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CLINICAL TRIAL REPORT

Tegileridine versus Oliceridine for Acute Postoperative Pain Management in Patients After Minimally Invasive Esophagectomy: A Preliminary Randomized Controlled Trial

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Purpose: Tegileridine, a new highly selective biased μ-opioid receptor agonist, demonstrated a favorable profile in relief of moderate-to-severe pain, but comparative data with other μ-opioid receptor agonists are sparse. We aimed to compare the analgesic efficacy of tegileridine to oliceridine with morphine as the active control in patients undergoing minimally invasive esophagectomy (MIE).

Patients and Methods: We conducted a preliminary randomized trial involving patients having moderate-to-severe pain after MIE. Patients were randomized 2:2:1 to receive a loading dose of 0.75 mg tegileridine, 1.5 mg oliceridine, or 3 mg morphine, followed by a patient-controlled analgesia pump composed of the corresponding same agent over a 48-hour period. The primary endpoint was the time-weighted sum of the resting pain-intensity difference over 24 hours ($rSPID_{24h}$).

Results: A total of 75 patients were randomized and finally analyzed (n = 15 in morphine group, n = 30 in tegileridine and oliceridine groups). Neither the time-weighted $rSPID_{24h}$ nor motion-$SPID_{24h}$ ($mSPID_{24h}$) was statistically different among the three groups. The numerical rating pain scale (NRS) at rest or during movement was significantly less in patients receiving tegileridine compared to oliceridine ($P < 0.01$) within postoperative 48 hours, and there was no statistical significance between tegileridine and morphine ($P > 0.05$). The sum of total pain relief demonstrated a similar tendency that morphine and tegileridine were better than oliceridine at postoperative 24h ($P = 0.057$) and 48h ($P = 0.033$).

Conclusion: Tegileridine showed comparable or slightly superior analgesic efficacy to oliceridine for moderate-to-severe pain following MIE. These findings support that tegileridine may provide promising profiles for postoperative pain management.

Keywords: thoracic surgery, acute pain, postoperative analgesia, biased μ-opioid receptor agonist, opioid-related adverse events

Introduction

Driven by surgical and technological innovation, minimally invasive esophagectomy (MIE) gains increasing popularity and has been considered as the standard of care for patients with oesophageal cancer over the last decades.[1] MIE is associated with less postoperative pain when compared to open surgery,[2] but substantial pain still exists in the light of the comprehensive trauma from thoracoscopic, laparoscopic and cervical incisions.[3] Although most patients were given patient-controlled intravenous analgesia (PCIA), more than 50% of patients after esophagectomy still have moderate to severe resting pain in the postanaesthesia care unit.[4] Another recent study confirmed that the acute pain after MIE was perhaps underestimated and the mean numerical pain scores could reach to 6.03 on the first postoperative day and sustained at 4.75 on the second postoperative day.[5] Adequate postoperative pain management is thus essential to facilitate patient recovery and reduce postoperative pulmonary complications after MIE.[6]

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Although epidural analgesia is the gold standard for postoperative pain management strategy in oesophageal cancer surgery,[7,8] epidural analgesia is still insufficient to treat acute pain in 45% of patients undergoing MIE[3] and may cause prolonged hypotension and procedure-related injuries. Thoracic paravertebral analgesia is a viable alternative to epidural analgesia and achieves comparable pain control with fewer side-effects such as hypotension,[9–11] but pain originating from the abdominal and cervical manipulations still deserves prompt treatment. Thus, based on thoracic paravertebral blockade, perioperative systemic analgesia may be warranted for effective management of postoperative pain in patients undergoing MIE.

Opioids are the principal systemic analgesics for the management of moderate to severe pain in clinical settings. These mu-opioid receptor agonists relieve pain through mediating Gi/o proteins but may contribute to opioid-induced side effects by activating β-arrestin2 signaling pathways.[12,13] Theoretically, biased μ-opioid receptor (MOR) agonists can exert a favorable profile by selectively activating G protein-coupled receptor signaling while minimizing β-arrestin-2 activation. Oliceridine and tegileridine (also known as SHR8554) are two novel G protein-biased μ-opioid receptor agonists currently under investigation for the management of acute pain in surgical patients.[14–16] The cumulative clinical evidence showed that oliceridine is an effective intravenous analgesic in patients with postoperative pain and appears to be associated with lower risk of nausea and vomiting.[14,16–20] Nonetheless, the published data from APOLLO-2 demonstrated that the gastrointestinal adverse events increased in a dose-dependent manner across the single demanding doses of oliceridine (0.1 mg: 49.4%; 0.35 mg: 65.8%; 0.5 mg: 78.8%), which indicated that β-arrestin2 activation still existed in the application of oliceridine, especially in the moderate or larger dose.

Tegileridine is another novel μ-opioid receptor biased agonist and received its first approval in China for the treatment of moderate to severe pain in 2024. Tegileridine selectively activates the G-protein-coupled pathway, only weakly (nearly 10%) activates the β-arrestin2 pathway and has half-life of approximately 6–7 hours, which may exert potent analgesic efficacy with less respiratory depression and gastrointestinal dysfunction.[15] A Phase III clinical trial confirmed the postoperative analgesic efficacy of tegileridine compared to placebo, and the safety of tegileridine was comparable to morphine in patients undergoing orthopaedic surgery.[21] However, evidence remains limited regarding the analgesic profile of either agent in thoracic patients, and no comparative data between tegileridine and oliceridine have been reported to date. Herein, we aimed to compare the efficacy and safety of tegileridine and oliceridine with morphine as the active control in the management of acute pain following MIE.

Methods

Study Design

This was a single-centre, randomized, patient- and outcome-assessor-blinded trial conducted at Shanghai Chest Hospital. The study protocol was approved by the Institutional Review Board of Shanghai Chest Hospital (No. KS24057) on May 21, 2024. This trial was registered on ClinicalTrials.gov (NCT06458400; principal investigator, Yuwei Qiu; date of registration, June 13, 2024). Written informed consent was obtained from each patient the day before surgery. Our study complied with the Declaration of Helsinki.

Patients

Eligible patients were between 18 and 70 years old, regardless of gender, had an American Society of Anaesthesiologist physical status (ASA) of I–III, were scheduled for elective MIE under general anaesthesia, had a body mass index (BMI) between 18 kg/m^2 and 30 kg/m^2, and had a resting numerical rating pain scale (NRS) of ≥4 at any time within 4 hours after the end of surgery.

Patients were excluded if they had a history of difficult airway, severe respiratory depression with oxygen saturation <90%, or a history of acute bronchial asthma, or severe cardiovascular and cerebrovascular diseases, or had known or suspected gastrointestinal obstruction. Patients were also excluded for the following reasons: having chronic pain or taking any pain medications one month before the surgery; allergic to opioids; previous psychiatric disorders (such as schizophrenia, depression, etc.) or cognitive impairment; concurrent other somatic pain that may affect postoperative

pain assessment; inability to complete the pain assessment; a history of drug and/or alcohol abuse within 1 year before randomization; or current pregnancy or lactation.

Randomization and Masking

Patients and the outcome assessors who were not involved in clinical care were masked to group assignment. A set of computer-generated random numbers and group assignment were kept in sealed envelopes. After the outcome assessors confirmed patients' baseline resting NRS ≥4 in PACU at least twice in three minutes, the envelopes were then opened immediately.

The patients were then randomly allocated in a 2:2:1 ratio into one of three treatment groups: 1) tegileridine group: a loading dose of 0.75 mg administered via an infusion pump for about 10 minutes, followed by self-administration of 0.05 mg on demand via patient-controlled analgesia (PCA) after 30 minutes, with a lockout interval of 10 minutes; 2) oliceridine group: a loading dose of 1.5 mg, followed by 0.35 mg per PCA dose on demand after 10 minutes, with a lockout interval of 6 minutes; 3) or morphine group: a loading dose of 3 mg, followed by 1 mg per PCA dose on demand after 10 minutes, with and a lockout interval of 6 minutes. A research nurse was responsible for medication preparation after confirmation of the group assignment and all trial medications were identical in appearance and the volume of a single effective PCA pump compression was 1 mL. The outcome assessors thereafter were responsible for pain assessment within postoperative 48-hour period.

Protocol

None of the patients were given premedication. All eligible patients received total intravenous anaesthesia and multimodal pain management. General anaesthesia was induced with 0.5 μg/kg sufentanil and a target-controlled infusion of propofol set to a plasma concentration of 4 μg/mL. Rocuronium (0.9 mg/kg) was administered to facilitate single-lumen tube intubation. After anesthesia induction, patients were positioned in the left semi-prone position and paravertebral blocks were performed at the T5, T6 and T7 vertebral levels. Using an in-plane approach, 20 mL of 0.5% ropivacaine was injected with 5–7 mL at each vertebral level.

Intraoperative propofol and remifentanil administration were adjusted to maintain a Bispectral Index between 40 and 50 and a surgical pleth index below 50. Sufentanil (0.1–0.2ug/kg) was added as clinically indicated. Rocuronium was infused at 0.6 mg/kg/hour per clinical request until 30 minutes before the end of surgery.

For the prophylaxis of postoperative nausea and vomiting (PONV), a single dose of dexamethasone (5 mg) was administered at the anaesthesia induction and 12.5 mg of dolasetron was injected intravenously at skin closures.

After surgery, patients were transferred to the PACU for extubation. When the resting pain scores were observed to be ≥4 at any time within the four hours after surgery, patients were then immediately randomized and given the corresponding assignment PCA.

Patients were allowed to use the PCA pump for up to 48 h (± 5 minutes) and received the same rescue analgesia regimen. After completion of the loading dose infusion of the investigational drug, if the investigator determined that the patient's NRS was ≥4 in PACU or surgical ward, then rescue analgesics were administered with an initial 40 mg of parecoxib sodium injection, followed by an additional 40 mg every 6 hours as needed, with a total daily dose not exceeding 80 mg. If the cumulative dose of parecoxib sodium reached the maximum dose, or the patient's analgesic needs still could not be met, other rescue analgesic strategies including other opioids were adopted. If the patients had postoperative nausea and vomiting, 12.5 mg of dolasetron was given intravenously as needed.

Assessments and Outcomes

Pain intensity, pain relief and opioid-related adverse events (ORADEs)[22] were monitored and recorded within postoperative 48 hours.

Pain intensity was assessed using the NRS score, ranging from 0 ("no pain") on the left end of the scale to 10 ("worst pain imaginable") on the right end.[23] After completing the infusion of the loading dose, NRS scores at rest and during movement were assessed by the investigator at 10 minutes (±1 minute), 30 minutes (±5 minutes), 6 hours, 12 hours, 24 hours and 48 hours. When the NRS score was assessed, the investigator simultaneously guided patients to assess the

degree of pain relief using total pain relief (TOTPAR). TOTPAR is a validated pain assessment tool that reflects pain relief using a five-point categorical scale.[24,25] Patients were asked after administering trial medication at predefined time points: "How much relief have you had since your starting pain?" with the following response choices: none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.[24] For ORADEs, we observed and recorded PONV and respiratory depression as the most common events. Respiratory depression was defined as the respiratory rate less than 8 breaths·min^{-1} and/or SpO_2< 90%.[26] Within 30 minutes after stopping the PCA pump at 48 hours (±5 minutes), both the patients and the outcome assessors independently completed the analgesic satisfaction score.

The primary outcome was the time-weighted sum of the resting pain-intensity difference (rSPID) within 24 hours ($rSPID_{24h}$) after administration of the loading dose. The SPID was calculated as the sum of the absolute difference in pain intensity over a specific period based on a recent clinical trial,[21] and $SPID_{24h}$ was calculated the difference in pain intensity as measured by NRS scores at each time point as compared with baseline. A higher absolute SPID means greater pain relief.[27]

The secondary outcomes included pain intensity at rest and during movement at 10 minutes, 30 minutes, 6 hours, 12 hours, 12–24 hours and 24 hours after surgery; time to first rescue analgesia; frequency and cumulative dose of rescue analgesics; and the number of effective and total presses of PCA within postoperative 24 hours. The rSPID, motion-SPID (mSPID), the sum of total pain relief (TOTPAR) over 10 minutes, 30 minutes, 6 hours, 12 hours, 12–24 hours and 24 hours ($rSPID_{10min}$, $rSPID_{30min}$, $rSPID_{6h}$, $rSPID_{12h}$, $rSPID_{12\text{-}24h}$; $mSPID_{10min}$, $mSPID_{30min}$, $mSPID_{6h}$, $mSPID_{12h}$, $mSPID_{12\text{-}24h}$, $mSPID_{24h}$; $TOTPAR_{10min}$, $TOTPAR_{30min}$, $TOTPAR_{6h}$, $TOTPAR_{12h}$, $TOTPAR_{12\text{-}24h}$, $TOTPAR_{24h}$) was also recorded. The sum of TOTPAR was calculated using the formula: $TOTPAR_t = \Sigma[PRt^* (TIME_t\text{-}TIME_{t\text{-}1})](h)$ at each predefined TOTPAR period of assessment.[24] The length of stay from the end of surgery to discharge was also assessed.

Statistical Analysis

There was no previous data on the rSPID difference between tegileridine and oliceridine, we thus conducted a preliminary trial to compare the analgesic efficacy between these two biased MOR agonists without conducting a formal sample size calculation. For a continuous outcome, 12 to 35 patients per group are typically enrolled in preliminary studies.[28] Accordingly, with a 2:2:1 allocation ratio among the three groups, 30 patients were enrolled in the tegileridine group, 30 in the oliceridine group, and 15 in the morphine group in this study.

SAS 9.4 and R4.3.2 statistical software was used for statistical analysis. Baseline data and efficacy parameters were analyzed based on the intention-to-treat population. Missing efficacy data were filled by the last observation carried forward (LOCF) method, that is, the case data that failed to observe the whole treatment process were transferred with the last observation data to the final results of the trial. The incidence of adverse reactions was calculated with the safety analysis population as the denominator.

For the primary and secondary analyses, we compared the differences in $rSPID_{24}$ and $mSPID_{24}$ among the three groups using analysis of covariance, with the baseline NRS as a covariate for adjustment. The differences in rSPID and mSPID at other time points and pain intensity were also analyzed using analysis of covariance and have included the full CONSORT flow diagram as Figure 1 to ensure full compliance with CONSORT guidelines. Pain scales among the three groups were compared using repeated measures ANOVA. The time to first rescue analgesia was compared using the Log rank test. The incidence of PONV was compared using the Chi-square test or Fisher's exact test.

Results

From June, 2024 to September, 2024, 90 patients were screened for eligibility, of whom 75 eligible patients were randomly assigned to receive either tegileridine (n = 30), oliceridine (n = 30), or morphine (n = 15). All enrolled patients received at least one dose of allocated treatment, completed follow-up, and were included in the efficacy and safety analysis populations (Figure 1). Baseline demographics, surgical and anesthesia data were comparable among the three groups (Table 1).

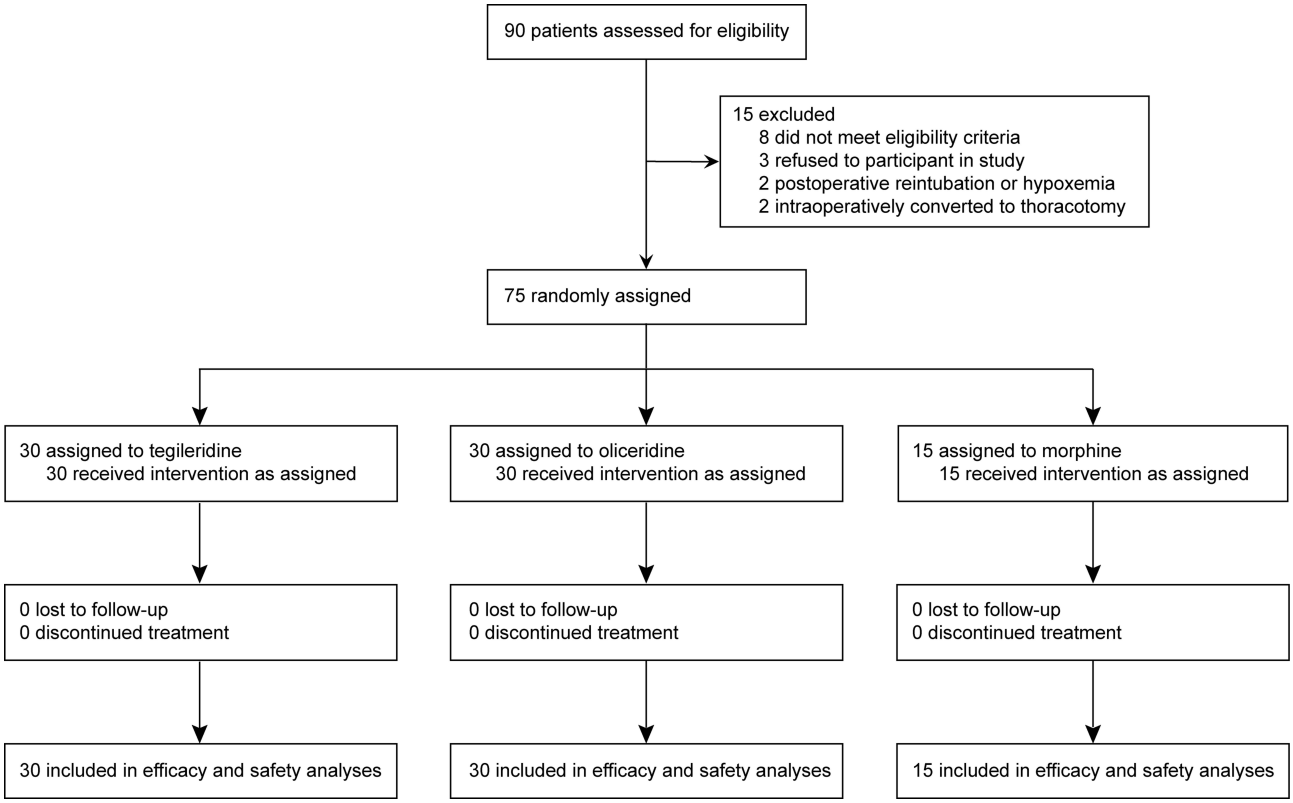

Figure 1 Trial profile.

The baseline resting and motion NRS before randomization were comparable among the three groups ($P = 0.252$ and $P = 0.259$, respectively; Table 2). After adjustment for baseline NRS, the $rSPID_{24h}$ was −55.93 ± 6.62 in the oliceridine group and −71.12 ± 6.60 in the tegileridine group (mean difference of tegileridine-oliceridine: −14.33, 95% CI: −33.96 to

Table 1 Characteristics, Surgical and Anaesthesia Data

Variables	Morphine Group (n = 15)	Oliceridine Group (n = 30)	Tegileridine Group (n = 30)	*P* value
Age, years	58 ± 11	63 ± 5	60 ± 8	0.093
Sex, male	14 (93.3%)	24 (80.0%)	25 (83.3%)	0.512
ASA				0.692
II	7 (46.7%)	11 (36.7%)	14 (46.7%)	
III	8 (53.3%)	19 (63.3%)	16 (53.3%)	
Smoking status				0.485
Never	2 (13.3%)	9 (30.0%)	9 (32.1%)	
Former	13 (86.7%)	20 (66.7%)	19 (67.9%)	
Current smokers	0 (0.0%)	1 (3.3%)	0 (0.0%)	
Alcohol status				0.476
Never	8 (53.3%)	15 (50.0%)	12 (42.9%)	
Former	7 (46.7%)	15 (50.0%)	14 (50.0%)	
Current drinkers	0 (0.0%)	0 (0.0%)	2 (7.1%)	
Height, cm	168.00 ± 8.59	168.63 ± 7.97	168.03 ± 7.84	0.949
Weight, kg	64.87 ± 10.00	64.91 ± 12.46	64.32 ± 8.74	0.974
BMI, kg/m^2	22.51 ± 2.63	22.72 ± 3.04	22.81 ± 2.98	0.949

(*Continued*)

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Table 1 (Continued).

Variables	Morphine Group (n = 15)	Oliceridine Group (n = 30)	Tegileridine Group (n = 30)	*P* value
Diabetes	0 (0.0%)	3 (10.0%)	5 (16.7%)	0.230
Hypertension	2 (13.3%)	3 (10.0%)	9 (30.0%)	0.116
Duration of surgery, hours	4.11 ± 0.88	4.08 ± 0.62	4.18 ± 0.80	0.902
Propofol administration, mg	1419 ± 250	1381 ± 391	1430 ± 326	0.546
Sufentanil, μg	64.33 ± 14.38	55.97 ± 16.02	62.83 ± 13.81	0.126
Remifentanil, μg	2085.71 ± 729.44	1894.67 ± 718.06	2120.00 ± 1024.66	0.680
Intraoperative fluid, mL	1840.00 ± 331.23	2025.86 ± 330.75	1998.33 ± 278.07	0.360

Note: Data are mean ± standard deviation or n (%).
Abbreviation: ASA, American Society of Anaesthesiologist; BMI, Body mass index

Table 2 Overall Comparison of Primary Outcome, Secondary Outcomes, Key Outcomes and Adverse Events Among the Three Groups

Variables	Morphine Group (n = 15)	Oliceridine Group (n = 30)	Tegileridine Group (n = 30)	*P* value
Baseline pain				
Resting NRS, mean ± sd	6.73 ± 1.49	7.23 ± 1.89	6.47 ± 1.81	0.252
Motion NRS, mean ± sd	6.93 ± 1.44	7.30 ± 1.88	6.53 ± 1.85	0.259
Primary outcome				
$rSPID_{24h}$ after adjustment for the baseline NRS, mean ± sd	−75.65 ± 9.26	−55.93 ± 6.62	−71.12 ± 6.60	0.147
Secondary outcomes				
$mSPID_{24h}$ after adjustment for the baseline NRS, mean ± sd	−53.25 ± 9.14	−31.28 ± 6.53	−43.81 ± 6.53	0.132
Percentage of rescue analgesics use within 24 hours, n (100%)	10 (66.7%)	19 (63.3%)	20 (66.7%)	0.957
Time to first use of rescue analgesia, hours, median (95% CI)	19.4 (95% CI: 0.7 to NA)	9.4 (95% CI: 0.7 to NA)	9.8 (95% CI: 3.0 to NA)	0.913
Total presses of PCA within 24 hours, median (Q1, Q3)	8 (2,16)	6 (3,26)	5 (2,17)	0.831
The number of effective presses of PCA within 24 hours median (Q1, Q3)	6(2,14)	6 (3,22)	4 (2,16)	0.847
Patients' satisfaction score, median (Q1, Q3)	5 (4,6)	5 (4,7)	5 (4.5,7.5)	0.559
Key outcomes and adverse events				
Investigators' satisfaction score, median (Q1, Q3)	5 (4.5,6.0)	5 (4,8)	6(5,8)	0.499
TOTPAR24h, median (Q1, Q3)	48.00 (18.50,53.33)	24.75 (18.00,36.50)	33.25 (23.75,47.88)	0.057
TOTPAR48h, median (Q1, Q3)	85.50 (48.33,120.00)	66.50 (48.21,93.17)	87.67 (64.92, 119.50)	0.033*
The incidence of PONV within 24 hours, n (%)	1 (6.7%)	4 (13.3%)	0 (0.0%)	0.117
The incidence of respiratory depression within 24 hours, n (%)	0	0	0	Not applicable

Notes: Data are mean ± standard deviation, n (%), median [Quartile 1, Quartile 3] or median (95% CI). SPID: the time-weighted sum of the pain-intensity difference. The SPID was adjusted with the baseline parameters. SPID24h was analyzed after adjusting for the baseline pain parameters. Baseline pain was measured as the pain intensity after patients were transferred into PACU.
Abbreviations: NRS, numerical rating pain scale; rSPID, resting SPID; mSPID, motion SPID; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting; TOTPAR, total pain relief.

5.30, $P = 0.149$, Table 3). Two participants had missing values at two time points during the follow up, therefore we performed sensitivity analysis to deal with the missing data using the dataset without imputation (Table R-1), and the results remained consistent with the main findings. We also performed additional regression analyses adjusting for resting $SPID_{24h}$, including age, sex, ASA physical status, and BMI. The adjusted results were consistent with our primary findings, indicating that these covariates did not materially influence the treatment effects (Table R-2).

Similarly, the adjusted $mSPID_{24h}$ was −31.28 ± 6.53 in the oliceridine group and −43.81 ± 6.53 in the tegileridine group (mean difference of tegileridine-oliceridine: −11.75, 95% CI: −30.76 to 7.26, $P = 0.221$, Table 3). The $rSPID_{48h}$ after adjustment was −183.71 ± 12.28 in the tegileridine group compared to −143.14 ± 12.31 in the oliceridine group ($P = 0.024$, Table 4) and the $mSPID_{48h}$ was −118.07 ± 12.06 in the tegileridine group compared to −84.38 ± 12.05 in the oliceridine group ($P = 0.054$, Table 4).

Table 3 Comparisons Between Oliceridine and Tegileridine

Variables	Oliceridine (n = 30)	Tegileridine (n = 30)	*Mean Difference (Tegileridine - Oliceridine) (95% CI)*	*P* value
Baseline pain				
Resting NRS, mean ± sd	7.23 ± 1.89	6.47 ± 1.81	−0.77 (−1.73 to 0.20)	0.114
Motion NRS, mean ± sd	7.30 ± 1.88	6.53 ± 1.85	−0.77 (−1.73 to 0.20)	0.117
Primary outcome				
$rSPID_{24h}$ after adjustment for the baseline NRS, mean ± sd	−55.93 ± 6.62	−71.12 ± 6.60	−14.33 (−33.96 to 5.30)	0.149
Secondary outcomes				
$mSPID_{24h}$ after adjustment for the baseline NRS, mean ± sd	−31.28 ± 6.53	−43.81 ± 6.53	−11.75 (−30.76 to 7.26)	0.221
Percentage of rescue analgesics use within 24 hours, n (%)	19 (63.3%)	20 (66.7%)	Risk difference = 0.03 (−0.21 to 0.27)	0.787
Time to first use of rescue analgesia, hours	9.4 (95% CI: 0.7 to NA)	9.8 (95% CI: 3.0 to NA)	Hazard ratio = 0.98 (0.52 to 1.85)	0.947
Total presses of PCA within 24 hours, median, 95% CI	6(3 to 25)	5 (2 to 14)	Location shift = −1 (−5 to 2)	0.640
The number of effective presses of PCA within 24 hours, median, 95% CI	6 (3 to 22)	4 (2 to 14)	Location shift = 1 (−4 to 2)	0.640
The incidence of PONV within 24 hours, n (%)	4 (13.3%)	0 (0.0%)	Risk difference = −0.13 (−0.30 to 0.01)	0.112
The incidence of respiratory depression within 24 hours, n (%)	0(0%)	0(0%)	Risk difference = 0.00 (−0.12 to 0.12)	1.000
$TOTPAR_{24h,}$ mean ± sd	28.05 ± 13.95	33.74 ± 14.70	5.70 (−1.85 to13.25)	0.136
$TOTPAR_{48h,}$ mean ± sd	69.19 ± 29.96	90.54 ± 30.29[c]	21.35 (5.49 to 37.22)	0.009[#]
Patients' satisfaction score, median (95% CI)	5(4 to 7)	5(5 to 7)	Location shift = 0 (−2 to 1)	0.417
Investigators' satisfaction score, median (95% CI)	5(4 to 8)	6(5 to 8)	Location shift = 0 (−1 to 1)	0.398

Notes: *Hazard ratio estimated by the Cox regression; Location shift was estimated by the Hodges-Lehmann estimation with Moses confidence interval; confidence interval for risk difference was estimated by using the Newcombe hybrid-score method. [#] Denote statistical significance of 0.01. The time to first rescue analgesia was compared using the Log rank test.

Table 4 SPID and Pain Relief Outcomes

Variables	Morphine Group (n = 15)	Oliceridine Group (n = 30)	Tegileridine Group (n = 30)	*P* value
SPID				
$rSPID_{10min}$	−0.23 ± 0.07	−0.26 ± 0.05	−0.28 ± 0.05	0.810
$rSPID_{30min}$	−1.15 ± 0.21	−1.07 ± 0.15	−1.25 ± 0.15	0.721
$rSPID_{6h}$	−13.93 ± 3.00	−11.25 ± 2.15	−13.46 ± 2.14	0.694
$rSPID_{12h}$	−29.13 ± 5.28	−23.93 ± 3.77	−28.79 ± 3.76	0.599
$rSPID_{12\text{-}24h}$	−46.52 ± 5.86	−32.01 ± 4.19[b]	−42.33 ± 4.18	0.089
$rSPID_{48h}$	−175.27 ± 17.23	−143.14 ± 12.31	−183.71 ± 12.28[c]	0.064
$mSPID_{10min}$	−0.23 ± 0.07	−0.22 ± 0.05	−0.25 ± 0.05	0.931
$mSPID_{30min}$	−1.10 ± 0.21	−0.93 ± 0.15	−1.07 ± 0.15	0.744
$mSPID_{6h}$	−9.85 ± 2.95	−7.52 ± 2.11	−10.26 ± 2.11	0.634
$mSPID_{12h}$	−19.79 ± 5.39	−16.79 ± 3.85	−21.03 ± 3.85	0.736
$mSPID_{12\text{-}24h}$	−33.46 ± 5.42	−14.49 ± 3.87[b]	−22.78 ± 3.87	0.020[a]
$mSPID_{48h}$	−121.73 ± 16.89	−84.38 ± 12.05	−118.07 ± 12.06	0.089
Pain relief parameters				
$TOTPAR_{10min}$	0.14 ± 0.15	0.16 ± 0.13	0.17 ± 0.13	0.805
$TOTPAR_{30min}$	0.70 ± 0.36	0.63 ± 0.37	0.73 ± 0.36	0.593
$TOTPAR_{6h}$	8.03 ± 5.77	5.75 ± 4.01	7.14 ± 4.37	0.252

(*Continued*)

Table 4 (Continued).

Variables	Morphine Group (n = 15)	Oliceridine Group (n = 30)	Tegileridine Group (n = 30)	*P* value
$TOTPAR_{12h}$	15.63 ± 8.56	12.17 ± 7.51	14.54 ± 6.88	0.282
$TOTPAR_{24h}$	39.63 ± 17.72	28.05 ± 13.95	33.74 ± 14.70	0.057
$TOTPAR_{48h}$	84.43 ± 33.51	69.19 ± 29.96	90.54 ± 30.29[c]	0.033[a]
Total pressing times of PCA within 48 hours	11	16	18	0.181
The number of effective presses of PCA within 48 hours	9	16	16	0.105

Notes: Data are mean ± standard deviation. The SPID was adjusted with the baseline parameters. [a]Denote statistical significance among the three groups ($P < 0.05$). [b]Denote statistical significance compared to morphine group. [c]Denote statistical significance compared to oliceridine group. Larger SPID and TOTPAR means better pain control.

Abbreviations: SPID, Summed Pain Intensity Difference; rSPID, resting SPID; mSPID, motion SPID; TOTPAR, the sum of total pain relief.

Pain scores at rest or during movement showed significant statistical differences among the three groups within postoperative 48 hours (Resting NRS: $P = 0.001$ and motion NRS: $P < 0.001$, Figure 2). No interaction was found between interventions and time on pain intensity (all interaction P values >0.50). Compared to the oliceridine group, patients endured less pain in tegileridine group ($P = 0.002$ at rest and $P < 0.001$ during movement) within postoperative 48 hours (Figure 2), and there was no statistical significance between tegileridine and morphine ($P > 0.05$). The sum of TOTPAR scores also demonstrated a better tendency of pain relief in the morphine and tegileridine groups than in the oliceridine group at both postoperative 24 hours and 48 hours (Table 3).

Within postoperative 48 hours, there were no significant differences among the three groups in the proportion of rescue analgesia ($P = 0.957$), time to first rescue analgesia ($P = 0.913$), and the number of effective and total presses of PCA ($P = 0.831$ and $P = 0.847$), as shown in Table 4. None of the patients in the tegileridine group experienced PONV within postoperative 24 hours, compared to 6.7% (1/15) in the morphine group and 13.3% (4/30) in the oliceridine group

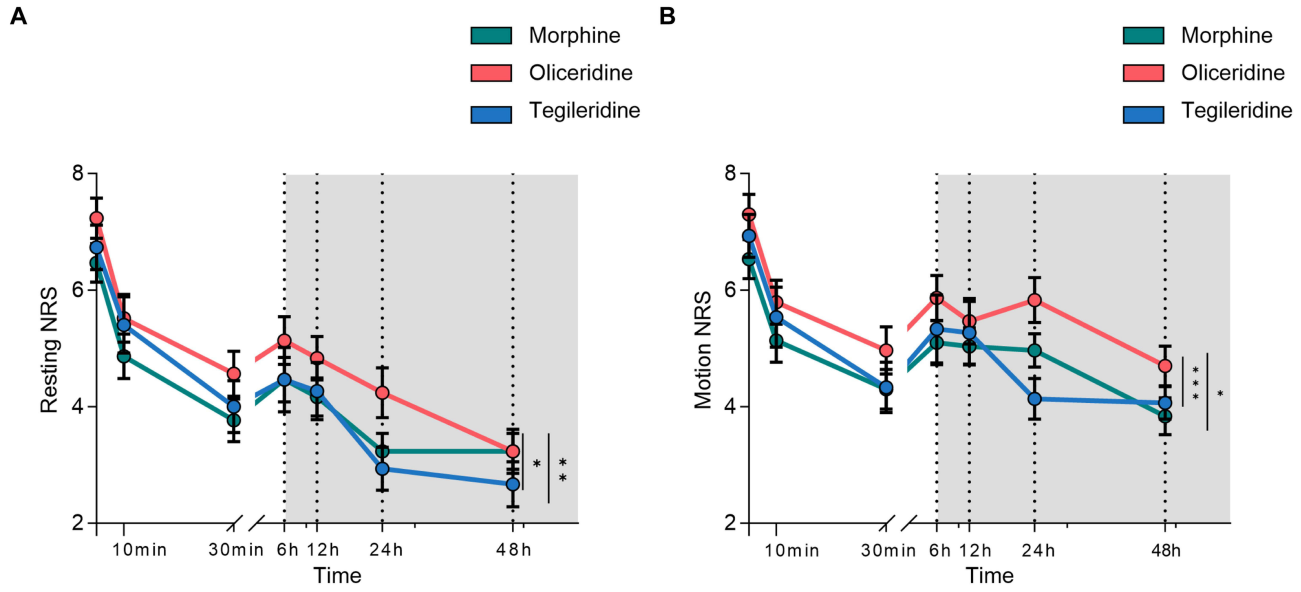

Figure 2 Comparisons of pain scores at rest or during movement over 48 hours among morphine group, oliceridine group and tegileridine group after minimally invasive esophagectomies. (**A**) Resting NRS score. *Denote statistical significance between morphine and oliceridine groups ($P < 0.05$) and **Denote statistical significance between tegileridine and oliceridine group ($P < 0.01$). (**B**) Motion NRS score. *Denote statistical significance between tegileridine and oliceridine groups ($P < 0.05$) and ***Denote statistical significance between morphine and oliceridine groups ($P < 0.001$). No interaction was found between intervention and time on pain outcomes (all interaction *P* values >0.50) in a linear mixed effects model.

Abbreviation: NRS, numerical rating pain scale.

($P = 0.117$, Table 2). Neither the patients' satisfactory score nor investigators' satisfactory score was detected statistically different among the three groups ($P = 0.559$ and $P = 0.499$, Table 2).

Respiratory depression and PONV were the most concerned ORADEs in thoracic populations. None of the patients experienced PONV within 48 hours postoperatively, nor did any develop respiratory depression within 48 hours after surgery among these three groups because all of the patients were given oxygen pretreatment via oxygen mask through the whole follow-up window.

Discussion

This randomized, patient-and-outcome assessor-blinded, controlled trial firstly compared the use of tegileridine and oliceridine for PCA after minimally invasive esophagectomy. No statistically significant difference was found between tegileridine and oliceridine in the sum of either resting or movement-evoked pain scores within postoperative 24 hours. Compared to oliceridine, patients had lower resting pain scores and movement-evoked pain scores in tegileridine group within postoperative 48 hours. Considering that both the pain scores and total pain relief are important pain assessment tools for acute pain management, our data indicated that tegileridine demonstrated comparable or slightly better pain relief compared to oliceridine within postoperative 48 hours. Along with pain relief, tegileridine showed a promising feature in the incidence of PONV among the three groups, which need larger trials to validate in the near future.

In this preliminary trial, all the patients received standard anesthesia and analgesia regime during and after MIE, and we did the primary efficacy analysis after adjustment of the baseline pain intensity, therefore we had some strength to compare these investigating drugs. We chose $SPID_{24h}$, the time-weighted sum of the pain-intensity difference within postoperative 24 hours, as the primary efficacy end point, because $SPID_{24h}$ represented the summing effects of pain relief within the time elapsed. After the initial loading dose, we did not detect the statistical difference of $SPID_{24h}$ between tegileridine or oliceridine. The challenge here and in many clinical trials is how to interpret results that suggest a clinically meaningful benefit but are not statistically significant. The first is whether the observed treatment effect is actually clinically meaningful. In this case, the answer is clearly yes: a nearly 40% improvement in the $SPID_{24h}$ and $TOTPAR_{24–48h}$ is highly meaningful in which the best cut-off point of adequate pain relief for both the % Max TOTPAR and the PID% over 60 min was 33%.[25] Moreover, the pain intensity curve showed a significant reduction between oliceridine and tegileridine demonstrated the potential benefit of tegileridine. Secondly, we need to consider how well the trial was powered. Because we conducted a preliminary trial, the post-hoc power estimate of 0.233 might restrict the results to be statistical significance. An appropriately powered purpose-designed trial thus would presumably have enrolled considerably more patients.

The benefits of tegileridine may be related to its pharmacokinetics profile. Based on our findings, tegileridine took effect after 10-minutes infusion of the loading dose, and further reduced the pain intensity after 30 minutes. Six hours after administration of the loading dose of tegileridine 0.75 mg followed by tegileridine 0.05 mg per PCA dose, the resting pain intensity of all the patients reduced to below an NRS score of 4 and maintained constantly until the end of postoperative 48-hour period. Clinical trials have revealed that tegileridine has a half-life of approximately 6–7 hours, whereas oliceridine has a half-life of only 1–3 hours.[21] The pharmacokinetics profile indicated that tegileridine might provide a more durable analgesic effect within a safe and controllable framework as a viable option, which is evidenced by significant improvement in $rSPID_{48h}$.

Optimal pain relief requires a balance between adequate analgesia and the risk of adverse effects. Although several post-hoc analyses from the APOLLO-2 and ATHENA trials reported that oliceridine was associated with fewer gastrointestinal complications compared to morphine,[14,29,30] we did not observe this benefit in our trial. In APOLLO-2, female patients constituted a much higher proportion (nearly 100%) and the very young age (mean age of 42 years old) lead to high risk of postoperative nausea (74.4% in morphine group versus 62% in 0.35 mg oliceridine). Similarly, the ATHENA trials included more than 70% patients with Apfel score ≥3. Contrary to APOLLO-2 and ATHENA, we included the patients at low risk of PONV, the limited PONV events and sample size may partly account for the inconsistent result. Even though our sample was relatively small, the results still showed a clinically meaningful difference in PONV between oliceridine (13.3%) and tegileridine (0%). Notably, we enrolled only patients undergoing esophagectomy who were not at high risk for PONV, the benefit of tegileridine should thus be validated in patients at

moderate-to-high risk of PONV. Notably, the zero incidence of respiratory depression across all treatment groups indicates that this study lacked sufficient data to characterize potential differences in respiratory safety between novel and conventional opioid analgesics.

This study has several limitations. Firstly, the sample size was small (post-hoc power estimate of 0.233) and there was a lack of a pre-specified statistical analysis plan, which indicated the findings should be interpreted more cautiously and warranted large trials to confirm. Tegileridine and oliceridine are the only two innovative agents with biased agonism mechanisms that have been approved and marketed in recent years. Due to limited drug accessibility, no head-to-head studies have yet compared the efficacy and safety of these two agents. This study observed trends in the differences in efficacy and safety between the two drugs and an active comparator, although these differences were not statistically significant. Naturally, these findings warrant further validation in larger confirmatory clinical trials. Secondly, as newly approved agents in China, the conservative dosing regimens for tegileridine and oliceridine were employed in this study, falling short of the maximum doses recommended by their respective prescribing information. As a result, the results of this study only reflect the efficacy and safety profiles of these two agents in comparison to morphine at the specific dosages administered and dose-escalation studies or comparisons were needed. Thirdly, this study only focused on patients receiving minimal invasive esophagectomy in a high-thoracic-volume center. The single-center design and single thoracic type limited external validity. Future directions should be focused on more general populations. Finally, due to the majority of included patients at low risk of PONV, our results thus should be interpreted more cautious.

In conclusion, our study found that tegileridine showed comparable or even slightly better analgesic efficacy to oliceridine for acute pain following minimally invasive esophagectomy. Tegileridine may provide promising profiles for postoperative pain management in thoracic patients. Based on the limited sample size and exploratory nature of design, further large-scale, confirmatory trials are warranted to elucidate the differences in efficacy and safety between tegileridine and oliceridine.

Data Sharing Statement

Deidentified data are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Shanghai Chest Hospital (No. KS24057), and written informed consent was obtained from all patients.

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Disclosure

The authors declare no competing interests.

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