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ORIGINAL RESEARCH

Efficacy and safety of immediate-release oxycodone combined with sustained-release oxycodone titration in opioid-tolerant patients with moderate to severe cancer pain

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Abstract

This study aimed to evaluate the efficacy of immediate-release (IR) oxycodone in combination with sustained-release (SR) oxycodone titration for managing moderate-to-severe cancer pain in opioid-tolerant patients. Participants were selected based on a numerical rating scale (NRS) score of $\geq$4 and a daily oxycodone dose of $\geq$50 mg. IR oxycodone was administered orally as a rescue medication for breakthrough pain (BTP). Pain intensity scores, frequency of BTP, daily doses of SR and IR oxycodone, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Advanced Cancer (EORTC QLQ-C15-PAL) scores were assessed over a three-day period. Adverse effects were also recorded. A total of 109 patients were enrolled in the study. Pain relief rates were 32% (35/109) on day 1, 44% (48/109) on day 2, and 67% (73/109) on day 3. Compared to baseline, the average NRS score decreased significantly on day 1 ($p = 0.0030$), day 2 ($p < 0.0001$), and day 3 ($p < 0.0001$). On day 1, 100% of patients experienced $\leq$2 BTP episodes per day, while 95% had $\leq$1 episode per day by day 3. There was a significant reduction in BTP episodes on days 2 and 3 compared to day 1 ($p = 0.0187$ and $p < 0.0001$, respectively). All eight EORTC QLQ-C15-PAL items showed significant improvements ($p < 0.0100$) from baseline. The incidence of adverse events was 42%. The combination of IR oxycodone with SR oxycodone titration is both feasible and tolerable for opioid-tolerant patients with moderate-to-severe cancer pain.

Keywords

Cancer pain; Oxycodone; Immediate-release; Titration; Efficacy

1. Introduction

Cancer pain is one of the most common symptoms among cancer patients, with a reported prevalence of up to 44.5% and 30.6% of patients experiencing moderate to severe pain [1]. Among those with advanced cancer, 59% report experiencing pain during anti-tumor therapy, and 33% continue to suffer from cancer pain even after effective treatment [2]. Opioid titration is considered the optimal approach for balancing pain relief with manageable side effects [3]. According to the European Association for Palliative Care (EAPC) guidelines [4] and the European Society for Medical Oncology (ESMO) guidelines [5], sustained-release (SR) formulations are recommended for managing long-term stable pain, while immediate-release (IR) formulations should be used as supplementary medications for treating breakthrough pain (BTP). Despite standard titration protocols, some patients may still experience inadequate pain control or develop end-of-dose failure and BTP while on a regular opioid regimen [6].

BTP is defined as pain that is inadequately managed or "breaks through" a regular opioid regimen. It can be classified into three types: (1) episodic or sporadic pain associated with specific activities or events, (2) end-of-dose failure, and (3) persistent or spontaneous pain [7]. BTP can occur in highly opioid-tolerant patients, especially those receiving high doses of opioids for background analgesia [5, 8], as well as in those receiving low doses of opioids (<60 mg/day of oral morphine equivalents) or even in those not receiving opioids [9]. For opioid-tolerant cancer patients experiencing pain, it

is essential to use an analgesic that can effectively manage BTP while allowing for adjustments to the background SR opioid regimen. Proper dose titration of opioids, particularly oxycodone, is essential for achieving optimal pain control and ensuring that the patient's overall pain management strategy remains effective [10]. Currently, short-acting opioids are commonly used to manage BTP [11], with IR morphine being the predominant choice in China [12]. However, IR morphine may not be the optimal option for treating BTP. BTP typically has a rapid onset and relatively short duration (median 30 minutes), while IR morphine often requires 45 minutes to exhibit analgesic effects. Furthermore, managing BTP with IR morphine necessitates frequent adjustments of SR oxycodone, increasing the clinical workload [13]. In contrast, IR opioids are frequently used to manage BTP through individualized titration aimed at achieving effective analgesia [6, 12, 14]. Currently, rapid-onset opioids, particularly fentanyl-based formulations, are commonly utilized in Europe and the United States, and these formulations, which are administered orally or nasally, offer rapid onset of action, potent analgesic effects, and a brief duration of action, which are consistent with the characteristics of BTP [15]. However, they are not yet available in China.

Oxycodone is recognized as one of the most bioavailable oral strong opioids, with an oral bioavailability ranging from 60% to 87% [16]. Pain relief from IR oxycodone typically begins within 15 minutes of oral administration, with peak drug concentrations achieved approximately 1 hour later [17]. In comparative studies, oxycodone has been shown to be superior to morphine in relieving visceral pain [18]. In the context of postoperative analgesia for percutaneous radiofrequency ablation of hepatocellular carcinoma, oxycodone has been found to provide patients with superior pain relief, reduced postoperative pain, less respiratory depression, and more stable hemodynamic parameters compared to fentanyl [19]. Additionally, oxycodone is effective in managing pain following colorectal cancer surgery and head and neck cancer radiotherapy, especially for visceral pain [20, 21], which aligns with the observation that BTP is often characterized by visceral pain [22]. Currently, oral IR opioids are the most commonly used medications for managing BTP [23]. When used in conjunction with SR oxycodone for background pain, IR oxycodone facilitates effective dose conversion [24]. Moreover, using the same opioid for both persistent pain and BTP has additional advantages, such as simplifying dose titration and improving the management of opioid-related adverse effects [24].

However, the efficacy and safety of titrating SR oxycodone in combination with IR oxycodone for opioid-tolerant patients with moderate to severe cancer pain remain unclear. To address this gap, we conducted a prospective, single-arm study to evaluate the efficacy and safety of oral IR oxycodone (OxyNorm®, oxycodone hydrochloride capsule, Mundipharma Pharmaceutical Co., 223980, Beijing, China) for managing BTP and re-titration in opioid-tolerant patients who were already receiving oral SR oxycodone (Oxycontin®, oxycodone hydrochloride controlled-release tablet, Mundipharma Pharmaceutical Co., 209504, Beijing, China) as a long-term analgesia. This pilot study aimed to explore a rapid, convenient and safe opioid titration regimen that combines SR oxycodone as a background medication with IR oxycodone for the treatment of BTP.

2. Methods

2.1 Patients

This study was a prospective, single-arm, multicenter clinical trial conducted between January 2020 and January 2021. Patients hospitalized with cancer pain at all the participating centers were screened during this period.

2.2 Inclusion and exclusion criteria

Patients were eligible for inclusion if they (1) were $\geq$18 years of age, (2) had histological or cytological evidence of malignancy, (3) were opioid-tolerant, defined as taking an oral equivalent of SR oxycodone at a daily dose of $\geq$50 mg prior to the protocol application, (4) were hospitalized and had a BTP with a numeric rating scale (NRS) score $\geq$4, (5) demonstrated high compliance with treatment regimens and had adequate communication skills, (6) were willing to provide written informed consent. However, those with the following criteria were excluded: (1) pregnant or lactating, (2) allergic to oxycodone or any other ingredients present in the study drug, (3) had non-cancer pain or unexplained pain, (4) had acute cancer pain, (5) were suffering from intractable constipation, (6) had received monoamine oxidase inhibitors (MAOIs) or similar drugs within the past 2 weeks, (7) were at potential risk for gastrointestinal disorders or surgical treatments that might lead to gastrointestinal stenosis, blind loop or obstruction, (8) had unstable co-morbidities or vital organ dysfunction, (9) presented with persistent symptoms of infection, abscesses or fever, (10) had liver or kidney dysfunction, (11) were currently receiving antiepileptic or antiarrhythmic medications, (12) had contraindications, adverse drug reactions (ADRs), or drug interactions with oxycodone or morphine as described in the product package insert or investigator's brochure, (13) had a history of drug or alcohol abuse, (14) were participating in another clinical trial within 1 month prior to this study, and (15) were expected to change their drug regimen during the study period.

For each eligible patient, we documented the following information: gender, age, body mass index (BMI), date of protocol enrollment, hospital discharge, primary tumor type, presence of metastases and metastatic sites, and the daily dose of oral SR oxycodone and any adjuvant analgesic medications prior to protocol application. During the subsequent three days of assessments, we recorded pain intensity scores, number of BTP episodes, daily doses of SR and IR oxycodone prescribed and consumed, and any opioid-related adverse effects. The highest, lowest, and average NRS scores were recorded for each 24-hour period.

2.3 Study design

This study adhered to the analgesic treatment principles outlined in the National Comprehensive Cancer Network guidelines for cancer pain [25] and the ESMO guidelines [5]. The initial daily dose of SR oxycodone was based on the patient's

pre-study pain treatment regimen and was administered orally in two equal doses every 12 hours. Morphine and oxycodone doses were converted: morphine (oral):oxycodone (oral) = 1.5–2:1. IR oxycodone was dosed at 10–20% of the total opioid intake from the previous 24 hours and used as needed for BTP. If BTP occurred, IR oxycodone could be taken after a minimum of 1 hour following SR oxycodone administration, with a minimum interval of 1 hour between doses of IR oxycodone.

Efficacy and adverse effects were assessed every 24 hours. If the average NRS score was $\leq$3 and BTP episodes were $\leq$2, the SR oxycodone dose was maintained. If the NRS score was $\leq$3 but BTP episodes were $\geq$3, the total oral opioid dose from the previous 24 hours was calculated and converted to an equivalent SR oxycodone dose for maintenance. If the NRS score was $\geq$4 and BTP episodes were $\geq$3, the SR oxycodone dose was increased by 25–100% of the initial dose. This assessment and adjustment process was repeated three times a day, as illustrated in Fig. 1.

2.4 Study assessments

The primary endpoint was the achievement of NRS scores $\leq$3 and BTP episodes $\leq$2 after 3 days. The regimen was considered effective if more than 65% of patients met these criteria after 3 days [26, 27]. Secondary endpoints included pain relief rates (average NRS $\leq$3) on days 1, 2 and 3, SR oxycodone dosage, the number of BTP episodes per 24 hours, and quality of life (QoL) assessments. Adverse events were defined as any unintended signs, symptoms or illnesses potentially related to the use of IR or SR oxycodone. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-15-Palliative Care (EORTC QLQ-C15-PAL) was used to evaluate QoL [28], with assessments recorded before protocol initiation and at discharge.

2.5 Data presentation and statistical analysis

Data are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. EORTC QLQ-C15-PAL scores were calculated following EORTC recommendations [29]. Changes in pain scores and EORTC QLQ-C15-PAL scores were compared using paired *t*-tests, while analysis of variance (ANOVA) was used to determine differences between groups [30]. Statistical analyses were performed using GraphPad Prism (version 8, GraphPad Software, Boston, MA, USA), with a significance threshold set at $p < 0.05$.

The CoDem protocol [30] is a well-established study examining the efficacy of combining SR oxycodone with IR morphine for managing moderate to severe cancer pain. In the CoDem study, effectiveness was defined by achieving an NRS score $\leq$3 in more than 50% of patients after 72 hours. For the present study, we aimed for a more stringent criterion, anticipating that over 65% of patients would achieve an NRS score $\leq$3 after 72 hours. The sample size was determined with a type I error (α) of 0.05, a type II error (β) of 0.2 and a power of 0.8, using PASS software 15.0 (NCSS, LLC, Kaysville, UT, USA) according to the following formula:

$$N = \frac{p_0 q_0 \{Z_{1-\alpha/2} + Z_{1-\beta}\sqrt{\frac{p_1 q_q}{p_0 q_0}}\}}{(p_1 - p_0)^2}$$

We calculated that a minimum of 85 patients was required for the study. To account for potential dropouts, we included a total of 109 patients.

3. Results

3.1 Baseline characteristics of the enrolled patients

A total of 109 patients were enrolled between January 2020 and January 2021. The mean age of the participants was 61 $\pm$ 10.67 years, with an age range of 31 to 89 years. The cohort comprised 66 males (61%) and 43 females (39%), and they had a BMI range from 14.5 to 26.9 kg/m^2. The types of cancer are summarized in Table 1. The average daily dose of SR oxycodone was 83.49 $\pm$ 44.29 mg at baseline. Fourteen patients (13%) were also receiving oral adjuvant analgesics, including 11 (10%) on oral pregabalin capsules and 3 (3%) on oral cyclooxygenase 2 (COX-2) inhibitors. All patients had a baseline NRS score of $\geq$4 for BTP. The patients' baseline characteristics, including analgesic regimens and BTP intensity, are detailed in Table 2.

3.2 Pain relief rate

The pain relief rate, defined as a reduction in average NRS to $\leq$3, was 35% (38/109) on the first day, 48% (52/109) on the second day, and 71% (77/109) on the third day, as shown in Table 1. The average NRS score, as well as the highest and lowest NRS scores, significantly decreased over the study period (Table 1). Specifically, compared to baseline, the average NRS score decreased significantly on the first day ($p = 0.0030$) (Fig. 2A). Although the highest and lowest NRS scores also decreased, these changes were not statistically significant ($p = 0.1310$ and $p = 0.2395$, respectively). On the second day, all NRS scores were significantly lower compared to baseline (average NRS: $p < 0.0001$; highest NRS: $p = 0.0002$; lowest NRS: $p = 0.0061$) (Fig. 2B). The third day also showed significant reductions in average, highest and lowest NRS scores compared to baseline (all p values < 0.0001) (Fig. 2C). Fig. 2D illustrates the gradual decrease in average, highest, and lowest NRS scores over the three days.

3.3 NRS endpoint

Initially, 102 patients experienced BTP on the first day, with the numbers decreasing to 79 and 57 on the second and third days, respectively. Fig. 2E displays the mean number of BTP episodes per day with standard deviation. The results showed a significant reduction in BTP episodes on days 2 and 3 compared to day 1 ($p = 0.0187$ and $p < 0.0001$, respectively). The NRS endpoint, defined as an average NRS score $\leq$3 and $\leq$2 BTP episodes, was achieved by 32% (35/109) of patients on the first day, 44% (48/109) on the second day, and 67% (73/109) on the third day (Table 2).

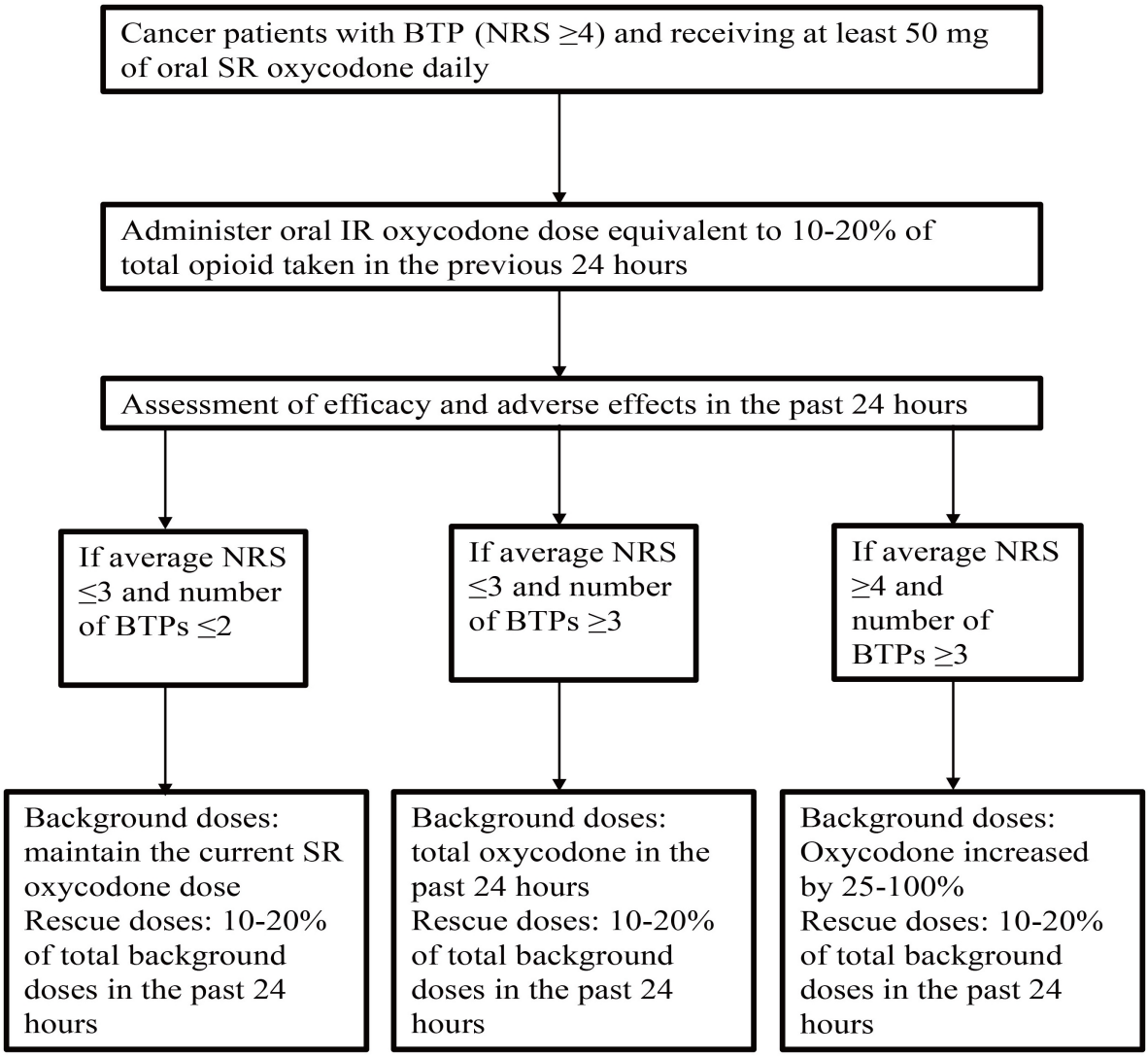

FIGURE 1. Flowchart of the study. BTP: breakthrough cancer pain; NRS: numeric rating scale; SR: sustained release; IR: immediate-release.

TABLE 1. Pain relief rates based on the NRS scores.

Time	Average NRS score		Highest NRS score		Lowest NRS score	
	≤3 (n, %)	>3 (n, %)	≤3 (n, %)	>3 (n, %)	≤3 (n, %)	>3 (n, %)
Baseline	0	109 (100%)	0	109 (100%)	93 (85%)	16 (15%)
1st day	38 (35%)	71 (65%)	7 (6%)	102 (94%)	101 (93%)	8 (7%)
2nd day	52 (48%)	57 (52%)	34 (31%)	75 (69%)	103 (94%)	6 (6%)
3rd day	77 (71%)	32 (29%)	61 (56%)	48 (44%)	108 (99%)	1 (1%)

NRS: numeric rating scale.

TABLE 2. NRS endpoints and breakthrough pain episodes.

Time	Average NRS score		Breakthrough pain episodes		NRS endpoint
	Median, 95% CI	≤3 (n, %)	Median, 95% CI	≤2	n, %
1st day	3.991 (3.763–4.218)	35 (32%)	1.183 (1.062–1.305)	104 (95%)	38 (35%)
2nd day	3.578 (3.341–3.815)	48 (44%)	0.945 (0.811–1.079)	109 (100%)	52 (48%)
3rd day	3.083 (2.856–3.309)	73 (67%)	0.569 (0.458–0.680)	109 (100%)	77 (71%)

NRS: numeric rating scale; NRS endpoint: NRS ≤3 and Breakthrough pain episodes ≤2; CI: confidence interval.

3.4 Daily dose of oxycodone

Table 3 details the daily doses of SR oxycodone and IR oxycodone throughout the study. The data show a gradual increase in the daily dose of SR oxycodone, while the daily dose of IR oxycodone gradually decreases. Moreover, there was no significant change in the SR oxycodone dose on the first day compared to baseline ($p = 0.5572$) (Fig. 2F). However, significant increases in SR oxycodone doses were observed on the second ($p = 0.0189$) and third ($p = 0.0006$) day. Conversely, we found no significant change in the reduction of IR oxycodone dose on the second day compared to the first day ($p = 0.2356$) but a significant reduction on the third day ($p < 0.0001$) (Fig. 2G).

3.5 EORTC QLQ-C15-PAL

The scores from the EORTC QLQ-C15-PAL and the results of ANOVA for the functional and symptom scales are shown in Table 4. Higher scores on item 15, which evaluates overall QoL, indicate better QoL. Conversely, higher scores on the functional and symptom scales indicate worse QoL. Physical and emotional functioning scores significantly decreased before discharge compared to baseline ($p = 0.0046$ and $p = 0.0021$, respectively), reflecting a decline in these aspects of QoL. In contrast, overall QoL significantly improved ($p < 0.0001$), and symptoms such as pain ($p < 0.0001$), fatigue ($p < 0.0001$), insomnia ($p < 0.0001$), appetite loss ($p < 0.0001$), and nausea ($p = 0.0079$) also showed significant improvement. Although dyspnea ($p = 0.0623$) and constipation ($p = 0.0906$) exhibited trends toward improvement, these changes were not statistically significant.

3.6 Adverse effects

The incidence of adverse effects was 42% (46/109), as detailed in Table 5. Constipation was the most common adverse effect, occurring in 27% of patients (29/109). Other reported adverse effects included nausea and vomiting (6% each), dysuria and somnolence (1% each), and dizziness (2%). Overall, the adverse effects were generally manageable.

4. Discussion

Effective management of cancer pain typically involves the use of SR opioids for continuous pain control and IR opioids for BTP [31]. According to recommendations from the EAPC, SR oxycodone is suitable for both initial titration and maintenance treatment of cancer pain [4]. SR oxycodone is characterized by a biphasic absorption profile, providing an initial rapid onset followed by a prolonged phase of pain relief, and requires twice-daily (every 12 hours) administration, which supports efficient titration and sustained pain control [31]. Despite these advantages, our study observed suboptimal medication compliance among patients, potentially due to frequent BTP episodes. This study represents the first to examine a titration regimen combining SR oxycodone with IR oxycodone specifically for managing BTP in opioid-tolerant cancer patients. Our findings indicate that 67% of patients achieved an average NRS score of $\leq$3, and all patients experienced $\leq$2 episodes of BTP, with an overall improvement in QoL and manageable opioid-related adverse effects after 3 days, suggesting that the combination of SR oxycodone as a background therapy with IR oxycodone for BTP is a feasible and effective regimen.

The percentage of patients with an average NRS score of $\leq$3 at baseline was only 20% (13/109). This percentage increased to 32% (35/109) on the first day of treatment and further improved to 67% (73/109) by the third day. These results in pain control align with previous studies using titration protocols involving SR oxycodone as a background therapy combined with IR morphine for BTP management. In opioid-tolerant cancer patients, pain relief rates with such titration regimens were 25.6%, 61.5% and 83.3% for achieving NRS $\leq$3 on days 1, 2 and 3, respectively [10]. Similarly, the CoDem protocol reported pain relief rates of 46.2%, 61.5% and 84.6% for achieving NRS $\leq$4 on days 1, 2 and 3, respectively [30]. It is important to note that in the CoDem study, only 57.1% of patients were on strong opioids prior to the protocol, whereas all patients in our study were already opioid-tolerant. Additionally, our study compared the probability of achieving a $\geq$30% and $\geq$50% reduction in NRS scores within 24 hours, a measure also used to evaluate pain control effectiveness [26]. We observed a significant reduction in average NRS scores on day 1, and both the highest and lowest NRS scores showed statistically significant decreases on days 2 and 3 compared to baseline.

In patients receiving opioid doses $\geq$60 mg of oral morphine equivalents for background pain, the distribution of BTP episodes was as follows: 63.42% had 1–2 episodes per day, 30.44% had 3–4 episodes per day, and 6.15% had $\geq$5 episodes per day [13]. In our study, all 109 patients experienced BTP, with the number of patients reporting BTP episodes decreasing from 102 on the first day to 79 on the second day and 57 on the third day. By the second and third days, all patients had a reduction in BTP episodes to $\leq$2, and 95% had $\leq$1 episode on the third day, demonstrating that IR oxycodone effectively reduced the frequency of BTP episodes. These findings align with previous studies involving IR morphine for BTP management alongside SR oxycodone, though direct comparative randomized controlled trials are lacking [10].

The mean daily dose of SR oxycodone prior to protocol implementation in our study was 83.49 mg. Over the course of three days, the mean daily doses of SR oxycodone were 87.16 mg, 99.27 mg and 108.4 mg, respectively. No significant difference was observed in the mean dose increase of SR oxycodone on day one compared to baseline; however, significant differences were noted on days two and three. This pattern of gradual dose escalation is consistent with findings from the Good Pain Management (GPM) titration protocol [10], where opioid-tolerant patients also experienced a gradual increase in SR oxycodone dosage. In the GPM protocol, which involved 78 opioid-tolerant patients using SR oxycodone in combination with IR morphine for managing BTP, the mean daily doses of SR oxycodone were 72.9 mg, 95.0 mg and 112.0 mg over three days [10]. Comparing our present study with the GPM study reveals a similar trend of increasing SR oxycodone dosage over the three days of treatment, whether combined with IR oxycodone or IR morphine. The mean daily doses of IR oxycodone in our study were 14.59 mg, 12.84 mg

TABLE 3. Daily dose of SR and IR oxycodone.

Time	SR oxycodone (mg)			IR oxycodone (mg)		
	Mean	SD	95% CI	Mean	SD	95% CI
Baseline	83.49	44.29	75.08–91.90			
1st day	87.16	47.81	78.08–96.23	14.59	8.556	12.96–16.21
2nd day	99.27	53.74	89.06–109.50	12.84	11.23	10.71–14.98
3rd day	108.40	60.39	96.98–119.90	8.44	10.82	6.387–10.49

SR: sustained release; IR: immediate-release; SD: standard deviation; mg: milligram: CI: confidence interval.

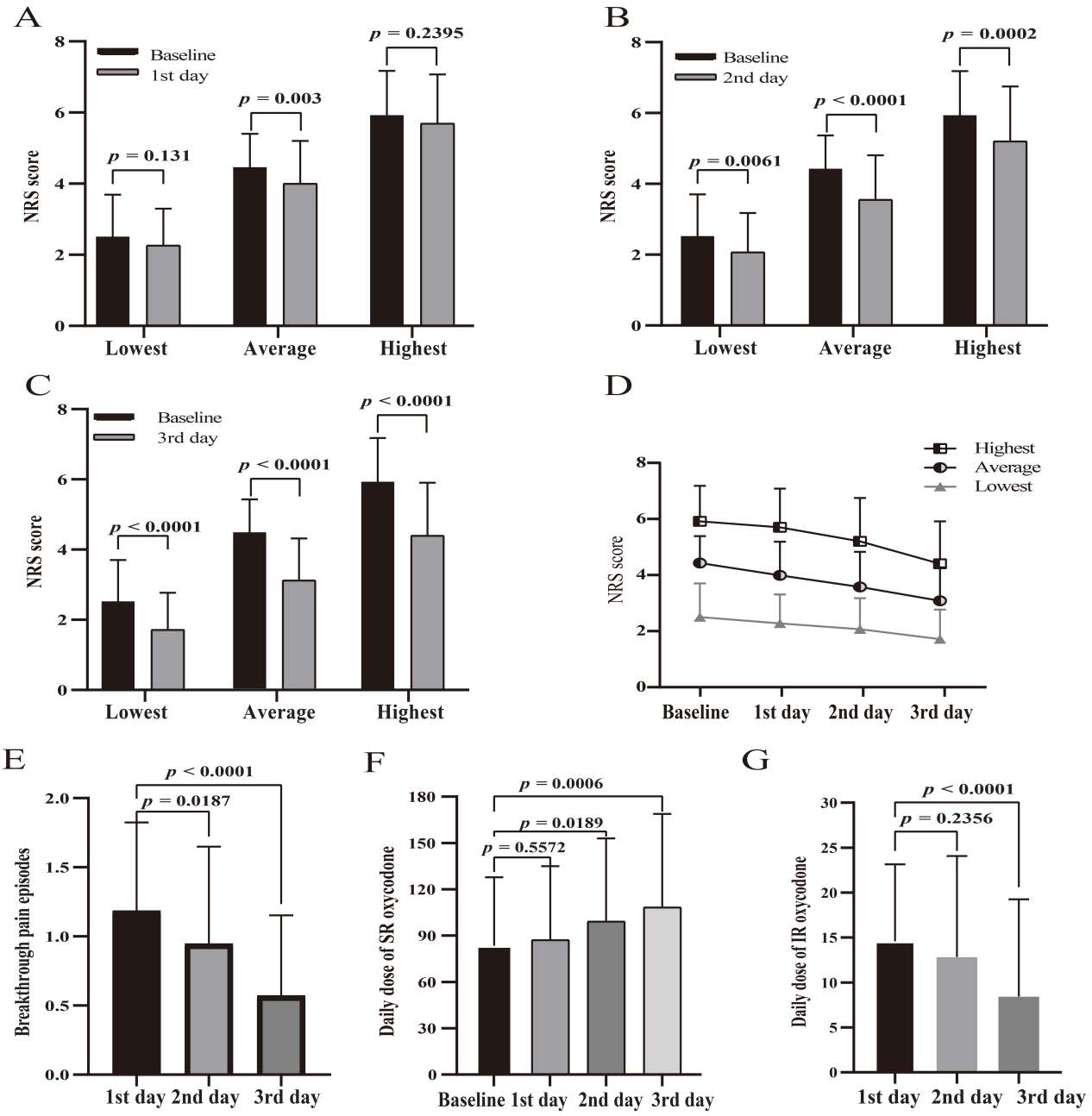

FIGURE 2. Changes in NRS scores, breakthrough pain episodes and daily oxycodone doses. (A) NRS scores on day 1 compared to baseline, showing average, highest and lowest scores. (B) NRS scores on day 2 compared to baseline. (C) NRS scores on day 3 compared to baseline. (D) Trends in NRS scores over the three days. (E) Number of breakthrough pain episodes per day over the three days. (F) Daily dose of SR oxycodone over the three days. (G) Daily dose of IR oxycodone over the three days. Values are expressed as mean ± standard deviation. NRS: numeric rating scale; SR: sustained-release; IR: immediate-release.

TABLE 4. EORTC QLQ-C15-PAL scores at baseline and before discharge.

EORTC QLQ-C15-PAL	Baseline	Before discharge	*p* value
Physical functioning (1–3)	30.99 ± 20.51	23.65 ± 17.18	0.0046
Emotional functioning (13, 14)	31.50 ± 31.50	20.95 ± 16.10	0.0021
Overall quality of life (15)	43.26 ± 13.04	67.26 ± 14.64	<0.0001
Pain (5, 12)	45.83 ± 17.37	24.77 ± 15.65	<0.0001
Fatigue (7, 11)	34.10 ± 15.11	24.01 ± 14.06	<0.0001
Dyspnea (4)	28.44 ± 19.15	23.46 ± 20.00	0.0623
Insomnia (6)	43.73 ± 17.39	22.53 ± 19.77	<0.0001
Appetite loss (8)	36.08 ± 20.85	23.45 ± 17.80	<0.0001
Nausea (9)	28.44 ± 19.68	21.60 ± 17.83	0.0079
Constipation (10)	20.99 ± 17.99	16.97 ± 16.74	0.0906

Description: mean values ± standard deviation. The number of items from the questionnaire is given in brackets.
EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Advanced Cancer.

TABLE 5. Incidence of adverse effects in the study.

Adverse effects	Number	Percent
Total	46	42%
Constipation	29	27%
Nausea	7	6%
Vomiting	6	6%
Dysuria	1	1%
Somnolence	1	1%
Dizziness	2	2%

and 8.44 mg across the three days. The gradual reduction in IR oxycodone dosage reflects the progressive control of BTP episodes. In comparison, patients on the CoDem protocol, using SR oxycodone and IR morphine for moderate to severe cancer pain, reported a mean daily dose of IR morphine of 60.0 mg on the first day [30]. Considering the oral administration of oxycodone and morphine, the dose equivalence ratio is approximately 1:1.5 to 1:2 [25]. The mean daily dose of IR oxycodone in our study on the first day was lower than that reported in the CoDem protocol, suggesting that a smaller dose of IR oxycodone is required to manage BTP compared to IR morphine. It is important to note that only 13% of the enrolled patients used adjuvant analgesia (*e.g.*, pregabalin and COX-2 inhibitors) in the proportion of medications. We consider that the reason for this may be that the fourth and eighth exclusion criteria of this study excluded this group of patients with predominantly neuropathic pain.

According to the EORTC QLQ-C15-PAL, there were significant improvements in overall QoL, physical function, and emotional functioning. Additionally, significant improvements were observed in the symptom scales for pain, fatigue, insomnia, loss of appetite and nausea. The primary adverse reactions associated with opioids include constipation, nausea/vomiting and dizziness, with variations in adverse effects among different opioids being relatively minor [26]. In our study, the most common adverse reactions were constipation (27%), nausea (6%), vomiting (6%), dysuria (1%), somnolence (1%), and dizziness (2%). Constipation was managed with laxatives and did not interfere with the overall treatment.

However, this study has several limitations. First, the absence of a randomized comparison between the SR oxycodone and IR morphine titration regimen and the SR oxycodone and IR oxycodone regimen may limit our ability to fully assess the advantages of the latter. Second, the relatively short observation period necessitates further studies to address existing uncertainties. Third, the study did not explore potential confounding factors such as age, gender or cancer type.

5. Conclusions

In conclusion, our study demonstrates that the use of IR oxycodone in combination with SR oxycodone for the treatment of BTP is both feasible and well-tolerated in cancer patients who are already receiving high doses of SR oxycodone for background pain. The findings suggest that this opioid titration regimen may improve pain control and enhance patient comfort. Further research is warranted to validate these results and to explore the optimal dosing and long-term efficacy of this combined approach.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed are available from the corresponding authors upon reasonable request.

AUTHOR CONTRIBUTIONS

SSW, YFH and JX—participated in study conception and design, data acquisition and interpretation, and drafting of the manuscript. GC, SND, WPL, YLX, XSC and PX—participated in data acquisition, analysis, interpretation of data. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed in accordance with the principles of the Declaration of Helsinki of 1964 and its subsequent revisions. The study was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (no. 23/2019, 25 November 2019). Informed consent was obtained from all subjects involved in the study. The study was registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR1900028175, Date of registration: 14 December 2019).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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