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Original Article

Relationship between morphine rescue dose and respiratory safety during breakthrough cancer pain in lung cancer patients treated with high-dose opioids

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Abstract: To investigate the efficacy and safety of different morphine rescue doses for breakthrough cancer pain (BTcP) in lung cancer patients receiving high-dose opioid therapy. Between August 2023 and January 2025, 150 hospitalized patients with at least one documented BTcP episode were retrospectively assigned to three groups based on their initial rescue dose: a fixed 10 mg dose (Group A, n=47), 5% of their daily opioid dose (Group B, n=62), and 10% of their daily opioid dose (Group C, n=41). Pain intensity (numerical rating scale, NRS) and vital signs were recorded at baseline and up to 180 minutes after administration. The primary outcome was the proportion of patients with a ≥30% or ≥50% reduction in NRS at 60 minutes; safety outcomes included a ≥5% reduction in respiratory rate or oxygen saturation (SpO_2). The pain relief rates in groups B and C were significantly higher (≥30% reduction: 95.2% and 95.1%, respectively, compared to 68.1% in group A, P<0.001; ≥50% reduction: 83.9% and 90.2%, respectively, compared to 57.4% in group A, P<0.001), and the onset of relief was faster. Multivariate logistic regression confirmed that proportional dosing was an independent predictor of successful analgesia (adjusted odds ratio (aOR) for ≥50% relief: 4.63 in group B and 8.00 in group C, both P=0.001). No significant differences were observed among the three dosage groups in terms of respiratory rate or SpO_2 reduction (both P>0.05). However, brain metastasis (65.52% vs. 4.96%, P<0.001) and background opioid dose >720 mg/day (35.14% vs. 14.16%, P=0.005) were significant risk factors for respiratory depression. For lung cancer patients receiving high-dose opioid therapy, a rescue dose of 5%-10% of the daily opioid dose provides superior analgesia compared with a fixed dose of 10 mg, and has acceptable respiratory safety in patients without brain metastasis.

Keywords: Lung cancer, opioids, morphine, respiratory safety

Introduction

Cancer pain is one of the most common and frightening symptoms among patients with malignant tumors, especially those with advanced cancer, with an incidence rate as high as 40%-80% [1, 2]. High-dose opioids are commonly used to control pain in these patients, but breakthrough cancer pain (BTcP) remains a significant concern [3]. BTcP is defined as a brief exacerbation of pain occurring within the past week on top of well-controlled, persistent background pain [4]. The sudden onset and severity of BTcP not only severely impact patients' quality of life but may also accelerate disease progression, making it a major challenge in the management of clinical cancer pain [5].

Opioids are a fundamental medication for cancer pain management, especially for patients with moderate to severe pain [6]. However, the choice of rescue drug dosage remains highly controversial in patients using high-dose opioids (defined as 200 mg morphine equivalent or more daily) during BTcP attacks [7, 8]. Currently, authoritative guidelines from organizations such as the European Society for Medical Oncology (ESMO, 2018 Clinical Practice Guidelines for Adult Cancer Pain Management) and the American Society of Clinical Oncology (ASCO, 2022 Guidelines for Integrative Medicine in Cancer Pain Management) recommend a relatively wide range of rescue doses for BTcP, typically 5%-20% of the total daily opioid dose [9]. However, these recommendations

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are mostly based on expert consensus and lack support from high-quality evidence-based medicine. The lack of evidence means that when faced with patients experiencing BTcP after high-dose opioid treatment, clinicians often tend to choose a fixed low dose of morphine (such as 10 mg subcutaneously) as a rescue drug to avoid potentially fatal adverse reactions such as respiratory depression and coma [10]. However, the efficacy and safety of this approach have not been fully verified. On the one hand, it is unclear whether a fixed low dose of morphine can provide sufficient pain relief for patients; on the other hand, there is a lack of clear evidence as to whether a high-dose morphine rescue dose calculated according to the guideline recommendation ratio will actually bring safety risks such as respiratory depression and coma [11].

Lung cancer is one of the malignant tumors with the highest incidence and mortality rates worldwide [12]. Patients often suffer from severe pain due to tumor invasion of structures such as the pleura, ribs, or nerves [13]. Pain management is more challenging for lung cancer patients than for other cancers, especially when patients require high-dose opioid therapy. Frequent burst pain attacks can not only exacerbate the patient's suffering but may also lead to further increases in opioid dosage, thereby amplifying the risk of adverse reactions such as respiratory depression [14]. Although some studies have explored management strategies for BTcP, research specifically targeting lung cancer patients is still relatively scarce. In view of this, this study retrospectively analyzed the clinical data of lung cancer patients receiving high-dose opioid therapy who used intravenous morphine for burst pain rescue. The aim was to clarify the analgesic effect of different doses of immediate-release morphine and its impact on respiratory function, and to explore the effective and safe dose range of morphine rescue therapy in this population. The results are expected to provide evidence-based medical support for individualized treatment of BTcP in lung cancer patients, fill the current research gap, optimize clinical pain management strategies, minimize respiratory risks while ensuring pain relief, and improve the quality of life of patients.

Materials and methods

Selection of patients

This study retrospectively analyzed the cases of lung cancer patients hospitalized in the Hospital of Shunyi District Beijing from August 2023 to January 2025. All patients were pathologically diagnosed with lung cancer and had at least one recorded episode of BTcP. All clinical data of the patients were obtained from the hospital's electronic medical record system and special records for cancer pain management, including medical records, medication records, nursing records and pain assessment forms. After strict inclusion and exclusion criteria, data from 150 patients were analyzed. This study strictly followed all the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Hospital of Shunyi District Beijing.

Diagnostic criteria for BTcP

The numerical rating scale (NRS) was used to assess the pain level of patients [15]. The diagnosis of BTcP requires meeting the following criteria simultaneously: (1) the patient has persistent background pain (NRS score ≤3 in the past week, indicating stable control); (2) the pain suddenly worsens, with an NRS score ≥4, usually lasting less than 30 minutes; (3) the nature of the pain worsening differs from the background pain, and other non-cancer-related factors (such as fractures, infections, etc.) are excluded. All BTcP attacks are confirmed by the attending physician based on the patient's self-reported symptoms and clinical assessment, and are clearly documented in the medical record.

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) Patients with lung cancer diagnosed by pathology and/or cytology; (2) Patients with a confirmed diagnosis of "cancer pain" and meeting the diagnostic criteria for BTcP: a brief increase in pain occurs despite adequate control of background pain [16]; (3) Age ≥18 years old; (4) Daily opioid dose converted to oral morphine equivalent ≥480 mg; (5) Patients whose expected survival of ≥12 weeks based on the patient's physical condition, tumor burden, laboratory parameters and clinical course at the time of screening by the attending oncologist. The exclusion criteria are as follows: (1) Patients with past or current cognitive impairment; (2) Patients whose clinical data were incomplete for various reasons and key research data cannot be extracted; (3) Patients who were also participating in other clinical research projects.

Grouping criteria

The opioid dose conversion followed the oral morphine equivalent (OME) standard recommended in the Chinese Guidelines for the Management of Cancer Pain in Adults (2025 Edition) [17]. The main conversion formulas include: oral morphine 30 mg = parenteral morphine 10 mg (conversion factor = 3); oral hydromorphone 7.5 mg = parenteral hydromorphone 1.5 mg (conversion factor = 2.5-5.0); oral oxycodone 15-20 mg = 10 mg parenteral oxycodone (conversion factor = 1.5-2.0); oral tramadol 300 mg = OME 100 mg (conversion factor = 3); transdermal fentanyl patch (mcg/hour) × 2.4 = daily OME (mg). The daily doses of all non-morphine opioids were converted to OME based on these criteria to calculate the proportional rescue dose (5% or 10% of the total daily OME). Patients were retrospectively categorized into three groups based on the first morphine rescue dose actually administered during a BTcP attack: (1) Fixed low-dose group (Group A, n=47): a fixed dose of 10 mg morphine was administered subcutaneously; (2) 5% proportional dose group (Group B, n=62): the rescue dose was approximately 5% of the total daily oral morphine equivalent; (3) 10% proportional dose group (Group C, n=41): the rescue dose was approximately 10% of the total daily oral morphine equivalent. The choice of rescue dose was not governed by a uniform departmental protocol, but rather determined by the attending physician's clinical judgment. Specific considerations documented at the time of prescription included patient age, baseline respiratory rate and oxygen saturation, presence of brain metastases, concurrent use of central nervous system depressants (e.g., benzodiazepines or gabapentin), renal/hepatic function, and prior opioid tolerance; these variables are retrospectively extracted and summarized in **Table 1** to allow readers to assess potential selection bias.

Data collection and observation indicators

Data were retrospectively extracted from the electronic medical record system using a standardized data collection form. The collected information included: (1) Baseline characteristics: Age, gender, educational level, pathological type and stage of lung cancer, number of chronic comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status score at admission, presence of brain metastases, and daily background opioid dose (converted to oral morphine equivalent). (2) BTcP) attack characteristics: NRS score at the onset, pain characteristics. (3) Rescue treatment data: Morphine rescue dose, route of administration. (4) Efficacy outcomes: NRS scores recorded at preset time points (5, 15, 30, 45, 60, 120, and 180 minutes) after rescue drug administration. If the initial rescue dose failed to reduce the NRS score by ≥30%, or if the attending physician determined the dose is insufficient, a second rescue morphine dose (10% of the patient's total daily oral morphine equivalent) may be administered at any time after 30 minutes. These repeated doses were recorded, but the primary efficacy analysis will only consider the response to the initial dose. The primary efficacy endpoints were the proportion of patients achieving pain relief (defined as a ≥30% reduction in NRS score) and significant pain relief (≥50%) within 60 minutes of administration, as well as the time to achieve effective pain relief. (5) Safety outcomes: respiratory rate and peripheral SpO_2. The primary safety endpoints were the incidence of a ≥5% decrease in respiratory rate or SpO_2 from baseline within 60 minutes of administration. (6) Non-respiratory adverse events: In addition to respiratory parameters, a retrospective review of medical records (including nursing records and physician progress notes) was conducted to obtain records of common opioid-related non-respiratory adverse events occurring during the 180-minute observation period. Specifically, events such as drowsiness, dizziness, nausea, vomiting, and itching were systematically extracted.

Statistical analysis

SPSS 21.0 (IBM, Armonk, NY, USA) software was used for statistical analysis. Given that this study was retrospective and aimed to analyze

Table 1. Baseline characteristics of the patient

Variables	Total (n=150)	A group (n=47)	B group (n=62)	C group (n=41)	Statistic	*P*
Age, Mean ± SD	66.52±7.60	67.21±6.94	65.68±7.84	67.00±7.99	F=0.66	0.521
Gender, n (%)					X^2=0.04	0.978
Female	64 (42.67)	20 (42.55)	27 (43.55)	17 (41.46)		
Male	86 (57.33)	27 (57.45)	35 (56.45)	24 (58.54)		
Education level, n (%)					X^2=2.67	0.263
Junior high school and below	82 (54.67)	28 (59.57)	29 (46.77)	25 (60.98)		
Senior high school and above	68 (45.33)	19 (40.43)	33 (53.23)	16 (39.02)		
Pathological type, n (%)					X^2=1.00	0.910
Adenocarcinoma	64 (42.67)	21 (44.68)	26 (41.94)	17 (41.46)		
Squamous cell carcinoma	47 (31.33)	13 (27.66)	19 (30.65)	15 (36.59)		
Others	39 (26.00)	13 (27.66)	17 (27.42)	9 (21.95)		
Pathological staging, n (%)					X^2=0.24	0.886
I and II	55 (36.67)	16 (34.04)	23 (37.10)	16 (39.02)		
III and IV	95 (63.33)	31 (65.96)	39 (62.90)	25 (60.98)		
Chronic disease, n (%)					X^2=2.35	0.309
≤2	64 (42.67)	18 (38.30)	31 (50.00)	15 (36.59)		
>2	86 (57.33)	29 (61.70)	31 (50.00)	26 (63.41)		
ECOG at admission, n (%)					X^2=0.08	0.961
1	94 (62.67)	30 (63.83)	39 (62.90)	25 (60.98)		
2	56 (37.33)	17 (36.17)	23 (37.10)	16 (39.02)		
Brain metastasis, n (%)					X^2=1.14	0.566
No	125 (83.33)	40 (85.11)	53 (85.48)	32 (78.05)		
Yes	25 (16.67)	7 (14.89)	9 (14.52)	9 (21.95)		
Background dose of opioids, n (%)					X^2=0.09	0.958
480-720 mg/d	113 (75.33)	36 (76.60)	46 (74.19)	31 (75.61)		
>720 mg/d	37 (24.67)	11 (23.40)	16 (25.81)	10 (24.39)		

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

all eligible cases within a specific period, no formal pre-analysis sample size was performed. The sample size was determined by the number of eligible patients meeting the inclusion criteria between August 2023 and January 2025 (n=150). Post-hoc power analysis was performed using G*Power 3.1. Based on the observed response rates (Group A: 57.4%, Group B: 83.9%, Group C: 90.2%), the effect size was calculated as Cohen w=0.327. At an α level of 0.05 and a total sample size of 150, the statistical power obtained exceeded 0.99, indicating sufficient power to detect the observed significant differences. Normally distributed continuous data were expressed as mean ± standard deviation (±SD), and one-way ANOVA was used for comparisons between groups. Repeated measures ANOVA was used for dynamic comparisons of NRS scores at multiple time points. Count data were expressed as frequencies (percentages), and comparisons between groups were performed using the x^2 test or Fisher's exact test (when the expected frequency was <5). To identify the independent effect of the rescue dose regimen on analgesic outcomes while adjusting for potential confounding factors, multivariate logistic regression analysis was conducted. Two independent models were constructed with binary dependent variables: 1) a ≥30% reduction in NRS score at 60 minutes (yes/no); 2) a ≥50% reduction in NRS score at 60 minutes (yes/no). Variable selection was based on clinical relevance and prior evidence: age and gender were included as basic demographic covariates; brain metastasis and baseline opioid dose (>720 mg/d vs. 480-720 mg/d) were included because univariate analysis showed

Table 2. Characteristics of BTcP attacks

Group	NRS score	4	5-6	≥7
A group	5.70±1.12	8 (17.02)	27 (57.45)	12 (25.53)
B group	6.02±1.05	5 (8.06)	36 (58.06)	21 (38.87)
C group	6.05±1.14	3 (7.32)	24 (58.54)	14 (34.15)
F/x^2	1.45		3.34	
P value	0.239		0.502	

Abbreviations: BTcP, breakthrough cancer pain; NRS, numerical rating scale.

Table 3. Pain relief rate

Group	Total	Decrease by ≥30%	Decrease by ≥50%
A group	47	32	27
B group	62	59	52
C group	41	39	37
x^2		20.45	16.01
P value		<0.001	<0.001

they were associated with respiratory depression and analgesic response (**Tables 6** and **7**). The rescue dose group (with group A as a reference) was forced into the model as the primary independent variable of interest. Stepwise selection was not used to avoid data-driven overfitting; all pre-specified covariates were retained in the final model. Multicollinearity was assessed using variance inflation factors (VIFs); all VIFs <5.0 indicated the absence of significant multicollinearity. Results are presented as aORs with 95% confidence intervals (CI). A two-tailed *P* value <0.05 was considered statistically significant.

Results

Baseline characteristics of the patients

There were no statistically significant differences among the three groups in terms of age (F=0.66, P=0.521), gender (χ^2=0.04, P=0.978), education level (χ^2=2.67, P=0.263), pathological type (χ^2=1.00, P=0.910), pathological stage (χ^2=0.24, P=0.886), number of chronic diseases (χ^2=2.35, P=0.309), ECOG score (χ^2=0.08, P=0.961), and proportion of brain metastasis (χ^2=1.14, P=0.566). Of the patients, 113 (75.33%) had a daily opioid dose of 480-720 mg, and 37 (24.67%) had a daily dose >720 mg, with this distribution being balanced across the groups (**Table 1**).

Characteristics of BTcP attacks

A total of 319 BTcP events were recorded in all patients, with a mean of 2.13 ± 0.74 events per patient. At the time of BTcP, the mean NRS scores for groups A, B, and C were 5.70±1.12, 6.02±1.05 and 6.05±1.14, respectively (**Table 2**). The proportions with an NRS score ≥7 were 25.53% (12 cases), 33.87% (21 cases), and 34.15% (14 cases), respectively. However, there was no statistically significant difference among the three groups (P=0.502).

Comparison of pain relief rates and duration

Within 1 hour after Rescue administration, the overall proportion of patients with a ≥30% reduction in NRS score was 86.7% (130/150), with 68.1% (32/47) in group A (fixed 10 mg), 95.2% (59/62) in group B (5% proportional dose), and 95.1% (39/41) in group C (10% proportional dose). The difference among groups was statistically significant (χ^2=20.45, df = 2, P<0.001) (**Table 3**). For the endpoint of a ≥50% reduction in the more stringent NRS score, the overall rate was 77.3% (116/150), with groups A, B, and C reaching 57.4% (27/47), 83.9% (52/62), and 90.2% (37/41), respectively (χ^2= 16.01, df = 2, P<0.001). Repeated measures ANOVA (**Table 4**) revealed a significant main effect of time (F=898.598, P<0.001), indicating a significant decrease in NRS scores in all groups during the 180-minute observation period. A significant main effect between groups was also observed (F=3.425, P=0.035), reflecting the overall difference in pain scores among the three dosing regimens. Furthermore, the time × group interaction was statistically significant (F=2.381, P=0.025), demonstrating that the trajectory of pain relief differed depending on the rescue dosing strategy. Posthoc pairwise comparisons at 60 minutes confirmed that the NRS score in group A was significantly higher than that in groups B and C (all P<0.05), suggesting that the analgesic onset was slower in the fixed low dose group (**Figure 1**).

Changes in respiratory rate and SpO_2

The overall incidence of a ≥5% decrease in respiratory rate within 60 minutes after drug

Table 4. Analysis of pain relief time

Time	A group (n=47)	B group (n=62)	C group (n=41)	F value	*P* value[a]
BTcP attack	5.70±1.12	6.02±1.05	6.05±1.14	F=1.45	0.239
5 min	5.34±0.84	5.58±0.82	5.56±0.92	F=1.20	0.305
15 min	4.51±0.72	4.39±0.86	4.27±0.90	F=0.94	0.392
30 min	3.68±0.81	3.42±0.71	3.29±0.81	F=2.96	0.055
45 min	2.79±0.81	2.60±0.56	2.44±0.50	F=3.35	0.038
60 min	2.53±1.32	2.11±0.87	1.85±0.61	F=5.45	0.005
120 min	1.04±0.75	0.81±0.51	0.83±0.44	F=2.49	0.086
180 min	1.23±0.43	1.10±0.47	1.12±0.56	F=1.16	0.318
F value	373.330	442.600	221.149		
P value[b]	<0.001	<0.001	<0.001		
Between-group effects		F=3.425, P=0.035			
Within-group effects		F=898.598, P<0.001			
within-group*between-group		F=2.381, P=0.025			

[a]One-way ANOVA; [b]Repeated measures ANOVA; Mauchly's test indicated that the assumption of sphericity was violated (W=0.324, P<0.05), therefore the Greenhouse-Geisser correction was applied. The reported within-group and interaction effects are based on corrected degrees of freedom. Abbreviations: BTcP, breakthrough cancer pain; ANOVA, Analysis of Variance.

Table 5. Respiratory safety analysis

Variables	Total (n=150)	A group (n=47)	B group (n=62)	C group (n=41)	Statistic	*P*
Respiratory rate						
BTcP attack, Mean ± SD	18.63±0.82	18.62±0.80	18.63±0.83	18.66±0.85	F=0.03	0.971
60 min, Mean ± SD	18.39±0.92	18.40±0.85	18.37±1.00	18.41±0.89	F=0.03	0.968
Decrease by ≥5%	29 (19.33%)	8 (17.02%)	11 (17.74%)	10 (24.39%)	x^2=0.93	0.627
SpO_2						
BTcP attack, Mean ± SD	99.87±0.46	99.87±0.45	99.89±0.41	99.83±0.54	F=0.20	0.820
60 min, Mean ± SD	99.18±1.95	99.26±1.84	99.32±1.75	98.88±2.34	F=0.69	0.503
Decrease by ≥5%	17 (11.33%)	5 (10.64%)	6 (9.68%)	6 (14.63%)	x^2=0.64	0.728

Abbreviations: BTcP, breakthrough cancer pain; SD, standard deviation; SpO_2, peripheral oxygen saturatio.

Table 6. Respiratory rate and combined brain metastasis

Variables	Total (n=150)	Stable (n=121)	Declining 5% (n=29)	Statistic	*P*
Brain metastasis, n (%)				X^2=57.49	<0.001
No	125 (83.33)	115 (95.04)	10 (34.48)		
Yes	25 (16.67)	6 (4.96)	19 (65.52)		

administration was 19.3% (29/150) (**Table 5**). The percentages of patients with a ≥5% decrease in respiratory rate in the three groups were 17.02% (8/47), 17.74% (11/62), and 24.39% (10/41), respectively. The overall incidence of a ≥5% decrease in SpO_2 was 11.3% (17/150), with the percentages in the three groups being 10.64% (5/47), 9.68% (6/62), and 14.63% (6/41), respectively, suggesting that the intervention in this study had no significant adverse effect on respiratory function.

Influence of brain metastasis on respiratory rate

Among patients with a respiratory rate decrease of ≥5%, 65.52% (19/29) had brain metastasis, while only 4.96% (6/121) of patients without a respiratory rate decline had brain metastasis, a statistically significant difference (P<0.001) (**Table 6**). It indicates that brain metastasis may increase the risk of respiratory depression.

Table 7. Pain and respiratory indicators in different opioid background dose groups

Variables	Total (n=150)	480-720 mg/d group (n=113)	>720 mg/d group (n=37)	Statistic	*P*
NRS decreased by 30%, n (%)				X^2=0.10	0.752
No	20 (13.33)	14 (12.39)	6 (16.22)		
Yes	130 (86.67)	99 (87.61)	31 (83.78)		
NRS decreased by 50%, n (%)				X^2=4.36	0.037
No	34 (22.67)	21 (18.58)	13 (35.14)		
Yes	116 (77.33)	92 (81.42)	24 (64.86)		
Respiratory rate decreased by 5%, n (%)				X^2=7.86	0.005
No	121 (80.67)	97 (85.84)	24 (64.86)		
Yes	29 (19.33)	16 (14.16)	13 (35.14)		
SpO_2 decreased by 5%, n (%)				X^2=0.61	0.435
No	133 (88.67)	102 (90.27)	31 (83.78)		
Yes	17 (11.33)	11 (9.73)	6 (16.22)		

Abbreviations: NRS, numerical rating scale; SpO_2, peripheral oxygen saturatio.

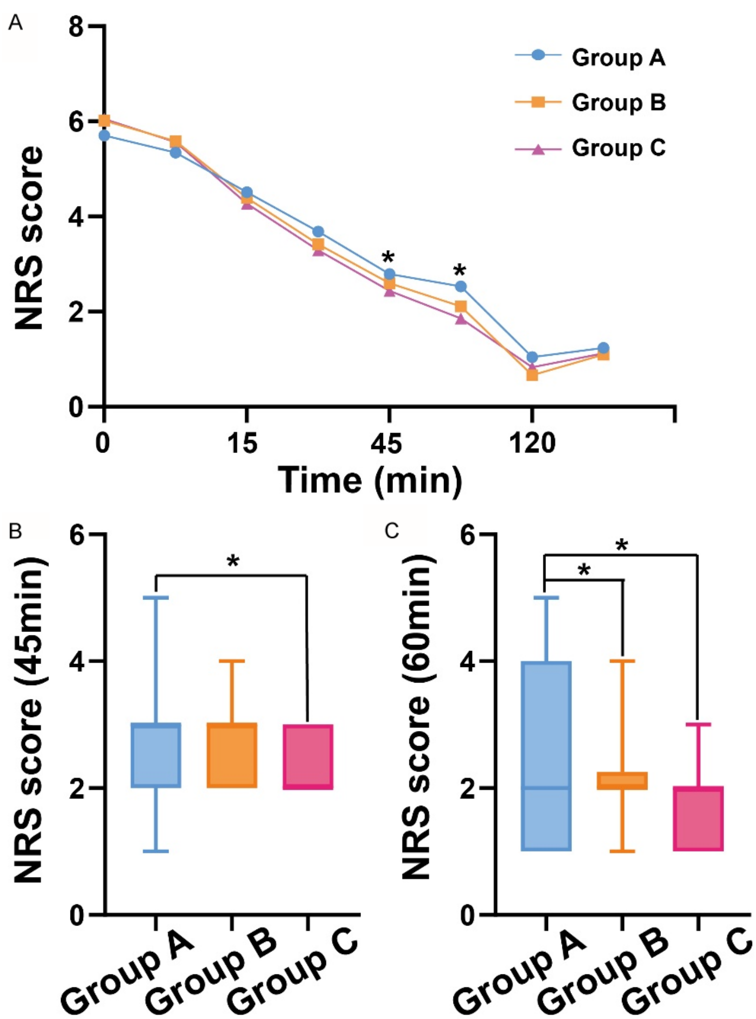

Figure 1. Comparison of pain relief among the three groups of patients. A. NRS scores at different time points, *One-way ANOVA, P<0.05; B. NRS scores at 45 minutes, *LSD method, P<0.05; C. NRS scores at 60 minutes, *LSD method, P<0.05. Abbreviation: NRS, numerical rating scale; ANOVA, Analysis of Variance; LSD, least significant difference.

Pain and respiratory indicators at different opioid background dose

In the group with an opioid background dose of 480-720 mg/d (n=113), 81.42% (92 cases) of patients experienced a pain intensity decrease of ≥50%, significantly higher than the 64.86% (24 cases) in the dose group >720 mg/d (n=37) (P=0.037) (**Table 7**). Meanwhile, the proportion of patients with a respiratory rate decrease of ≥5% in the >720 mg/d group was 35.14% (13 cases), significantly higher than the 14.16% (16 cases) in the 480~720 mg/d group (P=0.005), suggesting that high-dose opioids may increase the risk of respiratory depression.

Subgroup analysis of the high-dose group (> 720 mg/d)

Among patients with a dose >720 mg/d (n=37), there was no statistically significant difference in the 30% response rate among the three groups (P=0.138), but there was a statistically significant difference in the 50% response rate (P=0.012): only 27.27% (3/11) in group A, 81.25% (13/16) in

Table 8. Changes in pain and respiratory indicators under the background of high-dose opioids (>720 mg/d)

Variables	Total (n=37)	A group (n=11)	B group (n=16)	C group (n=10)	Statistic	*P**
NRS decreased by 30%, n (%)					-	0.138
No	6 (16.22)	4 (36.36)	1 (6.25)	1 (10.00)		
Yes	31 (83.78)	7 (63.64)	15 (93.75)	9 (90.00)		
NRS decreased by 50%, n (%)					-	0.012
No	13 (35.14)	8 (72.73)	3 (18.75)	2 (20.00)		
Yes	24 (64.86)	3 (27.27)	13 (81.25)	8 (80.00)		
Respiratory rate decreased by 5%, n (%)					-	0.617
No	24 (64.86)	8 (72.73)	11 (68.75)	5 (50.00)		
Yes	13 (35.14)	3 (27.27)	5 (31.25)	5 (50.00)		
SpO_2 decreased by 5%, n (%)					-	0.330
No	31 (83.78)	9 (81.82)	15 (93.75)	7 (70.00)		
Yes	6 (16.22)	2 (18.18)	1 (6.25)	3 (30.00)		

*Fisher exact. Abbreviations: NRS, numerical rating scale; SpO_2, peripheral oxygen saturatio.

Table 9. Multivariate logistic regression analysis of factors associated with analgesic success at 60 minutes

Variables	Category	≥30% NRS Reduction		≥50% NRS Reduction	
		Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Rescue Dose Group	Group A (Ref)	-		-	
	Group B	10.75 (2.76-41.82)	<0.001	4.63 (1.81-11.89)	0.001
	Group C	10.77 (2.19-52.83)	0.003	8.00 (2.30-27.86)	0.001
Age	(Per year increase)	1.06 (0.98-1.14)	0.146	1.05 (0.99-1.11)	0.111
Gender	Female (Ref)	-		-	
	Male	0.49 (0.16-1.50)	0.212	0.88 (0.37-2.07)	0.766
Brain Metastasis	No (Ref)	-		-	
	Yes	0.68 (0.18-2.62)	0.574	1.84 (0.52-6.47)	0.341
Background Opioid Dose	480-720 mg/d (Ref)	-		-	
	>720 mg/d	0.84 (0.25-2.88)	0.787	0.41 (0.16-1.07)	0.069

Abbreviations: NRS, numerical rating scale; OR, odds ratio; CI, confidence interval.

group B, and 80.00% (8/10) in group C (**Table 8**). There were no statistically significant differences in the rate of decrease in respiratory rate (P=0.617) and the rate of decrease in pulse SpO_2 (P=0.330) among the three groups.

Multivariate analysis of predictors of successful analgesia

The results of multivariate logistic regression analysis are presented in **Table 9**. After adjusting for age, gender, brain metastasis, and background opioid dose stratification, the rescue dose regimen remained a strong independent predictor of the primary analgesic outcome. Regarding a ≥30% decrease in the NRS at 60 minutes post-dose, compared to group A, the aOR for patients in group B was 10.75 (95% CI: 2.76-41.82; P<0.001); and for patients in group C, the aOR was 10.77 (95% CI: 2.19-52.83; P=0.003). For the more stringent outcome of a ≥50% decrease in NRS score, the above association remained statistically significant: compared to group A, the aOR in group B was 4.63 (95% CI: 1.81-11.89; P=0.001), and the aOR in group C was 8.00 (95% CI: 2.30-27.86; P=0.001).

Non-respiratory adverse reactions

The incidence of common non-respiratory adverse reactions recorded within 180 minutes

Table 10. Incidence of non-respiratory adverse events within 180 minutes post-rescue dose

Adverse Event	Total (N=150)	Group A (n=47)	Group B (n=62)	Group C (n=41)	*P* value
Central Nervous System					
Somnolence	25 (16.67)	6 (12.77)	9 (14.52)	7 (17.07)	0.849
Dizziness	4 (2.67)	1 (2.13)	1 (1.61)	2 (4.88)	0.685[a]
Gastrointestinal System					
Nausea	20 (13.33)	5 (10.64)	8 (12.90)	7 (17.07)	0.670
Vomiting	9 (6.00)	3 (6.38)	2 (3.23)	4 (9.76)	0.385[a]
Dermatological					
Pruritus	7 (4.67)	3 (6.38)	2 (3.23)	2 (4.88)	0.886[a]
Total	65 (43.33)	18 (38.30)	22 (35.48)	22 (53.66)	0.164

[a]*P* value calculated using Fisher's exact test due to small expected frequencies; otherwise, the Chi-square test was used.

after the rescue dose is summarized in **Table 10**. Among the 150 patients, 65 (43.3%) experienced at least one such adverse reaction. The most common was somnolence (16.7%, 25/150), followed by nausea (13.3%, 20/150); vomiting (6.0%, 9/150), pruritus (4.7%, 7/150), and dizziness (2.7%, 4/150) occurred less frequently. There were no statistically significant differences in the incidence of any individual adverse reaction or the total incidence of non-respiratory adverse reactions among the three rescue dose groups (P>0.05). All recorded adverse reactions were mild to moderate.

Discussion

When lung cancer patients experience BTcP and have received high-dose opioid therapy (oral morphine equivalent ≥480 mg/d), how to safely and rapidly relieve pain has always been a clinical challenge [18]. This study retrospectively analyzed the efficacy and safety of different morphine rescue doses during BTcP in 150 lung cancer patients receiving high-dose opioid therapy. For the first time, the differences between three dosing regimens were systematically compared in a real clinical setting: fixed low dose (10 mg), 5% of the total dose, and 10% of the total dose. The results showed that although there were no significant differences in respiratory safety indicators (respiratory rate, SpO_2 decline rate) among the three groups, the proportional dosing in groups B and C were significantly better than the fixed low dose group in terms of pain relief rate (especially 50% significant relief rate) and relief speed Additionally, patients with brain metastasis had a significantly increased risk of respiratory depression, and those with a baseline opioid dose >720 mg/day had a lower pain relief rate and a higher respiratory risk. These findings provide an important basis for individualized treatment of breakthrough pain in lung cancer patients. This study found that proportional dosing groups (5% and 10% of the total dose) were significantly better than fixed low-dose groups in terms of pain relief rate and duration, especially in patients with a baseline dose >720 mg/d. A study by Rahmadi et al. showed that 43.78% of BTcP patients received a morphine rescue dose higher than the recommended dose, ranging from 6.67% to 60% of the daily dose [19]. This suggests that conventional doses may be insufficient to suppress BTcP, especially with high-dose opioid therapy. Mechanistically, opioids inhibit pain signal transmission by binding to opioid receptors in the central and peripheral nervous systems [20, 21]. Long-term use of high-dose opioids may lead to downregulation or internalization of central μ-opioid receptors, resulting in reduced responsiveness to fixed low-dose morphine [22, 23]. Rescue doses calculated based on proportions of the total dose better meet individualized analgesic needs, achieving effective blood concentrations more quickly and activating a sufficient number of opioid receptors for more adequate pain control [24]. Furthermore, subgroup analysis showed that among patients with a background dose >720 mg/d, the proportion of patients with a ≥50% reduction in the NRS score in group A (27.27%) was significantly lower than that in group B (81.25%) and group C (80.00%), further validating the hypothesis of "underdose". When the daily opioid dose exceeds 720 mg, the body's tolerance to opioids enters a "plateau phase", and the gap between the fixed dose and individual needs is amplified. Proportional dosing can be dynamically adjusted to bridge this gap [25]. In addition, proportional dosing regimens accelerate the rate of pain relief. In the present study, the NRS scores in the fixed low-dose group were significantly higher than those in the proportional dosing groups at 60 minutes after morphine rescue administration. The fixed low-dose regimen may not be able to quickly achieve effective blood drug concentrations, especially for patients who have already received high-dose opioid therapy, whose drug metabolism and excretion rates may be faster, requiring higher doses of the drug to maintain effective blood drug concentrations [26]. Furthermore, multivariate logistic regression analysis confirmed that even after controlling for potential confounding factors including age, sex, brain metastasis, and high background opioid doses, proportional dosing regimens remained an independent positive predictor of analgesic success. Patients receiving 5% or 10% of their daily opioid dose were approximately 11 times more likely to achieve ≥30% pain relief within 1 hour compared to those receiving a fixed 10 mg dose. For the more clinically significant endpoint of ≥50% pain relief, the odds ratios for the 5% and 10% dose groups were 4.6 and 8.0, respectively. These robust aORs, with CIs well above the null value of 1 provide strong statistical evidence that the superior efficacy of proportional dosing stems not from patient baseline characteristics but from the dosing strategy itself. Notably, rescue dose groups based on higher proportional regimens (such as 15% or 20% of the daily opioid dose) were not included in this study because such regimens are rarely used in clinical practice during the study period. Although the guidelines recommend a wide range (5%-20%), our results in the 5%-10% range suggest that the ceiling effect of analgesic benefit may occur at the 10% dose level, as evidenced by the similarly high response rates between group B (≥30% response rate of 95.2%) and group C (≥30% response rate of 95.1%). In addition, studies by Rahmadi et al. [19] have reported that some patients used rescue doses exceeding 10% (up to 60%), which generally indicates poor baseline pain control or tolerance, but is also associated with increased variability in safety outcomes. In our study, there was no significant increase in respiratory depression between the 5% and 10% groups, suggesting that safety may still be acceptable within this lower range, while increasing the proportion to 15%-20% could disproportionately increase respiratory risk without providing substantial additional analgesic benefit, especially in patients with higher baseline doses (>720 mg/d) or brain metastasis. Therefore, our data support 5%-10% as an effective and relatively safe treatment window for BTcP rescue in this population, aligning with the lower limit of the guideline recommended range and underscores the importance of individualized risk assessment before considering higher proportion doses.

There were no statistically significant differences in the incidence of decreased respiratory rate and decreased SpO_2 among the three groups, suggesting that proportional high-dose morphine under routine real-world monitoring did not significantly increase the overall risk of respiratory depression. Algera et al. reported that patients on long-term opioid use had greater tolerance to morphine-induced respiratory depression [27]. Patients on long-term high-dose opioid use not only had reduced sensitivity to the drug in pain pathways, but also developed cross-tolerance to the inhibitory effects of opioids on the respiratory center. Downregulation or desensitization of respiratory center μ receptors reduced the risk of respiratory depression at the same dose compared to patients who had never used opioids [28]. However, it should be noted that the proportion of patients with brain metastasis whose respiratory rate decreased by ≥5% (65.52%) was significantly higher than that of patients without metastases (4.96%), which may be related to the direct compression or damage of respiratory center regulatory region by brain metastasis [29]. Metastases lead to decreased central sensitivity to carbon dioxide, which, combined with the inhibitory effects of opioids, results in a more pronounced decrease in respiratory rate [30]. In addition, disruption of the blood-brain barrier may allow morphine to more easily enter the central nervous system, increasing the risk of respiratory depression [31, 32]. This suggests that brain metastasis is a “high-risk factor” requiring special attention in the management of BTcP. Additionally, this study found a significantly higher incidence of respiratory depression in the group with >720 mg/day, suggesting that even proportionally, at high baseline doses, morphine doses may approach or exceed the threshold for respiratory depression, particularly when combined with high-risk factors such as brain metastasis, requiring extra caution. Regarding broader tolerability, the incidence of common non-respiratory adverse events (such as nausea, vomiting, and somnolence) was low, and there were no significant differences among the three dosing regimens. This suggests that within a dose range of 5%-10%, additional rescue doses do not lead to a disproportionate increase in acute side effects. However, it should be noted that the retrospective nature of this assessment may have resulted in the underreporting of mild or transient events not documented in medical records.

This study has several limitations. First, its retrospective design may introduce selection bias, such as physicians might prioritize a fixed low dose for patients with poor baseline respiratory function, potentially affecting group balance. Second, only the first BTcP episode was included, and dose adjustments during multiple episodes were not analyzed, limiting the understanding of long-term management outcomes. Third, the rescue dose group did not include regimens exceeding 10% of the daily opioid dose because such doses were rarely used clinically during the study period, making effective statistical comparisons impossible. Although guidelines recommend a range of 5%-20%, we focused on 5%-10%, reflecting actual clinical practice among high-dose opioid users, where higher doses would be cautiously avoided. Fourth, the small sample size (n=11) in the high-dose subgroup (>720 mg/d) within group A may reduce statistical power; however, the balanced baseline and consistent trend with the overall cohort mitigated this concern to some extent. Fifth, respiratory safety outcomes were systematically recorded only within the first 60 minutes after administration. Although the pharmacological effects of morphine typically last 4-6 hours, delayed respiratory depression remains theoretically concerning, but our monitoring protocol was designed to capture the immediate peak risk following rescue dose administration. While no delayed respiratory events were documented in medical records within the 180-minute observation window, the lack of structured respiratory parameter collection after 60 minutes limited our ability to comprehensively assess the time course of respiratory safety. Future prospective studies should incorporate extended respiratory monitoring (e.g., up to 4-6 hours) to more comprehensively assess the risk of delayed respiratory depression. Finally, the absence of recorded pharmacokinetic data (e.g., morphine plasma concentrations) prevents direct validation of the dose-concentration-effect relationship. However, these limitations do not diminish the clinical guidance value of the core findings: (1) For lung cancer patients receiving high-dose opioid therapy (especially daily doses >720 mg), morphine at 5%-10% of the total dose is recommended for relieving BTcP, offering significantly better analgesia compared to a fixed low dose, and is safe in patients without severe brain metastasis or underlying respiratory diseases; (2) For patients with brain metastasis, even with proportional dosing, enhanced respiratory monitoring (e.g., recording respiratory rate every 15 minutes within 1 hour after administration) is necessary; (3) For patients with daily doses of 480-720 mg and no high-risk factors, a fixed low dose may be considered as an alternative for mild to moderate BTcP (NRS score 3-6), but the analgesic effect should be closely assessed, and additional doses may be necessary. Future prospective multicenter studies with larger subgroup sample sizes, extended respiratory monitoring, and pharmacokinetic assessments may address these limitations.

Conclusion

This study systematically evaluated the efficacy and respiratory safety of different doses of morphine rescue therapy in management of BTcP in lung cancer patients receiving high-dose opioid therapy. For lung cancer patients receiving high-dose opioid therapy (≥480 mg/day oral morphine equivalent), BTcP rescue should preferentially use immediate-release morphine at 5%-10% of the background daily dose, rather than a fixed low dose of 10 mg. Retrospective analysis showed that proportional dosing increased the response rate to 95% for a ≥30% reduction in the numerical rating scale score within 1 hour, and the significant response rate (≥50%) exceeded 80%, without significantly increasing the incidence of decreased respiratory rate or decreased SpO_2. Brain metastasis and a baseline dose >720 mg/day are important risk factors for respiratory depression, requiring close monitoring in clinical practice. Proportional dosing is recommended as a priority in patients without brain metastasis or severe underlying respiratory diseases, while individualized dose adjustments should be made under close monitoring for patients with brain metastasis or receiving ultra-high-dose therapy. This study provides evidence-based guidance for the precise management of BTcP and has important reference value for future guideline updates and clinical practice.

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Disclosure of conflict of interest

None.

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