Comparing Patient-Controlled Analgesia Versus Non-PCA Hydromorphone Titration for Severe Cancer Pain: A Randomized Phase III Trial

Rongbo Lin, MD^{1,2,*}; Sunzhi Lin, MD^{3,*}; Shuitu Feng, MD^{4,*}; Qingyi Wu, MD^{5,*}; Jianqian Fu, MD⁶; Fang Wang, MD⁷; Hui Li, MD¹; Xiaofeng Li, MD⁸; Gaowang Zhang, MD⁹; Yongzhi Yao, MD¹⁰; Min Xin, MD¹¹; Tianyang Lai, MD¹²; Xia Lv, MD¹³; Yigui Chen, MD¹; Shangwang Yang, MD¹⁴; Yubiao Lin, MD⁴; Lixia Hong, MD¹⁵; Zhenyu Cai, MD¹⁶; Jianfeng Wang, MD¹; Gen Lin, MD¹⁷; Shaowei Lin, MD¹⁸; Shen Zhao, MD^{1,2}; Jinfeng Zhu, MD⁸; and Cheng Huang, MD^{13,17}

ABSTRACT

Background: Opioid titration is necessary to achieve rapid, safe pain relief. Medication can be administered via patient-controlled analgesia (PCA) or by a healthcare provider (non-PCA). We evaluated the efficacy of intravenous PCA versus non-PCA hydromorphone titration for severe cancer pain (≥ 7 at rest on the 11-point numeric rating scale [NRS]). **Patients and Methods:** Patients with severe cancer pain were randomized 1:1 to PCA or non-PCA titration, stratified by opioid-tolerant or opioid-naïve status. The PCA pump was set to no continuous dose, with a hydromorphone bolus dose 10% to 20% of the total previous 24-hour equianalgesic (for opioid-tolerant patients) or 0.5 mg (for opioid-naïve patients). For the non-PCA group, the initial hydromorphone bolus dose was identical to that in the PCA group, with the subsequent dose increased by 50% to 100% (for NRS unchanged or increased) or repeated at the current dose (for NRS 4–6). Hydromorphone delivery was initiated every 15 minutes (for NRS ≥ 4) or as needed (for NRS ≤ 3). The primary endpoint was time to successful titration (TST; time from first hydromorphone dose to first occurrence of NRS ≤ 3 in 2 consecutive 15-minute intervals). **Results:** Among 214 patients (PCA, n=106; non-PCA, n=108), median TSTs (95% CI) were 0.50 hours (0.25–0.50) and 0.79 hours (0.50–1.42) for the PCA and non-PCA groups, respectively (hazard ratio [HR], 1.64; 95% CI, 1.23–2.17; $P=.001$). TSTs in opioid-tolerant patients were 0.50 hours (0.25–0.75) and 1.00 hours (0.50–2.00) for the PCA and non-PCA groups, respectively (HR, 1.92; 95% CI, 1.32–2.78; $P=.003$); in opioid-naïve patients, TST was not significantly different for the PCA versus non-PCA groups (HR, 1.35; 95% CI, 0.88–2.04; $P=.162$). Pain score (median NRS; interquartile range) over 24 hours was significantly lower in the PCA group (2.80; 2.15–3.22) than in the non-PCA group (3.00; 2.47–3.53; $P=.020$). PCA administration produces significantly higher patient satisfaction with pain control than non-PCA administration ($P<.001$). **Conclusions:** Intravenous hydromorphone titration for severe cancer pain was achieved more effectively with PCA than with non-PCA administration.

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Background

Pain is a prevalent, distressing, and burdensome symptom in patients with advanced cancer.^{1,2} Opioids are recommended for moderate or severe cancer pain.^{3–10} Pure mu opioids do not have a known maximum dose; titration is a method of adjusting each patient's dosage to achieve optimal analgesia with the fewest adverse effects (AEs).^{8–12} Although medication is commonly administered orally, intravenous titration provides more rapid pain relief.^{4,7–10} Intravenous titration can be administered via patient-controlled analgesia (PCA) or by a healthcare provider (non-PCA).^{8,9,12–17}

The programmable PCA pump allows patients to control pain on demand. It promptly responds to patients' changing needs and reduces analgesic delay. PCA has been used widely for postoperative pain, labor pain, traumatic pain, and other types of pain. It provides more effective pain relief and produces higher patient satisfac-

¹Department of Gastrointestinal Medical Oncology, Fujian Cancer Hospital and Fujian Medical University Cancer Hospital, Fuzhou; ²Fujian Key Laboratory of Translational Cancer Medicine, Fuzhou; ³Department of Pain Medicine, Mindong Hospital, Ningde; ⁴Department of Medical Oncology, Xiamen Haicang Hospital, Xiamen; ⁵Department of Medical Oncology, Guangqian Hospital, Quanzhou; ⁶Department of Medical Oncology, Xiamen Fifth Hospital, Xiamen; ⁷Department of Medical Oncology, Longyan Hospital of Traditional Chinese Medicine, Longyan; ⁸Department of Medical Oncology, Quanzhou First Hospital, Quanzhou; ⁹Department of Oncology, Shouning Hospital, Ningde; ¹⁰Department of Oncology, Putian People Hospital, Putian; ¹¹Department of Medical Oncology, Fujian Armed Police Corps Hospital, Fuzhou; ¹²Department of Medical Oncology, Longyan Boai Hospital, Longyan; ¹³Department of Medical Oncology, Xiamen Humanity Hospital and Fujian Medical University Xiamen Humanity Hospital, Xiamen; ¹⁴Department of Medical Oncology, Rehabilitation Hospital Affiliated to Fujian University of Traditional Chinese Medicine, Fuzhou; ¹⁵Department of Gastroenterology, Hanjiang Hospital, Putian; ¹⁶Department of Pain Medicine, The First Affiliated Hospital of Xiamen University, Xiamen; ¹⁷Department of Thoracic Oncology, Fujian Cancer Hospital and Fujian Medical University Cancer Hospital, Fuzhou; and ¹⁸School of Public Health, Fujian Medical University, Fuzhou, China.

*These authors contributed equally to this study.

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tion than non-PCA.^{18–21} Moreover, opioid titration with PCA has been used and recommended for cancer pain management.^{3,8,15} However, evidence supporting its use is limited by reports of single-arm trials, small cohorts, and literature review articles.^{9,13,14,22–24} This study was designed to evaluate the efficacy and safety of intravenous PCA versus non-PCA titration with hydromorphone, a pure mu opioid, for severe cancer pain.

Patients and Methods

Trial Design

A 24-hour, open-label, randomized controlled trial was performed at 15 oncology centers in China. Patients were randomized 1:1 to PCA or non-PCA, stratified by opioid-tolerant or opioid-naïve status. Opioid tolerance was defined as having received a ≥ 25 mcg/h fentanyl patch, ≥ 60 mg oral morphine daily, ≥ 30 mg oral oxycodone daily, or an equianalgesic dose of another opioid for ≥ 1 week.^{3,8,10,25,26}

The protocol was approved by the central ethics committee of the Fujian Cancer Hospital and local ethics committees of all participating hospitals. All participants provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice.

Patients

Patients diagnosed with a malignant solid tumor by pathology or cytology and with persistent, severe cancer-related pain score (≥ 7 at rest on the 11-point numeric rating scale [NRS], with 0 = no pain and 10 = excruciating pain)^{7,13,14,21} were enrolled after being screened for eligibility, which included age 18 to 70 years, ECOG performance status ≤ 3 , no cognitive impairment or psychiatric illness, and no radiotherapy, chemotherapy, or hormone, targeted, or bisphosphonate therapy within 7 days before randomization. Exclusion criteria included contraindication to opioid use, paralytic ileus, brain metastasis, severe hepatic or renal failure, uncontrolled nausea or vomiting, or current use of hydromorphone or PCA devices.

Interventions

Any previous analgesics were stopped before titration was initiated. In the PCA group, pump settings were continuous dose (0), bolus of 10%–20% of the total previous 24-hour equivalent hydromorphone for opioid-tolerant patients (common opioid conversion chart in supplemental eTable 1, available with this article at JNCN.org),¹⁰ and 0.5 mg of hydromorphone for opioid-naïve patients. Lockout time was set to 15 minutes; patients with NRS was ≥ 4 were educated to self-press the PCA pump button every 15 minutes. Subsequent to NRS ≤ 3 , self-press was by demand in 15-minute minimum

intervals. The pump setting was not changed within the 24-hour period, which is consistent with the concept of patient self-control, reducing the need for healthcare providers. In the non-PCA group, titration was administered by a nurse having sole care of the patient, and each dose required a physician's order. The initial bolus dose of hydromorphone was identical to that in the PCA group. Thereafter, the dose was increased by 50% to 100% (for NRS unchanged or increased) or repeated at the current dose (for NRS 4–6). The nurse assessed patient pain every 15 minutes. For NRS ≥ 4 , the dose was administered as soon as possible; however, a physician's order and drug preparation could impact the timeliness of injection. Subsequent to NRS ≤ 3 , the dose was administered according to the patient's request and nurse assessment in 15-minute minimum intervals.⁸

All patients were trained to score pain according to NRS criteria. Pain scores were recorded every 15 minutes until successful titration (NRS ≤ 3 at 2 consecutive intervals). After successful titration was achieved, scores were recorded every hour (or if analgesic was needed at night). If the NRS score again increased to ≥ 7 , it was reassessed every 15 minutes until successful titration was reestablished. The information on hydromorphone dose and time of administration was collected from the PCA pump in the PCA group or from medical records in the non-PCA group.

PCA patients were trained and tested in the use of the PCA pump. A 15-minute lockout time was set to avoid mis-pressing. The device recorded the number of valid and invalid presses. If a patient pressed ≥ 3 times within 15 minutes, the reason was recorded. All nurses were trained in Chinese good pain management²⁷ and with opioid titration according to NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain.⁸

Baseline and 24-hour assessments included physical symptoms and overall well-being (measured with the Edmonton Symptom Assessment System [ESAS]), ECOG performance status, continuation or change in treatment, patient satisfaction, and AEs. The ESAS (Chinese version) assesses 10 symptoms (supplemental eTable 2) commonly experienced by patients with cancer during a 24-hour period.²⁸ Symptom severity was scored from 0 to 10, with 0 representing no symptoms and 10 representing worst severity.^{28–30} Satisfaction score for pain control was rated 0 to 4 (0 = very unsatisfied, 1 = unsatisfied, 2 = neutral, 3 = satisfied, 4 = very satisfied). Patients were asked about expected opioid-related AEs, including vomiting, constipation, dry mouth, itch, dizziness, somnolence, cognitive impairment, pseudohallucinations, and myoclonic jerks. Use of concomitant other analgesics, chemotherapy, radiotherapy, and other antitumor treatments was prohibited, although management of AEs was permitted.

Outcome Measures

The primary endpoint was median time to successful titration (TST), defined as time from the first hydromorphone dose to the first occurrence of NRS ≤ 3 in 2 consecutive 15-minute intervals.^{7,10,13,14,21} If NRS increased again to ≥ 7 after pain control was achieved, TST was recalculated as time from the first dose to the next successful titration. Secondary outcomes included improvement in physical symptoms and overall well-being (as assessed with ESAS), satisfaction scores, average pain score during 24-hour titration (calculated as sum of all NRS scores within 24 hours divided by number of ratings), and accumulated hydromorphone consumption (AHC) from titration start to TST or hour 24. AEs were evaluated at study completion.

Statistical Methods

Sample size was based on the log-rank test. Assuming as clinically significant a 33.3% decrease in TST in the PCA group from an expected 0.75 hours in the non-PCA group and a power of 80% at a significance level of a 2-sided *P* value of .05, 208 patients (104 per arm) were needed. Considering a dropout rate of 3%, the total number of patients enrolled was 214. Stratified block randomization was conducted centrally by computer with a block size of 6.

TST between-group differences were analyzed using the Kaplan-Meier method in all participants. Secondary study endpoints were analyzed in patients with completed pain scores. Safety analysis was based on all patients who received at least one hydromorphone dose. Categorical variables are presented as frequencies and proportions and continuous variables as medians and interquartile ranges (IQRs). Between-group differences were analyzed using the chi-square test or Fisher exact test and the Mann-Whitney *U* test. All statistical tests were 2-sided; *P* < .05 was considered statistically significant. Data were analyzed using R version 3.4.0 (R Foundation for Statistical Computing).

Results

Patients

Between January 2018 and November 2019, 214 patients with persistent cancer-related severe pain were randomly assigned to the PCA (*n* = 106; 49.5%) or non-PCA (*n* = 108; 50.5%) group (Figure 1). In the PCA and non-PCA groups, there were 61 opioid-tolerant patients in each group (57.5% and 56.5%, respectively), and 45 and 47 opioid-naïve patients, respectively (42.5% and 43.5%, respectively). One opioid-tolerant patient in each group withdrew consent because of dissatisfaction with pain control. Median initial dosages in opioid-tolerant patients were 1 mg (IQR, 0.5–2) and 1 mg (IQR, 0.5–2) in the PCA and non-PCA groups, respectively. Baseline characteristics (Table 1) were well balanced between the 2 groups, with comparable ESAS symptom severity (supplemental eTable 2).

Figure 1. Study profile.

Abbreviation: PCA, patient-controlled analgesia.

Efficacy

Among 214 randomized patients, there was a median 36.7% decrease in TST (95% CI): 0.50 hours (0.25–0.50) in the PCA group and 0.79 hours (0.50–1.42) in the non-PCA group (hazard ratio [HR], 1.64; 95% CI, 1.23–2.17; *P* = .001). For opioid-tolerant patients, median TST (95% CI) was 0.50 hours (0.25–0.75) in the PCA group versus 1.0 hour (0.50–2.00) in the non-PCA group (HR, 1.92; 95% CI, 1.32–2.78; *P* = .003). Among opioid-naïve patients, there was no significant difference in median TST (95% CI) in the PCA (0.5 hours; 0.25–0.75) versus non-PCA (0.5 hours; 0.25–1.00) groups (HR, 1.35; 95% CI, 0.88–2.04; *P* = .162). Kaplan-Meier curves are displayed in Figure 2. Most patients achieved successful titration at hour 24: 99.05% (PCA) versus 97.20% (non-PCA) overall, 98.33% (PCA) versus 95.00% (non-PCA) in opioid-tolerant patients, and 100% in opioid-naïve patients.

Overall, median average pain score [IQR] was significantly lower in the PCA versus the non-PCA group (2.80 [2.15–3.22] vs 3.00 [2.47–3.53]; *P* = .020). In opioid-tolerant or opioid-naïve patients, numeric average pain score was lower in the PCA versus the non-PCA group, although this did not reach statistical significance (Figure 3).

From the start of titration to TST, in all or opioid-naïve patients, decreased AHC in the PCA versus non-PCA group was not statistically significant. However, in opioid-tolerant patients, median AHC [IQR] was significantly decreased in the PCA group compared with the non-PCA group (1.0 mg [1.0–2.0] vs 2.0 mg [1.0–4.0]; *P* = .009) (supplemental eFigure 1).

From the start of titration to hour 24, there was no significant difference in AHC between the PCA and non-PCA groups in all patients. However, in opioid-tolerant

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	PCA n (%)	Non-PCA n (%)	P Value
Total, n	106	108	
Age, median (IQR), y	58 (50–64)	61 (54–67)	.041
Male sex	61 (57.5)	62 (57.4)	1.000
Opioid tolerance status			.875
Opioid tolerant	61 (57.5)	61 (56.5)	
Opioid naïve	45 (42.5)	47 (43.5)	
Education			.252
No education	3 (2.8)	7 (6.5)	
Primary school	36 (34.0)	32 (29.6)	
High school	48 (45.3)	41 (38.0)	
University and higher	19 (17.9)	28 (25.9)	
ECOG performance status			.995
0	7 (6.6)	7 (6.5)	
1	35 (33.0)	36 (33.3)	
2	35 (33.0)	37 (34.3)	
3	29 (27.4)	28 (25.9)	
ESAS overall symptom score, median (IQR)	36 (34–38)	37 (34–39)	.901
Pain intensity, median (IQR), NRS	8 (7–8)	8 (7–8)	.420
Pain type			.572
Nociceptive	83 (78.3)	80 (74.1)	
Nociceptive and neuropathic	23 (21.7)	28 (25.9)	
Tumor stage			.091
I–III	14 (13.2)	6 (5.6)	
IV	92 (86.8)	102 (94.4)	
History of surgery	52 (49.1)	48 (44.4)	.590
History of chemotherapy	72 (67.9)	74 (68.5)	1.000

(continued)

patients, the reduced median AHC [IQR] in the PCA group versus the non-PCA group was significant (5.5 mg [2.5–8.3] vs 6.3 mg [4.0–12.0]; $P=.028$), and in opioid-naïve patients, the increased median AHC [IQR] in the PCA group versus the non-PCA group was significant (4.0 mg [2.5–5.5] vs 2.5 mg [2.0–4.3]; $P=.048$) (supplemental eFigure 2).

Satisfaction scores for pain control were significantly higher in the PCA group than in the non-PCA group (Figure 4). In all patients, opioid-tolerant patients, and opioid-naïve patients, median satisfaction scores (IQRs) were 3 (3–4), 3 (3–4), and 4 (3–4) in the PCA group versus 3 (2–4), 3 (2–3), and 3 (2–4) in the non-PCA group ($P<.001$, $P<.001$, and $P=.003$), respectively.

The total numbers of valid PCA presses were 727 (median [IQR], 6 [4–9]), 404 (6 [4–9]), and 323 (7 [5–9])

Table 1. Patient Demographics and Baseline Characteristics (cont.)

Characteristic	PCA n (%)	Non-PCA n (%)	P Value
Primary cancer			
Lung	25 (23.6)	20 (18.5)	.458
Colorectal	16 (15.1)	15 (13.9)	.995
Gastric	13 (12.2)	21 (19.4)	.211
Hepatobiliary	13 (12.2)	14 (12.9)	1.000
Head and neck	11 (10.4)	2 (1.9)	.020
Gynecologic	9 (8.5)	8 (7.4)	.968
Esophageal	8 (7.6)	6 (5.6)	.755
Urinary tumor	3 (2.8)	8 (7.4)	.228
Pancreatic	3 (2.8)	8 (7.4)	.228
Breast	3 (2.8)	1 (0.9)	.601
Bone and soft tissue	2 (1.9)	4 (3.7)	.696
Lymphoma	0 (0.0)	1 (0.9)	1.000
Metastatic site	99 (93.4)	99 (91.7)	.825
Bone	36 (33.9)	26 (24.1)	.149
Lymph node	31 (29.3)	33 (30.6)	.952
Liver	26 (24.5)	28 (25.9)	.938
Lung	20 (18.9)	20 (18.5)	1.000
Peritoneum	13 (12.3)	20 (18.5)	.281
Renal	13 (12.3)	9 (8.3)	.471
Vertebrae	10 (9.4)	10 (9.3)	1.000
Uterus and adnexa	5 (4.7)	3 (2.8)	.699
Pleura	3 (2.8)	4 (3.7)	1.000
Other ^a	8 (7.6)	9 (8.3)	1.000

Abbreviations: ESAS, Edmonton Symptom Assessment System; IQR, interquartile range; NRS, 11-point Numeric Rating Scale; PCA, patient-controlled analgesia.

^aIncluding pancreas, spleen, head and neck, and bladder.

for all patients, opioid-tolerant patients, and opioid-naïve patients, respectively. In the non-PCA group, the total numbers of delivered boluses were 706 (median [IQR], 6 [4–9]), 419 (7 [4–9]), and 287 (4 [4–8]) for all patients, opioid-tolerant patients, and opioid-naïve patients, respectively (supplemental eFigure 3). Presses ≥ 3 times within 15 minutes occurred in 12 (20%) opioid-tolerant patients and in 8 (17.8%) opioid-naïve patients. The reason for multiple presses was inadequate pain control. ESAS scores at hour 24 were not significantly different between the PCA and non-PCA groups, and they were significantly decreased in both groups compared with baseline (supplemental eTable 2).

Safety

Treatment using either method was well tolerated. No difference in frequency of opioid-related AEs was observed (supplemental eTable 3). No patient in the PCA

Figure 2. Kaplan-Meier estimates of median TST in the PCA versus non-PCA groups, respectively, in (A) all patients [0.50 hours (95% CI, 0.25–0.50) vs 0.79 hours (95% CI, 0.50–1.42); HR, 1.64 (95% CI, 1.23–2.17); $P=.001$]; (B) opioid-tolerant patients [0.50 hours (95% CI, 0.25–0.75) vs 1.00 hours (95% CI, 0.50–2.00); HR, 1.92 (95% CI, 1.32–2.78); $P=.003$]; and (C) opioid-naïve patients [0.50 hours (95% CI, 0.25–0.75) vs 0.50 hours (95% CI, 0.25–1.00); HR, 1.35 (95% CI, 0.88–2.04); $P=.162$].

Abbreviations: HR, hazard ratio; PCA, patient-controlled analgesia; TST, time to successful titration.

group attempted suicide or opioid abuse using the pump, and there were no other catheter- or pump-related AEs.

Discussion

In our trial, intravenous PCA hydromorphone titration significantly reduced TST and average pain score and increased satisfaction compared with non-PCA titration for persistent severe cancer pain. Severe opioid-related, catheter-related, or pump-related AEs did not occur.

Analgesic delay can prolong TST and increase pain intensity. PCA titration avoids delays, shortens TST, and reduces pain intensity compared with non-PCA methods.

Delayed TST may also produce depression, anxiety, sleep disturbance, and fatigue, which negatively impact pain intensity.^{31–34} In subgroup analysis, a significant difference in TST between the PCA and non-PCA groups was seen only in opioid-tolerant patients, not in opioid-naïve patients. However, in opioid-naïve patients, the entire TST curve was lower in the PCA group than in the non-PCA group. We presumed that a higher number of bolus injections needed to achieve titration success in opioid-tolerant versus opioid-naïve patients would contribute to a delay effect, which might explain the significant difference in TST among opioid-tolerant and opioid-naïve patients.

The PCA bolus dose for opioid-tolerant patients is commonly 10% to 20% of the total equianalgesic over the previous 24 hours, with which our trial is consistent.^{8,12} However, the PCA bolus dosage in opioid-naïve patients is controversial. The MD Anderson Cancer Center adult cancer pain guideline recommends that PCA devices should be set to 0.2-mg (range, 0.1–0.5 mg) intravenous boluses of hydromorphone with a lockout interval of 10 to 30 minutes for opioid-naïve patients.¹² There is no specific mention of PCA settings in the NCCN Guidelines for Adult Cancer Pain for opioid-naïve patients. However, 2- to 5-mg boluses of morphine with a lockout interval of 15 minutes is indicated for intravenous titration (including PCA).⁸ Nevertheless, Radbruch et al¹³ reported a study of 28 opioid-naïve patients with severe cancer pain in whom PCA administration of 1-mg intravenous boluses of morphine and a lockout period of 5 minutes produced adequate pain relief (<30 on a 101-step NRS) within approximately 5 hours. No severe AEs were reported. Badner et al¹⁹ reported on postoperative patients treated with 1 of 3 intravenous PCA morphine schemas (1 mg with 6-minute lockout, 1.5 mg with 9-minute lockout, or 2 mg with 12-minute lockout), in which there were no between-group differences in total 24-hour morphine consumption, analgesia, or AEs. Number of dosing attempts, missed attempts, and dosage frequency and adjustments were all significantly lower for the 2 mg with 12-minute lockout group ($P<.05$). Mercadente³⁵ illustrated that small repeated boluses provide poor drug concentration compared with a single larger bolus. In our trial, the PCA bolus was set to 0.5 mg of hydromorphone (equal to 3.3 mg of morphine) for opioid-naïve patients, within the range recommended by the MD Anderson Cancer Center guideline and the NCCN guideline. Mean TSTs were 1.99 hours in opioid-naïve patients and 2.30 hours in opioid-tolerant patients (data not shown). The shorter TST in our trial may result from larger bolus doses than those used in the Radbruch et al¹³ trial. The maximum analgesic effect of hydromorphone was seen

Figure 3. Median average pain score over 24 hours in the PCA versus non-PCA groups, respectively, for (A) all patients [2.80 (IQR, 2.15–3.22) vs 3.00 (IQR, 2.47–3.53); $P=.020$]; (B) opioid-tolerant patients [2.88 (IQR, 2.38–3.46) vs 3.25 (IQR, 2.67–3.57); $P=.057$], and (C) opioid-naïve patients [2.65 (IQR, 2.06–3.00) vs 2.77 (IQR, 2.22–3.41); $P=.147$].

Abbreviations: IQR, interquartile range; NRS, Numeric Rating Scale; PCA, patient-controlled analgesia.

between 10 to 20 minutes.³⁶ Theoretically, overdose is less likely to occur with 15 minutes of lockout interval, because each subsequent dose is administered after peak concentration of the previous dose. In our study, no patient experienced a severe AE or respiratory distress.

AHC from the start of titration to hour 24 in opioid-naïve patients was higher in the PCA group than in the non-PCA group, which may reflect patients' true analgesic demand. However, it is reversed in opioid-tolerant patients. A pharmacodynamic model indicates that the magnitude of analgesic effect is incrementally linear with log hydromorphone dose,³⁶ meaning more

incremental dosing is needed for patients receiving high-dose versus low-dose hydromorphone to achieve the same analgesic effect. In opioid-tolerant patients, incremental dosing of hydromorphone due to higher pain intensity may exceed patients' true demand for analgesia in the non-PCA group versus the PCA group.

Given the potential for opioid misuse or abuse, we provided patient education and training concerning the risks and benefits of opioid therapy, coupled with medication monitoring by a dedicated nurse. No misuse or abuse was detected in our trial. There are also no previous studies focused on PCA use in outpatient care that have reported any misuse or abuse.^{22,37,38} Risk assessment

Figure 4. Median patient satisfaction scores for pain control in the PCA versus non-PCA groups, respectively, in (A) all patients [3 (IQR, 3–4) vs 3 (IQR, 2–4); $P<.001$]; (B) opioid-tolerant patients [3 (IQR, 3–4) vs 3 (IQR, 2–3); $P<.001$]; and (C) opioid-naïve patients [4 (IQR, 3–4) vs 3 (IQR, 2–4); $P=.003$].

Abbreviations: IQR, interquartile range; PCA, patient-controlled analgesia.

tools are warranted to screen patients and to monitor opioid consumption.^{8,10}

It is unsurprising that patient satisfaction with pain control was better in the PCA group, because PCA provides a greater degree of analgesic autonomy. Instant availability of medication together with decreased TST and lower pain intensity, which may improve fatigue, sleep disturbance, depression, or anxiety, may also contribute to greater satisfaction.^{16,18,21,22,39}

Our trial had some limitations. First, our trial duration was 24 hours. We are planning a new study that will incorporate a 7-day observation period to evaluate continued PCA versus conversion to oral sustained-release opioids after successful titration is achieved. We assume that severe pain fluctuates, such that as-needed analgesic may be an appropriate treatment approach. Second, despite human and financial resources associated with PCA administration, including equipment cost and maintenance and management of complications, PCA reduces provider time and effort and may confer additional cost savings.^{40–42} Cost benefits should be explored. Third, administration of opioid titration by a nurse having sole care of the patient, including availability every 15 minutes to reassess pain and/or titrate pain medication upward, may not be replicable in real practice. Fourth, a patient's pain experience is generally subjective and based on sociocultural, psychologic, cognitive, and emotion variables that may not be captured by pain scores.⁴³ Furthermore, subjectivity may be increased in the non-PCA group because providers (not patients, as in the PCA group) assess pain and ultimately control drug administration.⁴⁴ Last, because the trial was designed to compare PCA and non-PCA methods, double-blinding was not possible. However, because patient perception of pain is subjective,^{34,45} the open-label design may have provided a feeling of security, increasing satisfaction and, in turn, improving their pain experience.

Conclusions

Our study showed that, compared with conventional opioid titration, PCA titration provided earlier and superior analgesia for severe cancer pain, with good tolerability and improved patient satisfaction. Benefits were more evident in opioid-tolerant patients; although TST was not significantly decreased in opioid-naïve patients, the entire curve was lower in the PCA group than in the non-PCA group. Moreover, satisfaction with pain control in opioid-naïve patients was significantly better, with lower numeric average pain score in the PCA group. All of these findings support intravenous PCA opioid titration for both opioid-tolerant and opioid-naïve patients, with the additional advantage of reducing burden on healthcare providers and resources, which may be of particular importance during times of medical crisis, such as the COVID-19 pandemic. To our knowledge, this is the first study to provide high-level evidence for PCA-based intravenous opioid titration as a viable alternative to conventional administration for management of severe cancer pain.

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Correspondence: Cheng Huang, MD, Department of Thoracic Oncology, Fujian Cancer Hospital and Fujian Medical University Cancer Hospital, No. 420 Fuma Road, Jinan District, Fuzhou 350014, China. Email: cheng671@sina.com; and Jinfeng Zhu, MD, Department of Medical Oncology, Quanzhou First Hospital, No. 248-252 East Street, Licheng District, Quanzhou 362002, China. Email: hlzk_qz@163.com

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Supplemental online content for:

Comparing Patient-Controlled Analgesia Versus Non-PCA Hydromorphone Titration for Severe Cancer Pain: A Randomized Phase III Trial

Rongbo Lin, MD; Sunzhi Lin, MD; Shuitu Feng, MD; Qingyi Wu, MD; Jianqian Fu, MD; Fang Wang, MD; Hui Li, MD; Xiaofeng Li, MD; Gaowang Zhang, MD; Yongzhi Yao, MD; Min Xin, MD; Tianyang Lai, MD; Xia Lv, MD; Yigui Chen, MD; Shangwang Yang, MD; Yubiao Lin, MD; Lixia Hong, MD; Zhenyu Cai, MD; Jianfeng Wang, MD; Gen Lin, MD; Shaowei Lin, MD; Shen Zhao, MD; Jinfeng Zhu, MD; and Cheng Huang, MD

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eFigure 1: Median Accumulated Hydromorphone Consumption From the Start of Titration to TST

eFigure 2: Median Accumulated Hydromorphone Consumption From the Start of Titration to Hour 24

eFigure 3: Median Number of Delivered Boluses

eTable 1: Common Opioid Conversion Chart

eTable 2: ESAS at Baseline and Hour 24

eTable 3: Frequency of Main Adverse Effects

eFigure 1. Median accumulated hydromorphone consumption from the start of titration to TST in the PCA versus non-PCA groups, respectively, for (A) all patients [1.0 mg (IQR, 0.5–2.0 mg) vs 1.5 mg (IQR, 1.0–2.5 mg); $P=.086$]; (B) opioid-tolerant patients [1.0 mg (IQR, 1.0–2.0 mg) vs 2.0 mg (IQR, 1.0–4.0 mg); $P=.009$]; and (C) opioid-naïve patients [1.0 mg (IQR, 0.5–2.0 mg) vs 1.0 mg (IQR, 0.5–2.0 mg); $P=.793$]. Abbreviations: IQR, interquartile range; PCA, patient-controlled analgesia; TST, time to successful titration.

eFigure 2. Median accumulated hydromorphone consumption from the start of titration to hour 24 in the PCA versus non-PCA groups, respectively, for (A) all patients [4.5 mg (IQR, 2.5–6.0 mg) vs 4.0 mg (IQR, 2.3–8.3 mg); $P=.600$]; (B) opioid-tolerant patients [5.5 mg (IQR, 2.5–8.3 mg) vs 6.3 mg (IQR, 4.0–12.0 mg); $P=.028$]; and (C) opioid-naïve patients [4.0 mg (IQR, 2.5–5.5 mg) vs 2.5 mg (IQR, 2.0–4.3 mg); $P=.048$]. Abbreviations: IQR, interquartile range; PCA, patient-controlled analgesia.

eFigure 3. Median number of delivered boluses in the PCA versus non-PCA groups, respectively, in **(A)** all patients [6 (IQR, 4–9) presses vs 6 (IQR, 4–9) boluses per patient; $P = .400$]; **(B)** opioid-tolerant patients [6 (IQR, 4–9) presses vs 7 (IQR, 4–9) boluses per patient; $P = .687$]; and **(C)** opioid-naïve patients [7 (IQR, 4–9) presses vs 4 (IQR, 4–8) boluses per patient; $P = .143$]. Abbreviations: IQR, interquartile range; PCA, patient-controlled analgesia.

eTable 1. Common Opioid Conversion Chart

Opioid	Parenteral Dose	Oral Dose
Morphine	10 mg	30 mg
Hydromorphone	1.5 mg	—
Oxycodone	—	15–20 mg
Fentanyl ^a	15 mcg/h	—

^aFor transdermal patch conversions.

eTable 2. ESAS at Baseline and Hour 24

ESAS Item	Baseline			Hour 24		
	PCA Median (IQR)	Non-PCA Median (IQR)	P Value	PCA Median (IQR)	Non-PCA Median (IQR)	P Value
Total, n	106	108		105	107	
Pain	8 (7–8)	8 (7–8)	.419	2 (2–2)	2 (2–5)	.060
Tiredness	5 (4–6)	5 (4–6)	.718	2 (2–5)	3 (2–5)	.129
Nausea	1 (1–1)	1 (0–2)	.158	2 (2–5)	3 (2–4)	.316
Depression	3 (2–4)	3 (3–4)	.122	2 (2–3)	2 (2–4)	.107
Anxiety	3 (3–4)	3 (3–4)	.570	2 (1–2)	2 (2–3)	.074
Drowsiness	2 (2–3)	2 (1–3)	.182	2 (0–5)	2 (1–3)	.827
Appetite	5 (4–6)	5 (4–6)	.555	5 (2–5)	5 (2–5)	.630
Well-being	7 (6–7)	7 (6–7)	.759	5 (2–5)	5 (2–5)	.458
Itching	1 (0–1)	1 (0–1)	.803	1 (0–2)	0 (0–2)	.981
Dyspnea	2 (1–3)	2 (1–2)	.315	1 (1–2)	2 (1–2)	.173
Overall score	36 (34–38)	37 (34–39)	.154	25 (16–29)	26 (19–35)	.096

Abbreviations: ESAS, Edmonton Symptom Assessment System; IQR, interquartile range; PCA, patient-controlled analgesia.

eTable 3. Frequency of Main Adverse Effects

Adverse Effect	PCA n (%)	Non-PCA n (%)	P Value
Total, n	106	108	
Constipation	5 (4.7)	4 (3.7)	.747
Nausea	7 (6.6)	10 (9.3)	.615
Vomiting	2 (1.9)	3 (2.8)	1.000
Dizziness	2 (1.9)	4 (3.7)	.683
Pruritus	4 (3.8)	3 (2.8)	.720
Somnolence	3 (2.8)	5 (4.6)	.721
Dry mouth	5 (4.7)	3 (2.8)	.699

Abbreviation: PCA, patient-controlled analgesia.