Male	63 (66.3)	58 (64.4)	
Female	32 (33.7)	32 (35.6)	
Initial NRS score	4.6 ± 1.3	4.6 ± 1.1	.681*

NRS = numerical rating scale
* *t* test;
† Chi-square test

May 2015. The patients who had not taken a strong opioid before and had poor response to weak opioids were recruited from 12 centers in China. The patients who did not receive cancer-related treatment (chemotherapy, radiotherapy, targeted therapy, hormone therapy, or diphosphonate therapy) within 3 days prior to randomization or anticipate no such procedures during the study were given priorities for participation. To encourage participation and lower the discontinuation rate, patients who received stable doses of above treatments were also recruited into this study.

Patients were excluded if they had chronic noncancer-related pain, acute pain, or pain induced by exercise; had contraindication for oral medication, oxycodone or morphine; had not defecated for 3 days during the screening period; had surgery or radionuclide treatment within 3 days prior to randomization or during the study; received monoamine oxidase inhibitors within 7 days prior to randomization; or had compromised function of major organs (creatinine ≥2 of upper limit of normal [ULN], AST or ALT ≥ 2.5 of ULN or Child-Pugh C).

2.3. Assessments

The pain intensities were measured using an 11-point NRS of 0 to 10, with the left anchor 0 representing no pain and the right anchor 10 representing maximal imaginable pain.[17] Higher numbers indicated more severe pain. When mild pain was achieved (NRS ≤ 3),[18] it was considered reaching adequate pain control. The primary endpoint was the number of titration cycles needed for each patient to respond to dose titration, that is, to reach adequate pain control of NRS ≤3. Secondary endpoints included the proportion of patients achieving adequate pain relief during each cycle of titration, potential predictive factors for titration performance of the patients, and side effects that was assessed according to the Common Terminology Criteria for Adverse Events v 4.0 (CTCAE).

2.4. Statistical analysis

We calculated the sample size based on the ability to detect differences between the treatment groups, assuming a mean titration cycles of 1.5 with a standard deviation of 1.1. A total of 164 patients (82 in each group) provided 80% power with a one-sided α of 0.05 in this study with a noninferiority margin of 25% (0.375 titration cycles). Appropriately 192 patients were needed to be recruited allowing for an expected expulsion rate of 15%.

Statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc, Chicago, IL). Baseline comparisons were performed using chi-square test or Fisher exact test for categorical variables and *t* test or nonparametric Wilcoxon test for continuous variables. Association analysis of clinical data with the titration performance was carried out using generalized estimating equations (GEE).[19] A per protocol analysis was performed in this study. A *P* value of <.05 was considered as statistically significant.

3. Results

3.1. Clinical characteristics and titration cycles of the patients

A total of 192 patients, who required regular strong opioid for chronic cancer-related pain, were enrolled into this study. The patients were randomly assigned to oxycodone and morphine groups at a ratio of 1:1 ($n=96$ per group). Finally, 185 patients were analyzed (oxycodone group, $n=95$; morphine group, $n=90$), due to 1 patient in oxycodone group and 6 patients in morphine group dropped out. There was no significant difference between the 2 groups in terms of the age, gender, and initial NRS score (Table 1). Ninety patients (94.7%) in oxycodone group and 78 patients (86.7%) in morphine group achieved adequate pain control (NRS ≤ 3) during 1 to 4 cycles of titration. The number of titration cycles until adequate pain control was significantly different between the 2 groups ($P=.034$, Table 2). Prescription of oxycodone improved the efficiency of titration, and most patients (90/95, 94.7%) in oxycodone group reached adequate pain control within the first 2 cycles of titration (1.078 ± 0.269). By contrast, in patients of morphine group, the number of titration cycles needed to achieve adequate pain control ranged from 1 to 4 (1.218 ± 0.550). Figure 2 shows the pain level of 2 groups during the treatment.

3.2. Proportion of responders to morphine titration during each cycle

A total of 168 patients were successfully titrated during the 4 cycles of morphine titration. The cumulative percentage of cancer

Table 2

Effect of oxycodone on response rate to morphine titration during each titration cycle.

	Oxycodone group ($n=95$)			Morphine group ($n=90$)			
Titration cycle	Total	Responder	Non-responder	Total	Responder	Non-responder	P
1	95	83	12	90	65	25	.01*
2	12	7	5	25	10	15	NS*
3	5	0	5	15	2	13	NS†
4	5	0	5	13	1	12	NS†

NS = not significant.
* Chi-square test.
† Fisher exact test.

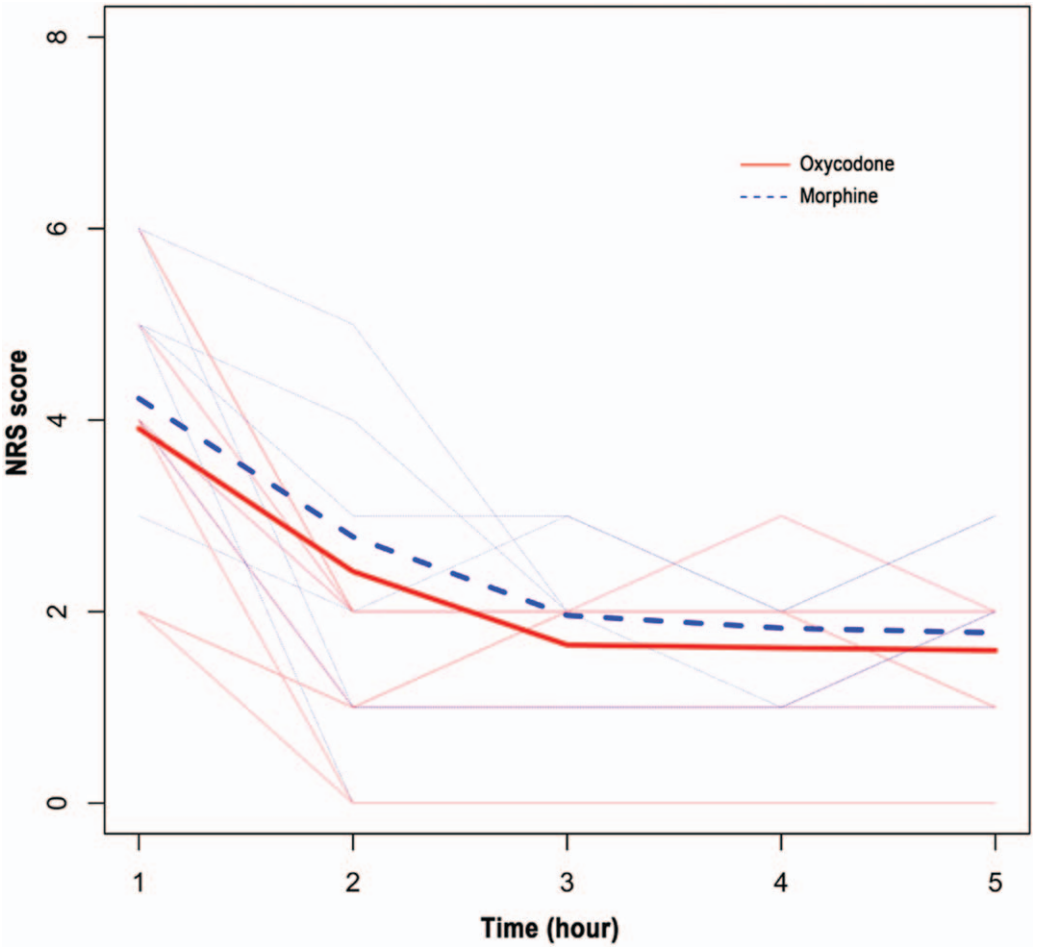

Figure 2. The pain level of 2 groups during the treatment.

patients completing titration during the sustained-release oxycodone introduction is shown in Figure 3. Oxycodone prescription significantly increased the response rate of patients compared to morphine titration during the first cycle of titration (87.4% vs 72.2%, $P=.010$). There was no significant difference in the proportion of patients responsive to dose titration between the 2 groups during the following titration cycles.

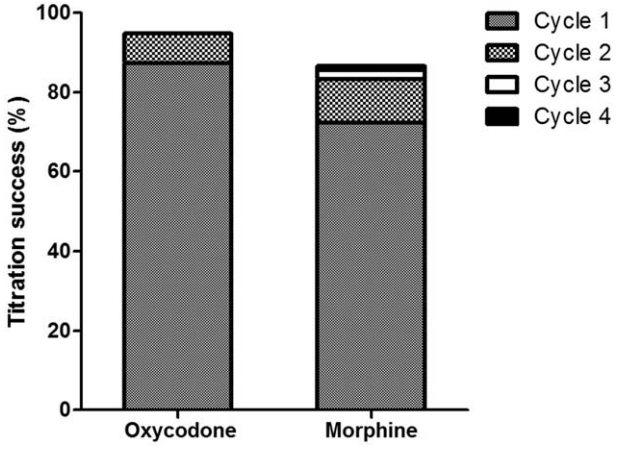

Figure 3. Proportion of responders during titration with oxycodone or morphine.

3.3. Predictive factors for titration response

GEE analysis showed a significant effect of initial NRS score and oxycodone prescribed on titration performance in cancer pain patients. Prescription of oxycodone was significantly associated with the higher response rate of dose titration ($P=.022$, OR = 3.54, 95% CI: 1.20−10.40) with the estimate partial regression coefficient 1.2642. Initial NRS score showed a negative association and patients with lower initial NRS score had a higher response rate ($P<.001$, OR = 0.39, 95% CI: 0.24−0.63) with the estimate partial regression coefficient −0.9448.

3.4. Adverse effects

The most common adverse effects were constipation, nausea, and vomiting. Most of the adverse effects were mild or moderate, and the rate profiles were similar in oxycodone and morphine groups. Nine severe adverse events were reported during the study, all occurred in patients of morphine group. There was a significant difference in severe adverse effect profile between the patients of 2 groups ($P=.001$, Table 3).

Table 3

Side effects reported during the procedure.

	Oxycodone group ($n=95$)	Morphine group ($n=90$)	P
Mild/moderate side effects (n, %)	53 (53.8)	56 (62.2)	.374*
Constipation	39 (41.1)	39 (43.3)	.754*
Nausea	19 (20.0)	23 (25.6)	.367*
Vomiting	20 (21.1)	12 (13.3)	.165*
Dizziness	15 (15.8)	10 (11.1)	.352*
Fever	7 (7.4)	6 (6.7)	.852*
Poor appetite	6 (6.3)	3 (3.3)	.498†
Feeble	4 (4.2)	3 (3.3)	.755†
Sweat	2 (2.1)	4 (4.4)	.434†
Somnolence	2 (2.1)	4 (4.4)	.434†
Pruritus	0	4 (4.4)	.054†
Severe side effects (n, %)	0	9 (10.0)	.001†
Constipation	0	4 (4.4)	.054†
Fever	0	1 (1.1)	.486†
Sweat	0	1 (1.1)	.486†
Dysphagia	0	1 (1.1)	.486†
Loss of consciousness	0	1 (1.1)	.486†
Death	0	1 (1.1)	.486†

* Chi-square test

† Fisher exact test

4. Discussion

Our study showed that oxycodone prescription as background dose improved the efficiency of dose titration for cancer patients. With the introduction of sustained-release oxycodone as background dose, the average number of titration cycles required to adjust the dose was significantly reduced, and most patients were stable in the titration dose during the first 2 cycles of dose titration. By contrast, the number of titration cycles needed in morphine group ranged from 1 to 4. It is worth mentioning that that prescription of oxycodone significantly increased the response rate of patients to dose titration during the first cycle of titration ($P=.01$). Our study also showed that the initial NRS score and oxycodone utilization may significantly influence the titration performance, and the patients who prescribed with oxycodone and had lower initial NRS score showed higher response rate to dose titration. All these results showed that the use of sustained-release oxycodone as background medication for dose titration provided superior efficiency for dose adjustment in cancer pain patients than morphine.

Individual dose titration with IR morphine has been recommended in clinical practice, which could allow to quickly achieve steady state through the short action of duration.[6] However, this 4-hourly regimen of morphine was cumbersome, and may cause the problem of adherence to prescribed treatment and confusion about medication, especially for old and frail patients.[8,20] Oxycodone, as a semisynthetic opioid analgesic, has no ceiling effect, and has been reported to be efficacious and well tolerated for treating patients with moderate-to-severe cancer-related pain.[21] The use of oxycodone hydrochloride sustained-release tablets as background medication for dose titration in our study not only shortened the time needed for dose titration, but also significantly reduced the incidence of morphine-induced side effects.

As recommended by European Association of Palliative Care (EAPC), the IR and slow-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration, and the oral IR opioids can be given for breakthrough pain in the titration schedules of both formulations.[14] However, to our knowledge, there were few studies which reported the effect of oxycodone administration on dose titration and the tolerability of cancer pain patients during pain management. Therefore, in the present study, based on the potential benefit of sustained-release oxycodone, we aimed to investigate the benefit of IR morphine on cancer pain management. The findings of our study showed the superior effect of oxycodone administration on dose adjustment of morphine during the start of cancer pain management, which spared the patients from a multiple dose schedule. Furthermore, oxycodone may omit the need for opioid switching from IR morphine to a controlled-release preparation, thus improve patient compliance.

The unwanted side effects have been described in patients treated with morphine, and the frequent occurrence of adverse events may be a barrier to optimal dosing and compliance of the patients.[22] The goal of morphine therapy has been suggested to yield a favorable balance between pain control and side effects.[23] The side effect profile of oxycodone has been reported to be similar to that of morphine. However, other studies also indicated that patients prescribed with oxycodone had less adverse effects.[11,24–26] Moreover, combination of controlled-release formulations of morphine and oxycodone provided added benefit for opioid-related adverse effect, with less nausea and vomiting reported when compared with morphine used alone.[27] In the present study, constipation, nausea, and vomiting were most common adverse effects. The majority of adverse effects were mild to moderate in severity, with the similar profiles between oxycodone and morphine groups. However, the incidence of severe adverse reactions was only found in the morphine group. All these results suggested a beneficial effect of oxycodone in management of cancer-related pain. However, we acknowledge some limitations in this study. A multicenter and double-blind study with a larger sample size is desirable to further confirm the results.

In conclusion, use of sustained-release oxycodone is more efficient and better tolerated on dose titration than IR morphine. The findings of our study may shed light on the rational use of sustained-release oxycodone as background dose for dose titration in clinical management of chronic cancer pain.

Author contributions

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Writing – review & editing: Hongming Pan, Kaifeng Wang.

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