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Original Article

Multicenter trial of titration of morphine versus oxycodone for cancer pain

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Abstract: Objective: The aim of this study was to compare the therapeutic effects of immediate-release morphine (IR) and controlled-release oxycodone (CR) tablets on cancer pain in patients with an analgesia history of opioid or non-opioid analgesics by titration. Methods: This study was completed by six medical institutions, together, which adopted perspective and double-blind open-label methods to randomly divide cancer pain patients, from December 2014 to December 2017, into four groups: naive IR, naive CR, tolerant IR, and tolerant CR. Results: Kaplan-Meier analysis showed that remission of pain in the naive CR group (n = 58) was superior to that in the naive IR group (n = 47) (P = 0.031). Pain control in the tolerant CR group (n = 52) was superior to that in the tolerant IR group (n = 49) (P < 0.001). Differences were observed in titration cycles among the four groups (P < 0.001). There were differences in total titration doses among the four groups (P < 0.001). Consumption of oxycodone hydrochloride tablets in the naive CR group was lower than that that in the naive IR group (All P < 0.001) during W1 & W2, whereas no significant differences were observed between the tolerant IR group and tolerant CR group during W1 (P = 0.061) & W2 (P = 0.060). The incidence rate of additional drug delivery in the naïve CR group was less than that in the naive IR group (P = 0.007). There was a lower incidence rate of additional drug delivery in the tolerant CR group, compared with that in the tolerant IR group (P = 0.014). There were no significant differences in adverse effects among the four groups (All P > 0.05). Conclusion: As a therapeutic oral drug, controlled-release oxycodone may obtain more stable analgesic effects than immediate-release morphine, whether the patient has an analgesia history of opioid analgesics or not. Fewer doses are required during treatment, thus it should be used in clinic for cancer pain.

Keywords: Immediate-release morphine, controlled-release oxycodone, cancer pain treatment, titration analgesia

Introduction

Cancer pain is generally persistent, with moderate to severe pain intensity [1]. Opioid analgesics are the cornerstone choice of management for alleviation of cancer pain [2, 3]. Oxycodone, as an μ, κ-opioid receptor specific ligand, may be used as the first choice [4]. Moreover, recent guidelines have suggested that morphine could also be a first-line cancer pain therapy option [5, 6]. The pharmacokinetic profiles of morphine and oxycodone differ in that the oral bioavailability of oxycodone is higher than that of morphine [7]. Since drug doses cannot be estimated or calculated in advance, the doses must be individually titrated.

Effective and safe titration of opioids may have major effects on patients suffering from cancer pain [2]. Titration is the adjustment of medication to maintain a seasonable balance between pain relief and side effects in response to patient reports of pain [8, 9]. Pure opioid agonists are suitable because they have no analgesic ceiling effects. They can be titrated upward until an acceptable balance is reached [10]. However, opioids, except for codeine, do not have a maximum dose. The right dose for each patient can only be assessed by responsiveness to opioids with a titration trial [5]. Opioids, such as oxycodone and morphine, are recommended for moderate to severe cancer pain management [9, 11]. Whether chronic moder-

ate to severe cancer-related pain can be brought to rapid and stable pain control with oral immediate-release (IR) morphine or controlled-release (CR) oxycodone tablets, administered according to recommendations of NCCN guidelines [12], remains unknown.

Therefore, in this study, these two titration protocols were used in opioid-naïve patients and patients that had already received opioids for adequate pain relief. This study compared mean titration cycles, doses to obtain stable analgesic effects, and postoperative side events.

Materials and methods

Study design

This prospective, randomized, parallel-group, open-label procedure, and multi-center study was conducted by six participating institutions in China. The study was sponsored by the Pain Treatment Committee Branch of Society of Anesthesiology of Chinese Medical Association. The protocol was designed in accordance with guidelines of NCCN and was approved by the Ethics Committee of all centers. Randomization was undertaken by biostatistics professionals, using SAS 9.1 statistics soft. Random sequence was conducted as blocks of two based on opioids received (tolerant groups) or not (naive groups), with a 1:1 ratio. Eligible patients were divided randomly into four groups (naive IR, naive CR, tolerant IR, and tolerant CR) by a random sequence generator.

Inclusion criteria: ① Patients that suffered from moderate (4-6/11 NRS) to severe (7-10/11 NRS) pain related to cancer, naïve to opioids or receiving treatment with opioids; ② Age above 18 years old; ③ Confirmed to assess pain intensity; ④ Written informed consent; and ⑤ Hospitalized during the study period.

Exclusion criteria: ① Patients with history of hypersensitivity to opioid analgesics; ② Use of oxycodone or morphine was contraindicated for any reason (paralytic or mechanical ileus, dyspnea, high intracranial pressure; ③ Had undergone surgery or palliative radiotherapy or treatment with monoamine oxidase inhibitors, tricyclic antidepressants, benzodiazepines or barbiturates, cimetidine, or ranitidine during the study period; ④ With neuropathic pain; ⑤ With hepatic impairment (ALT, AST, and total bilirubin ≥ 2.5 times the upper limit of normal reference range); ⑥ With renal impairment (serum creatinine (Scr) ≤ 1.5 times the upper limit of normal reference range); and ⑦ Inability to gain oral access if neither researcher was available in the ward at the time of the decision to administer opioids to the patient.

Treatment methods

This study was designed using a rapid titration protocol over 72 hours, achieving stable efficacy of analgesia on cancer pain. The protocol included three periods: 24 hours for drugs titration, followed by 24 hours and 48 hours for conversions.

Patients were randomly assigned to titrate starting with either IR morphine tablets (Mundipharma Pharmaceutical Co., Ltd. Beijing, China) or CR oxycodone hydrochloride tablets (OxyContin@, Mundipharma Pharmaceutical Co., Ltd. Beijing, China). For opioid-naive patients, the initial dose of IR morphine was 10 mg or CR oxycodone 10 mg. However, for patients that had taken WHO step II or step III opioid analgesics therapy, the total oral requirements of previous analgesics in 24 hours should be calculated. This should then be converted to equivalent analgesic doses of IR morphine or CR oxycodone, with 10% of total amounts as initial doses. After assessment of efficacy and side effects at 60 minutes, the titration procedure of dosing escalation cycles receiving oral IR morphine was conducted. The subsequent dosage of IR morphine was increased by 50% increments if pain scores were unchanged or increased 7-10/11 NRS. The same dose was repeated if pain scores decreased to 4-6/11 NRS. The same does was continued if pain scores decreased to 0-3/11 NRS in each titration cycle. Dose titration against the intensity of pain lasted for 12 hours until stable and adequate pain control, with minimal adverse effects, was obtained. A double dose of IR morphine or another initial dosage of CR oxycodone was administered at bedtime to avoid nocturnal dosing. Total amount of dosages (initial + subsequent) required for stable analgesia was determined. It could be switched to equal analgesic doses of CR oxycodone for pain control maintenance up to 72 hours.

Rescue analgesics of 5-10 mg IR morphine were permitted, as needed, for control of break-

Table 1. Assessment schedule for trial time points

Time Point	Description
T_0	Baseline
T_1	1 h after the initial drug administration
T_2	1 h after the first round of the titration
T_3	1 h after the second round of the titration
T_4	1 h after the third round of the titration
T_5	24 h after the initial drug administration

through or incident pain, to keep NRS < 4. When the regular dose was increased, the breakthrough dose was also increased. The breakthrough dose should be approximately 10% of the total daily dose, given every 1 hour as needed. If more than four doses of rescue medication per day were necessary, the dosage of scheduled opioids had to be adjusted the next day by an amount equal to the 24-hour fixed dose plus the daily rescue dose. This was done to decrease the frequency of need for breakthrough medications. If a patient met the criteria for controlled pain but side-effects were severe, a 25 percent reduction in the 24-hour opioid total was prescribed.

Strict observation and frequent and dose adjustments should be provided through a process of gradual dose titration. Clinical monitoring included respiratory rate (RR), saturation of pulse oximetry (SpO_2), sedation assessed according to Ramsay Score Scale, blood pressure, and heart rate (HR). Equianalgesic dosage conversion among opioids referred to the equianalgesic table from ESMO Clinical Recommendations [3] and rounded to an integral number. This study used a 1:2 ratio of oxycodone to morphine.

Titration was stopped if the patient was unable to receive two consecutive doses of the regular analgesic because of severe opioid-related side effects (respirations were compromised, such as RR ≤ 8 breaths/min and/or a SpO_2 ≤ 90%; trance or delirium; allergy with cutaneous rash and/or hypotension, vomiting, severe itching).

The protocol required that patients be removed from the study if pain became intractable. This was defined as patients needing six or more breakthrough analgesic doses in a 24-hour period, absence of pain relief (pain score > 4) after three consecutive dosing escalation cycles of titration(regarded as unsatisfactory pain relief), and acute complications of cancer or its treatment developed, including sudden acute changes in clinical conditions, such as sepsis and cardiovascular events.

Assessment

The following information of patients was collected in these four groups: (A) Before titration: (1) Gender, age, weight, primary tumor origin, confirmed metastatic sites, main pain region, and period of pain time; (2) Type of analgesic administered; (3) Previous equivalent daily dose of opioids; (4) Baseline pain intensity; (B) During the period of titration: (1) Initial dose and titration in each cycle; (2) Pain intensity after receiving drugs at every cycle; (3) Discontinuation of titration due to analgesic inefficacy or due to unwanted side effects (symptoms that the patient referred to as being directly associated with the administration of opioids and for which the patient or the doctor requested suspension of treatment); (4) Rescue medication use; (5) Cycles to stable pain control were recorded as zero for patients meeting the criteria for success in the first 24 h (i.e., no titration was needed); (6) Incidence of treatment-related adverse events; (7) Additionally, changes in morphine dosage, administration of any adjuvant analgesic therapy, and frequency of breakthrough pain were recorded; (C) During the period of maintenance: (1) Stabilization dose or steady state analgesic dose; (2) Pain intensity at the stabilization dose; (3) Rescue medication use; (4) Incidence of treatment-related adverse events; (5) Changes in the morphine dosage, administration of any adjuvant analgesic therapy, and frequency of breakthrough pain were recorded.

This study consisted of three phases: initial opioid phase, titration phase, and maintenance phase (first 24-hour maintenance phase: W1; second 24-hour maintenance phase: W2). Visual analog and 11-point (0 to 10) numeric rating scales (NRS) were used to measure pain intensity (PI), which consisted of a 10 cm line, with 0 equaling 'no pain' and 10 equaling 'worst pain you can imagine'. This process allowed frequent reassessment and, therefore, adequate treatment. Before titration and each dosing cycle titration during the study periods, average pain was recorded repeatedly included PI at rest and when moving/coughing. Data were col-

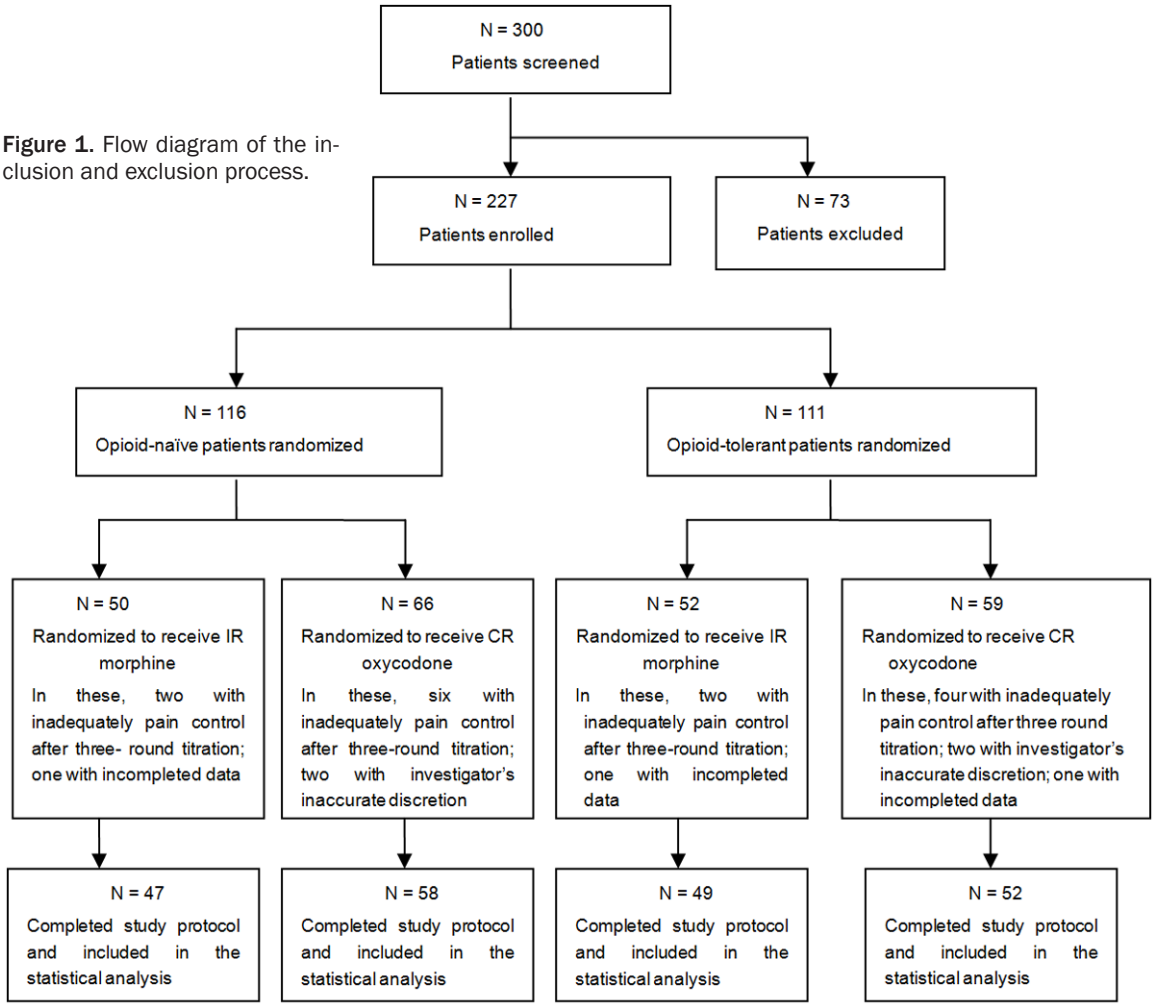

Figure 1. Flow diagram of the inclusion and exclusion process.

lected at several time points until study end point (**Table 1**). Pain and adverse events (nausea, vomiting, dyspnea, sedation, constipation, vertigo) were reported using an intensity scale from 1 to 3 (1 = mild, 2 = moderate, 3 = severe) by patients, daily, during dose titration phases and at each time point. Data concerning concomitant medications, opioid dose, and number of breakthrough doses in 24 hours were recorded.

Successful titration for pain relief was defined by stabilizing NRS pain scores at 3 or below (or reduction in pain intensity of at least 50% VS. baseline) for 48 hours, with no more than three doses of supplemental analgesic per 24 hours. The formula to calculate pain relief (PAF) is shown below. PAF = pain intensity difference (PID, difference between initial pain score and pain score after treatment)/initial pain score* 100%. Pain control was considered stable when pain was stabilized at 3 or below over a 48-hour period, the q12h dose was unchanged, no more than two supplemental analgesic doses were taken per day, the dosing regimen for any non-opioids or adjuvants was unchanged, and any side effects were tolerable. Effective rates of pain relief included complete remission, partial remission (PAF > 75%), and moderate remission (50% < PAF < 75%).

Statistics analysis

All data were analyzed using SPSS 19.0 version statistical software. Measurement data are expressed as mean ± standard deviation (mean ± SD). For multiple comparisons referring to more than two groups, one-way ANOVA was performed in conjunction with SNK test. Comparisons between variables of two groups were made using Student's t-test. Count data are expressed as percentages (rate) and were

Table 2. Demographic characteristics of patients among the four groups

Patient characteristic	Naive IR group (n = 47)	Naive CR group (n = 58)	Tolerant IR group (n = 49)	Tolerant CR group (n = 52)	ANOVA/X^2	P
Age (yr)	53.26 ± 12.50	53.53 ± 12.33	58.26 ± 9.66	55.27 ± 11.78	-1.438	0.187
Weight (kg)	57.30 ± 8.95	56.29 ± 10.90	59.49 ± 9.11	58.80 ± 8.79	0.281	0.778
Gender, n (%)					1.815	0.612
Male	28 (59.57)	29 (50.00)	29 (59.18)	32 (61.54)		
Female	19 (40.43)	29 (50.00)	20 (40.82)	20 (38.46)		
Primary tumor origin					4.211	0.397
Nasopharyngeal	3	6	1	4		
Lung	14	21	15	12		
Breast	2	4	1	5		
Oesophagus	0	1	1	1		
Gastric	2	3	3	0		
Colon	5	6	2	1		
Rectum	3	1	2	3		
Liver	5	2	2	1		
Pancreas	0	3	3	1		
Prostate gland	2	0	0	1		
Kidney	0	0	0	2		
Cervix	2	3	2	1		
Unknown	1	1	8	6		
Other	7	7	8	12		
Missing	1	0	1	2		
Presence of metastases					3.467	0.325
No	32 (68.09)	33 (56.90)	27 (55.10)	26 (50.00)		
Yes	15 (31.91)	25 (43.10)	22 (44.90)	26 (50.00)		
Confirmed metastatic sites					2.874	0.249
Lung metastases	1	2	1	2		
Liver metastases	2	3	4	2		
Skeletal metastases	8	12	7	9		
Retroperitoneal metastases	1	1	4	0		
Lymphonodal metastases	0	2	1	3		
Pelvic cavity metastases	0	1	0	1		
CNS metastases	0	1	0	0		
Many sites metastases	3	3	5	9		
Main pain region						
Chest	7	15	9	13		
Abdomen	13	9	10	8		
Back	6	5	2	8		
Head and neck	2	4	3	3		
Should and arms	3	2	1	4		
Buttocks and legs	4	2	6	4		
More sites	12	21	18	12		
Time from uncontrolled pain start (day)						
M (Q1-Q3)	30.00 (16.00~52.00)	29.00 (11.50~62.50)	64.00 (31.00~142.00)	59.00 (29.00~106.00)	0.481	0.133
Pain intensity (0-10)	6.45 ± 1.37	6.22 ± 1.33	6.51 ± 0.98	6.40 ± 1.42	0.237	0.719

Data are presented as mean (SD) or as frequency distributions (n) and simple percentages (%).

compared using the Cochran-Mantel-Haenszel Chi-squared (X^2) test. Analyses and graphics of Kaplan-Meier curve were performed using GraphPad Prism statistical software (GraphPad Software Inc., La Jolla, CA, USA). Differences are considered statistically significant at $P < 0.05$.

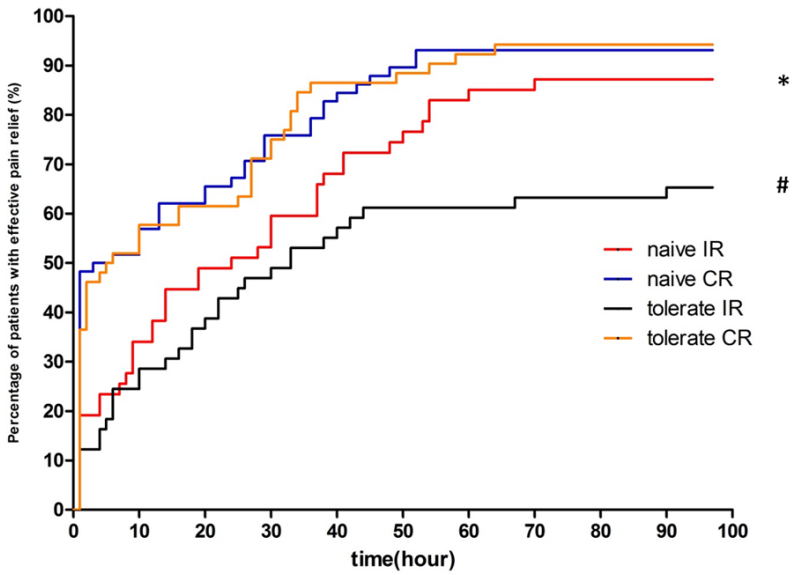

Figure 2. Kaplan-Meier curve showing cumulative percentage of patients that achieved pain control at each of the failure time-points. *P < 0.05, naive CR group VS. naive IR group; #P < 0.001, tolerant CR group VS. tolerant IR group.

Results

General information

From December 2014 to December 2017, six centers recruited 300 hospitalized patients with cancer pain. Seventy-three patients were excluded because data was not permitted to be collected. A total of 227 eligible patients were enrolled in this study, including 116 opioid-naive patients and 111 opioid-received patients. Of these, 105 opioid-naive patients and 101 opioid-received patients completed the titration period: naive CR group (n = 58), naive IR (n = 47) group, tolerant CR group (n = 52), and tolerant IR group (n = 49) (**Figure 1**). Differences in patient demographic characteristics among the four groups showed no statistical significance (All P > 0.05) (**Table 2**).

Effects of titration on pain outcomes

Kaplan-Meier analysis showed that, for patients that achieved pain control at each of the failure time-points, differences were statistically significant (P < 0.05). Remission of pain in the naive CR group (n = 58) was superior to that in the naive IR group (n = 47) (P = 0.031). Pain control in the tolerant CR group (n = 52) was superior to that in the tolerant IR group (n = 49) (P < 0.001) (**Figure 2**).

Titration cycles and doses

Titration cycles among the four groups were 1.68 ± 1.12, 1.17 ± 1.20, 2.47 ± 0.84, and 1.67 ± 1.20, respectively. Differences were observed in titration cycles among the four groups (P < 0.001) (**Table 3**). Total titration doses among the four groups were 32.80 ± 24.52, 19.26 ± 13.89, 32.66 ± 17.55, and 43.47 ± 33.83, respectively. Differences were observed in titration cycles among the four groups (P < 0.001) (**Table 3**).

Consumption of oxycodone hydrochloride tablets

Consumption of oxycodone hydrochloride tablets in the naive CR group was 24.56 ± 6.78 mg and 22.54 ± 6.22 mg during W1 and W2, lower than that that in the naive IR group (All P < 0.001). No significant differences were observed between the tolerant IR group and tolerant CR group during W1 (P = 0.061) & W2 (P = 0.060) (**Figure 3**).

Number of patients with additional drug delivery

There were eight patients with additional drug delivery in the naive CR group (four with once, one with twice, two with three times, one with five times) and 13 patients in the tolerant CR group (six with once, three with twice, one with three times, three with four times). The incidence rate of additional drug delivery in the naïve CR group was less than that in the naive IR group (P = 0.007) (**Table 4**).

Adverse effects

Adverse effects were observed during the titration phase, including nausea, vomiting, constipation, dizziness, somnolence, pruritus, respiratory depression, dysuria, severe sedation, hypertension, bradyarrhythmia, diarrhea, and euphoria. There were no significant differences in adverse effects among the four groups (All P > 0.05) (**Table 5**).

Table 3. Effective titration cycles and doses among the four groups ($\bar{x}$ ± SD)

	Naive IR (n = 47)	Naive CR (n = 58)	Tolerate IR (n = 49)	Tolerate CR (n = 52)	ANOVA	P
Cycles	1.68 ± 1.12	1.17 ± 1.20	2.47 ± 0.84	1.67 ± 1.20	12.24	< 0.001
Doses (mg)	32.80 ± 24.52	19.26 ± 13.89	32.66 ± 17.55	43.47 ± 33.83	8.84	< 0.001

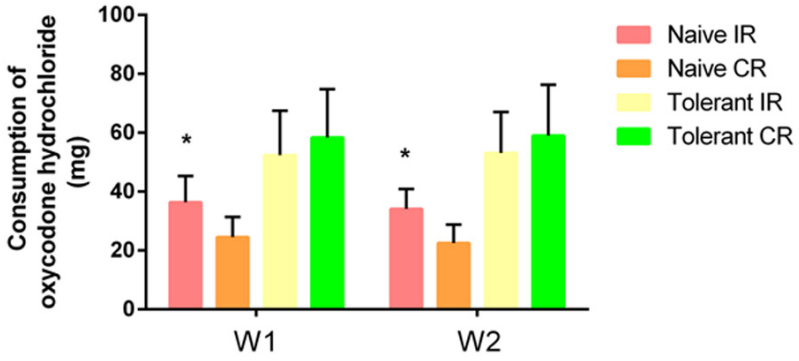

Figure 3. Comparison of consumption of oxycodone hydrochloride among the four groups during the maintenance period (W1 and W2), *P < 0.001, naive IR group VS. naive CR group.

Discussion

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage [13, 14]. Furthermore, cancer pain has been regarded as the fifth vital sign, threatening patient lives as an independent disease [15].

Opioid therapy is the cornerstone of management of severe chronic pain in the field of cancer patients and in palliative care medicine, according to the NCCN clinical practice management [12]. Oxycodone and morphine are both used to mitigate cancer pain [16]. Morphine is the most cost-effective analgesic and the main choice in the management of cancer pain [17]. Titration with normal morphine helps to rapidly achieve a steady state [18]. Opioid titration is the first challenging stage for rapid cancer pain relief. Studies have shown that a double-blind and randomized controlled study is feasible in chronic cancer pain [19]. This randomized, controlled, and double-blind study was designed to compare the efficacy of CR oxycodone titration and IR morphine titration on cancer pain in patients with or without a history of opioid analgesics.

Recent investigations have shown that opioids may have distinct profiles under various experimental conditions [20, 21]. Specifically marked differences in the antinociceptive profiles of oxycodone and morphine have been found in some experimental and clinical models, suggesting significant between-opioid differences in opioid receptor signaling [22, 23]. The current study demonstrated that oxycodone could have more significant analgesic effects than morphine in the initial opioid analgesic phase. According to the total middle pain relief efficacy of each group after accomplishing titration, CR oxycodone can be used as an initial analgesic as IR morphine. Results of this study demonstrated that naive-opioids patients, suffering from cancer pain and receiving CR oxycodone as initial an analgesic, consumed significantly less doses of IR morphine during the titration phase, compared with that of the naive-opioids IR morphine group. Tolerant-opioid patients, with cancer pain receiving controlled-release oxycodone as an initial analgesic, took more doses of IR morphine during the titration phase, compared with that of tolerant-opioids IR morphine group. Differences were observed in mean titration cycles among the four groups, suggesting that patients using oxycodone as an initial analgesic can achieve ideal pain relief with less titration procedures, whether they have an opioid history or not. Oxycodone is a μ- and κ-opioid receptor agonist, whereas its metabolite oxy-morphine is a pure μ-opioid receptor agonist, with clear agonist properties. The μ-opioid receptor binding affinity of oxycodone is, however, less than that of morphine [24, 25]. A study on rats demonstrated that part of the antinociceptive effects of oxycodone could be mediated by κ-opioid receptors [26].

It was observed that additional drug delivery in the naive CR group and tolerant CR group was less than that in the naive IR group and tolerant

Table 4. Number of patients with additional drug delivery in the four groups

	Number of patients without additional drug delivery	Number of patients with different times of additional drug delivery						X^2	P
		Once	Twice	Three times	Four times	Five times	Six times		
Naive IR group (n = 47)	30	8	5	3	1	0	0	7.166	0.007
Naive CR group (N = 58)	50	4	1	3	0	0	0		
Tolerant IR group (n = 49)	23	8	8	4	5	0	1	8.527	0.014
Tolerant CR group (n = 52)	39	6	3	1	3	0	0		

Table 5. Adverse events of patients in the four groups

Adverse effects	Naive IR group (n = 47)	Naive CR group (n = 58)	X^2	P	Tolerant IR group (n = 49)	Tolerant CR group (n = 52)	X^2	P
Nausea	14	11	1.676	0.196	9	13	0.651	0.420
Vomiting	7	6	0.495	0.482	6	2	2.440	0.118
Constipation	1	2	0.163	0.686	6	3	1.303	0.254
Dizziness	5	5	0.123	0.726	6	11	1.430	0.232
Somnolence	1	1	0.023	0.880	6	4	0.586	0.444
Pruritus	1	0	1.246	0.264	0	2	1.923	0.166
Respiratory depression	1	0	1.246	0.264	3	2	0.278	0.598
Dysuria	1	0	1.246	0.264	3	3	0.006	0.940
Severe sedation	2	0	2.516	0.113	5	2	1.581	0.209
Hypertension	0	0	-	-	0	2	1.923	0.166
Bradyarrhythmia	0	0	-	-	1	0	1.072	0.301
Diarrhea	0	0	-	-	0	2	1.923	0.166
Euphoria	0	0	-	-	1	0	1.072	0.301

IR group, indicating that oxycodone can decrease administration frequency and breakthrough pain frequency, clinically. This can be explained by the slow release technique of oxycodone hydrochloride CR tablets. Lower doses of drugs were consumed in the naive CR group than in the naive IR group, whereas no differences were observed between the tolerant IR group and tolerant CR group. Results suggest that an opioid analgesic history has an impact on the use of analgesic drugs during maintenance phase.

Adverse effects, including excessive sedation and myoclonus, euphoria, respiratory depression, hyperalgesia, constipation, sexual dysfunction, and delirium, are a common complication of opioids [26, 27]. A simple strategy includes reducing the opioid dose by 25% to 50%, using different opioids ("rotation"), changing the route of administration, and directly treating adverse effects [28]. However, there were no significant differences in adverse effects among the four groups. All patients suffering from side effects were alleviated by rational treatment. However, the small sample size and short follow-up times, in the present study, may have resulted in errors. Thus, prospective experimentation, with larger sample sizes, should be conducted to verify present results.

In conclusion, as an oral preparation, oxycodone hydrochloride CR tablets may be a better choice for alleviation of cancer pain, whether patients have an analgesic opioid history or not. Patients with oxycodone can accomplish titration quickly and smoothly, with less additional drug delivery and more stability after transferring to the maintenance phase.

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Disclosure of conflict of interest

None.

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