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ORIGINAL RESEARCH

Evaluating the Opioid-Related Adverse Events of Oliceridine Versus Conventional Opioids in Patient-Controlled Analgesia After Thoracoscopic Lung Resection: A Retrospective Cohort Study

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Background: Oliceridine, a novel biased mu-opioid receptor agonist, provides analgesia comparable to morphine but with a potentially improved side effect profile. However, the comparative incidence of opioid-related adverse events (ORADEs) in patient-controlled intravenous analgesia (PCIA) remains understudied. This study aims to elucidate the differences in ORADE rates between oliceridine and conventional opioids in PCIA.

Methods: We conducted a population-based retrospective cohort study at Shanghai Chest Hospital, analyzing linked healthcare data. Propensity score matching (PSM) addressed selection bias. The study included patients who received PCIA with either oliceridine or conventional opioids (sufentanil, hydromorphone and oxycodone) after thoracoscopic lung resection from January 2024 to June 2024. ORADEs assessed included postoperative nausea and vomiting (PONV), urinary retention, and opioid-induced respiratory depression (OIRD). Demographics, clinical characteristics, and outcomes within the first 24 hours post-surgery were collected.

Results: From 8208 eligible patients, 3171 received oliceridine and 5037 received conventional opioids. After PSM, 2803 matched pairs were analyzed, with similar demographics and morphine equivalent doses between groups. The incidence of ORADEs was significantly lower in the oliceridine group compared to the conventional opioids group, with rates of 24.30% versus 27.83% ($P < 0.01$). Specifically, the oliceridine group had a reduced likelihood of PONV (15.45% vs 19.73%; Relative Risk [RR], 0.78; 95% confidence interval [CI] 0.70–0.88; $P < 0.001$). No significant differences were found in OIRD or urinary retention rates.

Conclusion: Oliceridine use in PCIA was associated with a lower incidence of ORADEs, primarily driven by reduced PONV, compared to conventional opioids. These findings suggest oliceridine may be a safer alternative for postoperative pain management, warranting confirmation in larger prospective randomized trials. This study is among the first to provide a comprehensive comparative analysis of ORADEs between oliceridine and conventional opioids in a real-world PCIA setting, offering valuable insights into optimizing postoperative pain management strategies.

Keywords: oliceridine, patient-controlled intravenous analgesia (PCIA), opioid-related adverse events (ORADEs), postoperative nausea and vomiting (PONV)

Introduction

Traditional opioids, such as morphine, fentanyl, and oxycodone, remain widely used in clinical practice for managing moderate to severe postoperative pain. However, the prevalence of opioid-related adverse events (ORADEs) poses a significant clinical challenge that necessitates urgent attention. These adverse events, which can range from mild to severe, include respiratory depression, gastrointestinal disturbances, and increased healthcare costs. Studies have shown that ORADE rates can be as high as 23.92%, with 5.9% to 6.5% of patients potentially becoming long-term opioid users

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following surgery.[1–4] Additionally, there is a growing interest in opioid-free anesthesia due to concerns about opioid-related adverse effects.[5] This highlights the need for novel opioid formulations that can effectively reduce ORADEs while maintaining analgesic efficacy.

Oliceridine, a next-generation μ-opioid receptor agonist, has emerged as a promising candidate in this regard. Unlike traditional opioids, which activate both the G-protein-dependent and β-arrestin pathways, oliceridine selectively targets the G-protein pathway. This pathway is primarily responsible for mediating analgesia and sedation, while the β-arrestin pathway is associated with adverse effects such as respiratory depression, gastrointestinal dysfunction, and drug tolerance. By focusing on the G-protein pathway and minimizing β-arrestin activation, oliceridine acts as a biased μ-receptor agonist, potentially offering effective pain relief with a reduced risk of ORADEs.[6–8]

Several clinical studies have explored the analgesic potential of oliceridine in various surgical settings, demonstrating its efficacy and improved safety profile compared to traditional opioids.[9–12] However, these studies often involve limited sample sizes and controlled environments, which may not fully capture the drug's performance in routine clinical practice. Furthermore, there is a lack of large-scale, real-world evidence to substantiate the benefits of oliceridine in reducing ORADEs across diverse patient populations.

Postoperative pain control after thoracoscopic surgery remains a critical challenge, as inadequate analgesia compromises respiratory function, delays recovery, and increases the risk of chronic postsurgical pain. Thoracoscopic procedures, despite their minimally invasive nature, often provoke intense acute pain due to pleural irritation, intercostal nerve trauma, and chest tube placement.[13,14] Traditional opioids, while effective, are limited by dose-dependent side effects such as respiratory depression, gastrointestinal disturbances, and sedation—complications that are particularly detrimental in thoracic surgery patients with preexisting cardiopulmonary vulnerabilities.

To address this gap, our study aims to evaluate the impact of oliceridine on ORADEs in a real-world clinical setting. This research is among the first to provide a comprehensive comparative analysis of ORADEs between oliceridine and conventional opioids in PCIA. By offering valuable insights into the practical application of oliceridine, this study seeks to inform and optimize postoperative pain management strategies, ultimately enhancing patient outcomes.

Methods

Study Design, Setting, and Participants

This study is a propensity score-matched, retrospective, observational, single-center cohort study conducted at Shanghai Chest Hospital. The study was approved by the Clinical Research Ethics Committee of Shanghai Chest Hospital (IS24138) and adhered to the Helsinki Declaration. The reporting of the cohort study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Due to the retrospective nature and anonymity of the data, the requirement for written informed consent was waived.

Setting and Participants

Electronic records of patients undergoing elective thoracoscopic-assisted lung resection and receiving PCIA from January 2024 to June 2024 were collected. Exclusion criteria included age less than 18; postoperative continuous mechanical ventilation or ICU admission with a tracheal tube; conversion to open surgery; thoracic day surgery or absence of PCIA, and inadequate postoperative follow-up information.

Anesthesia and Analgesia Techniques

The anesthetic management in both study groups was standardized in accordance with institutional protocols. All enrolled patients received either general anesthesia (GA) alone or GA combined with ultrasound-guided thoracic paravertebral block (TPVB). TPVB were single-shot, administered pre-incision under ultrasound guidance, injecting 20 mL of 0.5% ropivacaine at T3–T7. Anesthesia was induced with: propofol (2.0–2.5 mg/kg) or remimazolam besylate (0.3–0.4 mg/kg), sufentanil (0.4–0.6 μg/kg), rocuronium bromide (0.6–0.9 mg/kg). Double-lumen bronchial catheter or single-lumen tracheal tube with bronchial blocker was placed under adequate neuromuscular blockade and bispectral index (BIS) values maintained at 40–60. Anesthesia Maintenance: Continuous infusion of Propofol (2–6 mg/kg/h) or remimazolam besylate (1–3 mg/kg/h) titrated to maintain BIS 40–60. Remifentanil (0.05–0.15 μg/kg/min) administered

via target-controlled infusion, with supplemental boluses of sufentanil (5–10 μg) and rocuronium bromide (0.1–0.2 mg/kg) as clinically indicated. All patients received sugammadex (4 mg/kg) until TOF ratio ≥0.9 in PACU. All patients received PCIA for postoperative pain management. The solution of the electronic analgesia pump was a mixture of the following agents: opioid agents, dexamethasone and/or dolasetron. The selection and dosing of opioid analgesics (sufentanil, hydromorphone, oxycodone or oliceridine) are guided by the clinical expertise of anesthesiologists. The background continuous rate was 2 mL/h, and the bolus dose was 2 mL with a 15-min lockout interval.

Data Collection

Data were collected retrospectively from the postoperative anesthesia follow-up database and electronic medical records. Collected data included patient demographics, clinical characteristics, analgesic and antiemetic use in PCIA, incidence and type of ORADEs, and pain scores on the first postoperative day. Opioid formulations in PCIA were converted to morphine milligram equivalent doses for comparison.[15]

Outcome Variables

ORADEs included postoperative nausea and vomiting (PONV), urinary retention, and opioid-induced respiratory depression (OIRD). PONV was defined as nausea and vomiting within 24 hours post-surgery. Urinary retention was defined as the inability to urinate requiring catheterization. OIRD was defined as oxygen saturation below 90% for more than 5 min or hypercapnia with arterial carbon dioxide tension over 50 mmHg, requiring naloxone or nalmefene.[16,17]

Additional outcomes included the incidence of moderate-to-severe pain (NRS ≥4) within 24 hours postoperatively, NRS pain score, recovery time after anesthesia (from PACU admission to endotracheal tube removal), and PACU length-of-stay. Anesthesia-related complications such as allergy, reintubation within 6 hours, cardiac arrest within 24 hours, death within 24 hours, and neurological complications were also recorded.

Sample Size

In the ATHENA trial, oliceridine demonstrated a favorable safety profile, with common adverse reactions including nausea (31%), constipation (11%), and vomiting (10%).[12] At our center, the incidence of ORADEs was approximately 30.0%, with a postoperative nausea and vomiting (PONV) incidence of 20.0%, similar to the findings by Suzuki Y et al.[18]

Assuming a control event rate (CER) of 30% and a relative risk (RR) reduction of 20% with oliceridine, the incidence of ORADEs in this population would be reduced to 24% within the first 24 hours postoperatively. Based on this assumption, we estimated that a minimum of 1149 cases per group would be required to achieve 90% power, using a two-sided $\chi 2$ test to detect the primary outcome in the oliceridine group versus the traditional opioid group at a significance level of $P < 0.05$.

Considering a potential 15% data loss due to incomplete or cleaned data and the estimate that approximately one-third of patients would be excluded during the propensity score matching period, we calculated that we would need to initially include at least 2028 patients per group to ensure sufficient sample size for the final analysis.

To achieve this sample size, we retrospectively collected data from a six-month period. Given the retrospective nature of this study, the sample size was ultimately determined by the number of eligible patients available within this timeframe. We initially included 8208 patients who met the inclusion criteria. Propensity score matching was then performed to balance the covariates between the oliceridine and conventional opioid groups.

Bias and Confounding

Propensity scores were calculated using logistic regression models for the following covariates: demographics (age, gender, body mass index), duration of surgery, type of surgery, anesthesia-related factors (ASA classification, duration of anesthesia, type of anesthesia, morphine equivalents of analgesic medication in PCIA), and whether admission was to the ICU. Patients were matched 1:1 with their nearest neighbor based on the closest propensity score for each subject. A caliper size of 0.25 was used to avoid poor matches.

Statistical Analysis

Categorical data are presented as absolute numbers (percentages), while continuous data are presented as mean ± standard deviation (SD) for normally distributed variables or median with interquartile range (IQR) for non-normally distributed variables. Continuous variables were compared using a two-sample *t*-test for normally distributed data or a Wilcoxon rank-sum test for non-normally distributed data. In the propensity score-matched cohort, absolute standardized mean differences (SMDs) were calculated to assess the balance between groups before and after matching. An SMD value of ≤ 0.1 indicated a lack of meaningful imbalance. Relative risk (RR), 95% confidence interval (CI) and P values for postoperative outcomes were calculated for both groups after PSM. The association between each factor and ORADEs was examined using univariate logistic regression analysis. Odds ratio (OR), 95% CI and beta coefficients were calculated. Subsequently, a logistic regression analysis was performed using the stepwise selection method, with these covariates as explanatory variables and ORADEs as the outcome variable. The following four covariates were identified as explanatory variables for ORADEs: age (≥ 65 years), gender (female), body mass index (BMI) based on the Asian Adult BMI Classification, and type of anesthesia. Adjusted odds ratio (aOR), 95% CI, and beta coefficients were calculated.

Additionally, groups were compared using a non-linear mixed model for continuous variables. We also assessed the primary outcome in prespecified subgroups to investigate the relationship between oliceridine and heterogeneous populations in a post hoc analysis. Restricted cubic splines were used to flexibly model and visualize the relationship between predicted oliceridine use and the risk of ORADEs. All P values were two-sided, and a P value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 24 and R software version 4.1.2.

Results

Between January 2024 and June 2024, a total of 9262 patients were retrospectively screened (Figure 1). Of these, 1054 patients were excluded based on the following criteria: age <18 years; postoperative continuous mechanical ventilation or admission to ICU with tracheal tube; thoracic day surgery or without PCIA; conversion to open surgery, or inadequate postoperative follow-up information. Leaving 8208 patients who met the study selection criteria. Among these, 3171 patients received oliceridine, and 5037 patients received conventional opioids. After propensity score matching, 2803 matched pairs (5606 patients) were further analyzed. Patient demographics and the morphine equivalent doses used were comparable between the matched cohorts.

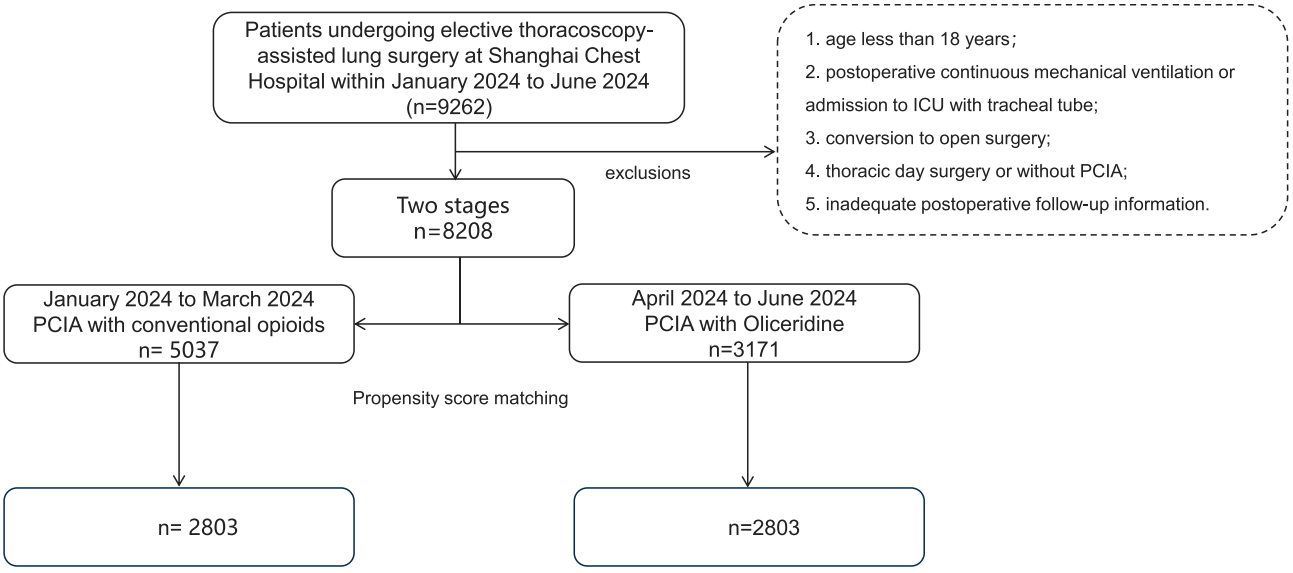

Figure 1 Flow diagram showing the process used to select patients for inclusion in this retrospective cohort study.

Patient characteristics and intraoperative information before and after matching are presented in Table 1. The standardized mean difference (SMD) after matching for all variables was less than 0.1, indicating that the propensity score matching was performed appropriately and resulted in balanced allocation between the two groups.

This analysis confirms that the matching process effectively balanced the covariates, allowing for a valid comparison of ORADE rates between the oliceridine and conventional opioid groups.

Postoperative Outcomes After Propensity Score Matching

The risk of postoperative outcomes for the matched groups is summarized in Table 2. After PSM, the incidence of ORADEs was significantly lower in the oliceridine group compared to the conventional group (24.3% [681/2803] vs 27.8% [780/2803], RR 0.87, 95% CI 0.80–0.95, P < 0.01). The incidence of PONV was significantly lower in the oliceridine group (15.5% [433/2803] vs 19.7% [553/2803], RR 0.78, 95% CI 0.70–0.88, P < 0.001).

There were no significant differences between the two groups in the incidence of opioid-induced respiratory depression (OIRD) (8.6% [242/2803] vs 8.3% [233/2803], RR 1.04, 95% CI 0.87–1.23, P = 0.66), urinary retention (0.9% [51/2803] vs 0.8% [42/2803], RR 1.21, 95% CI 0.81–1.82, P = 0.35), moderate to severe pain (22.2% [621/2803] vs 21.6% [606/2803], RR 1.03, 95% CI 0.93–1.13, P = 0.63), pain scores (median NRS 2 [0, 4] for both groups, P = 0.08), PACU length-of-stay (median 60 minutes [59.3, 63.0] for oliceridine vs 60 minutes [59.3, 64.4] for conventional, P = 0.51), and recovery time (median 20 minutes [20.0, 20.1] for both groups, P = 0.98). One patient in each group was reintubated within 6 hours after surgery. No other anaesthesia-related complications occurred in either group.

These results indicate that oliceridine is associated with a lower risk of ORADEs and PONV compared to conventional opioids, while other postoperative outcomes such as OIRD, urinary retention, pain severity, PACU length-of-stay, and recovery time show no significant differences between the two groups after PSM.

Table 1 Baseline and Procedural Characteristics Before and After Propensity Score Matching Between Oliceridine and Conventional Groups

Variable	Before PSM				After PSM			
	Conventional (n = 5037)	Oliceridine (n = 3171)	P-value	SMD	Conventional (n = 2803)	Oliceridine (n = 2803)	P-value	SMD
Age (yr)	59 ± 13	60 ± 12	0.017	0.056	59 ± 12	60 ± 12	0.579	0.015
Gender, female	2932 (58.2%)	1838 (58.0%)	0.826	0.005	1601 (57.1%)	1621 (57.8%)	0.589	0.014
BMI (kg/m²)	23.6 ± 3.2	23.7 ± 3.3	0.018	0.053	23.6 ± 3.2	23.7 ± 3.3	0.376	0.023
Morphine dose (mg)	79.1 ± 16.3	92.5 ± 28.3	<0.001	0.472	84.3 ± 17.7	85.2 ± 19.8	0.085	0.044
Anesthesia time (min)	102 (80, 135)	101 (79, 135)	0.342	0.014	100 (80, 135)	101 (79, 134)	0.540	−0.012
Operation time (min)	70 (50, 102)	70 (51, 102)	0.656	0.012	70 (50, 103)	70 (50.5, 100)	0.943	−0.001
Anesthesia			0.592				0.844	
- GA	472 (9.4%)	286 (9.0%)		−0.012	222 (7.9%)	226 (8.1%)		0.005
- GA + TPVB	4565 (90.6%)	2885 (91.0%)		0.012	2581 (92.1%)	2577 (91.9%)		−0.005
ICU	24 (0.5%)	24 (0.8%)	0.105	0.032	15 (0.5%)	15 (0.5%)	1.000	0.000
ASA			0.012				0.251	
- 1	188 (3.7%)	90 (2.8%)		−0.054	93 (3.3%)	88 (3.1%)		−0.010
- 2	3272 (65.0%)	2017 (63.6%)		−0.028	1833 (65.4%)	1772 (63.2%)		−0.045
- 3	1570 (31.2%)	1063 (33.5%)		0.050	876 (31.3%)	942 (33.6%)		0.050
- 4	7 (0.1%)	1 (0.0%)		−0.061	1 (0.0%)	1 (0.0%)		0.000
Type of surgery			0.043				0.940	
- Wedge resection	1076 (21.4%)	605 (19.1%)		−0.058	542 (19.3%)	532 (19.0%)		−0.009
- Segment resection	2243 (44.5%)	1407 (44.4%)		−0.003	1263 (45.1%)	1270 (45.3%)		0.005
- Lobectomy	1696 (33.7%)	1143 (36.1%)		0.049	986 (35.2%)	985 (35.1%)		−0.001
- Sleeve resection	14 (0.3%)	7 (0.2%)		−0.012	6 (0.2%)	7 (0.2%)		0.007
- Pneumonectomy	8 (0.2%)	9 (0.3%)		0.023	6 (0.2%)	9 (0.3%)		0.019
- Robotic surgery	81 (1.6%)	54 (1.7%)	0.742	0.007	43 (1.5%)	48 (1.7%)	0.597	0.014

Notes: Values are presented as mean ± SD, median (IQR), number of patients, or numbers (%).

Abbreviations: IQR, Interquartile Range; SMD, Standardized Mean Difference; ASA, American Society of Anesthesiologists; BMI, Body Mass Index; GA, General Anesthesia; TPVB, Thoracic Paravertebral Block.

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Table 2 Postoperative Outcomes Risk in Thoracoscopic Lung Resection with Oliceridine Vs Conventional Opioids (After PSM)

Variable	Conventional (n = 2803)	Oliceridine (n = 2803)	RR (95% CI)	P-value
Primary outcome				
ORADEs	780 (27.8%)	681 (24.4%)	0.9 (0.8–1.0)	<0.01
Secondary outcomes				
PONV	553 (19.7%)	433 (15.5%)	0.8 (0.7–0.9)	<0.001
OIRD	233 (8.3%)	242 (8.7%)	1.0 (0.9–1.2)	0.66
Urinary retention	42 (0.8%)	51 (1.0%)	1.2 (0.8–1.8)	0.35
Moderate to severe pain	606 (21.68%)	621 (22.2%)	1.0 (0.9–1.1)	0.63
Pain NRS	2 (0, 4)	2 (0, 4)		0.08
PACU length-of-stay (min)	60 (59.3, 64.43)	60 (59.3, 63.0)		0.51
Recovery time (min)	20 (20.0, 20.0)	20 (20.0, 20.1)		0.98

Notes: Values are presented as mean ± SD, median (IQR), number of patients, or numbers (%).
Abbreviations: ORADEs, Opioid-Related Adverse Drug Events; PONV, Postoperative Nausea and Vomiting; OIRD, Opioid-Induced Respiratory Depression; NRS, Numeric Rating Scale; PACU, Post-Anesthesia Care Unit; RR, Relative Risk; CI, Confidence Interval.

Analysis of Risk Factors for Opioid-Related Adverse Events

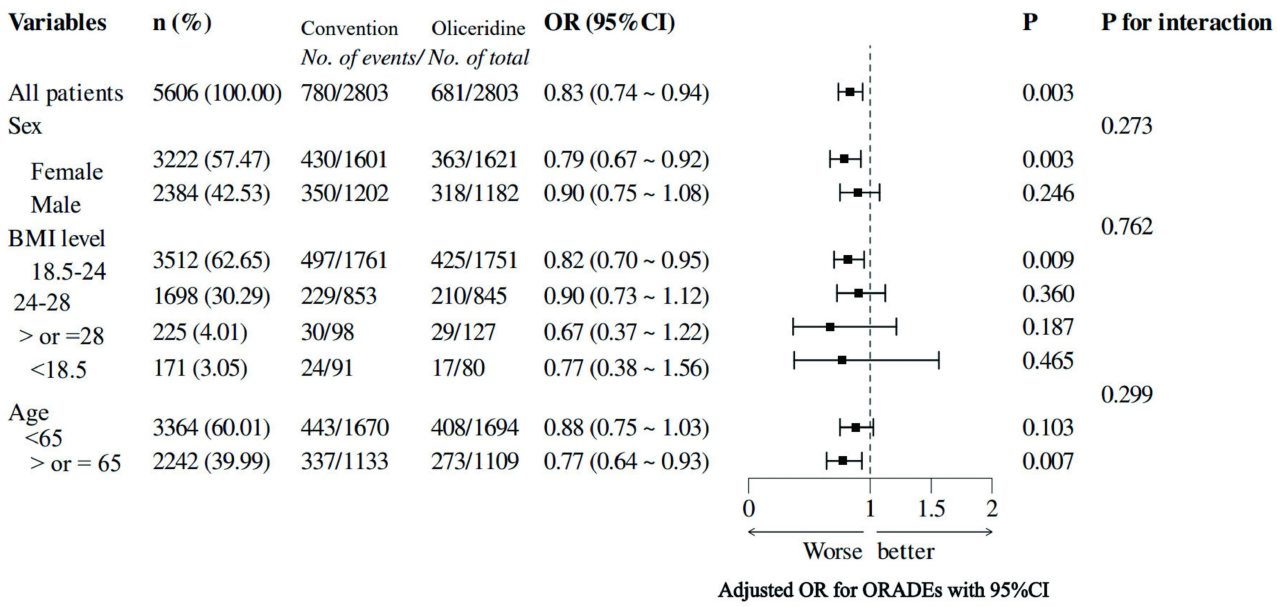
Table 3 presents the results of univariate and multivariable logistic regression analyses for the risk of ORADEs. The analyses utilized a stepwise selection method to identify significant predictors. The results indicate that age, gender, BMI, and type of anesthesia were not significantly associated with the development of ORADEs. However, the use of oliceridine was associated with a reduced risk of ORADEs compared to conventional opioids, as shown by both univariate (OR 0.83, 95% CI 0.74–0.94, P < 0.01) and multivariable analyses (OR 0.84, 95% CI 0.74–0.94, P = 0.003).

Detailed analyses of the risk factors for postoperative nausea and vomiting (PONV) were provided in Table S1. Notably, gender and the use of dexamethasone were significantly associated with PONV. Male gender and the addition of dexamethasone to PCIA were found to reduce the risk of PONV. The relative strengths of each risk factor for ORADEs and PONV are illustrated in Figure 2, with no significant interactions observed (P for interaction > 0.05).

Table 3 Univariate and Multivariable Analyses for ORADE Risk

Variables	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Group				
Convention	1.00 (Reference)		1.00 (Reference)	
Oliceridine	0.83 (0.74–0.94)	<0.01	0.84 (0.74–0.94)	0.003
Age				
<65	1.00 (Reference)		1.00 (Reference)	
≥65	1.08 (0.91–1.28)	0.41	1.06 (0.89–1.26)	0.505
Gender				
Female	1.00 (Reference)		1.00 (Reference)	
Male	1.10 (0.93–1.31)	0.27	1.09 (0.91–1.29)	0.357
BMI				
18.5–24.0	1.00 (Reference)		1.00 (Reference)	
<18.5	0.75 (0.46–1.21)	0.23	0.75 (0.46–1.21)	0.236
24-28	1.02 (0.85–1.23)	0.80	1.03 (0.85–1.24)	0.789
> or =28	0.89 (0.57–1.37)	0.59	0.90 (0.58–1.40)	0.648
Anesthesia				
GA	1.00 (Reference)		1.00 (Reference)	
GA + TPVB	0.85 (0.63–1.16)	0.31	0.86 (0.63–1.17)	0.339

Abbreviations: ASA: American Society of Anesthesiologists; BMI: body mass index; GA: general anesthesia; TPVB: thoracic paravertebral block; OR: odds ratio; CI: confidence interval.



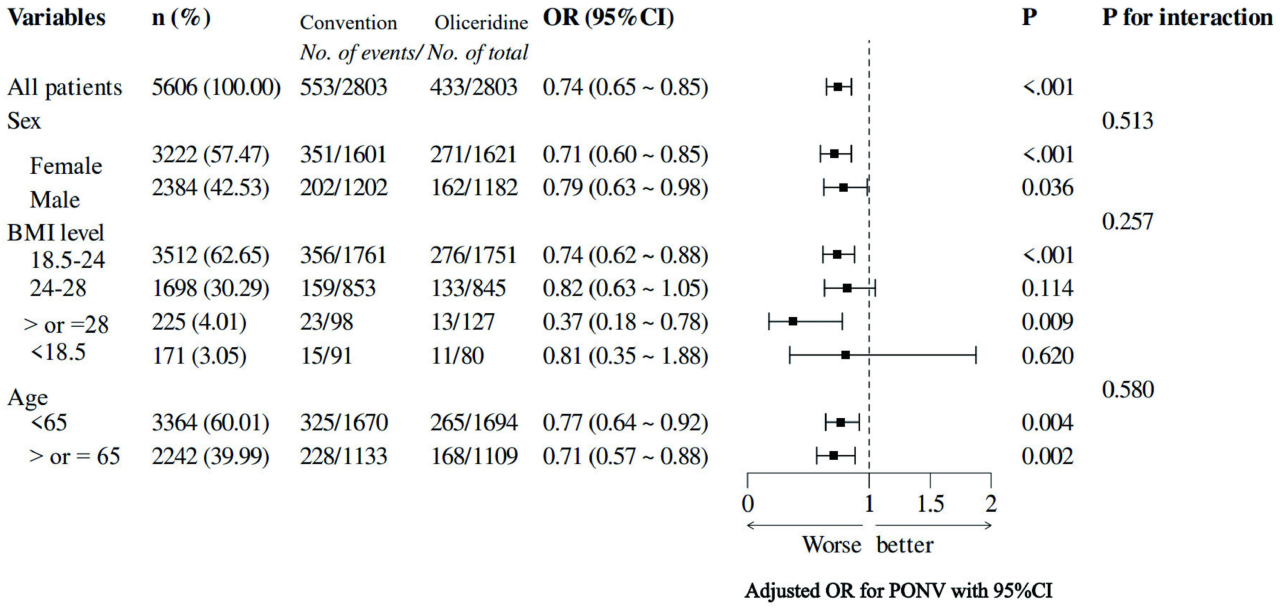


Figure 2 Intensity of ORADES and PONV risk factors. Forest plot showing adjusted ORs for ORADES and PONV after propensity score matching.The analysis included data from 5606 patients. Solid boxes indicate adjusted ORs and bars indicate 95% CIs. An adjusted OR < 1 indicates a favorable outcome for the variable. Values are expressed as adjusted OR with 95% CI.

Abbreviations: OR, odds ratio; ORADEs, Opioid-related adverse events; PONV, postoperative nausea and vomiting.

Visualization of Predicted Oliceridine and ORADEs Risk

Figure 3 illustrates the relationship between predicted oliceridine dosage and the risk of ORADEs in thoracoscopic-assisted surgery using restricted cubic splines. The analysis revealed a U-shaped relationship between predicted

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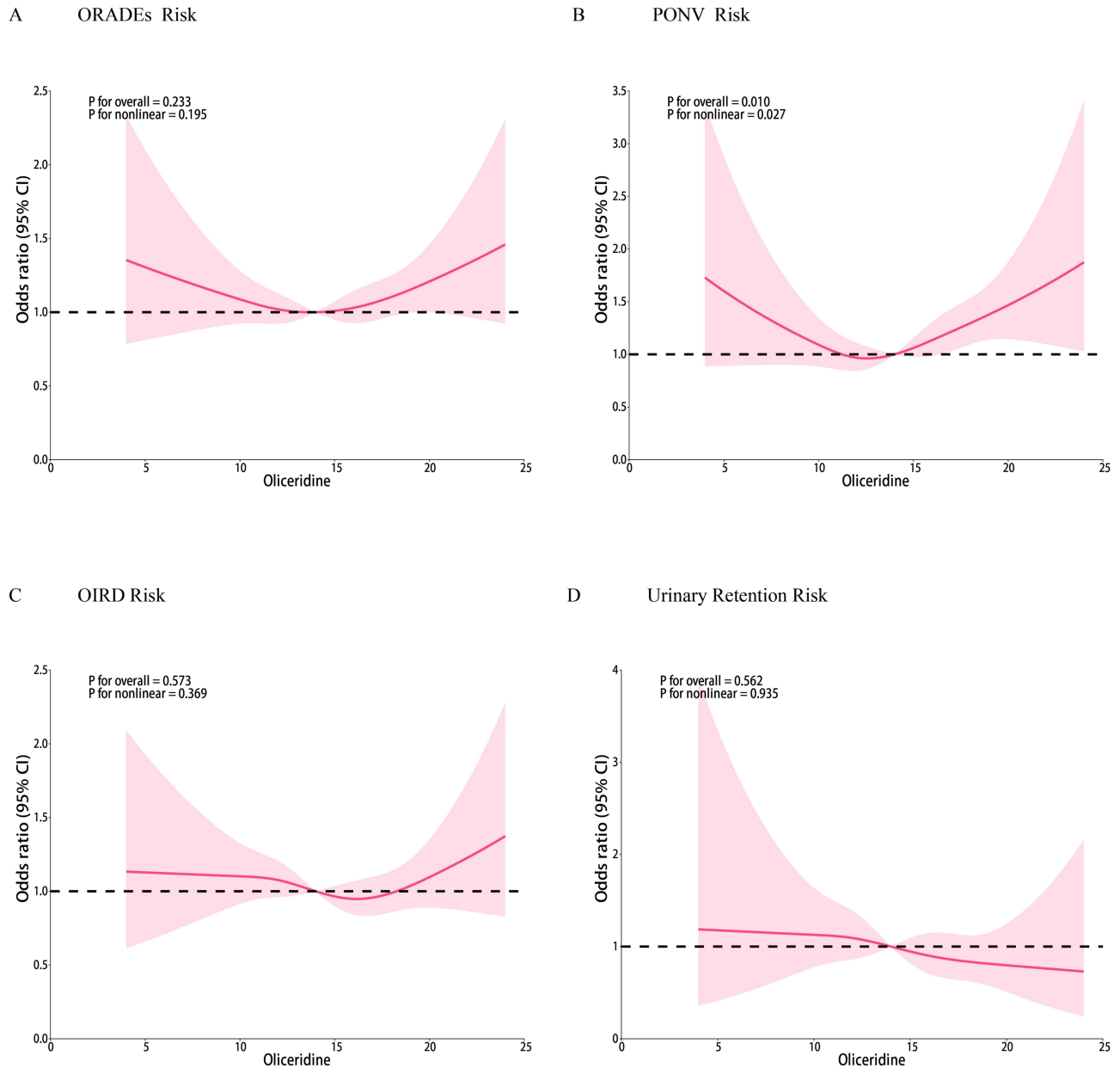

Figure 3 Dose-response relationship between oliceridine and ORADEs in PCIA. Restricted cubic spline analyses illustrating the non-linear association of oliceridine dose (mg) with the probability of ORADEs after thoracoscopic lung surgery. Analyses adjusted for covariates identified in propensity score matching. Dashed horizontal line indicates reference risk (odds ratio = 1). (**A**) Overall Opioid-related adverse events (ORADEs); (**B**) Postoperative nausea and vomiting (PONV); (**C**) Opioid-induced respiratory depression (OIRD); (**D**) Urinary retention.

oliceridine dosage and PONV risk. Specifically, there was a substantial reduction in risk within the lower range of predicted oliceridine dosages, with the lowest risk observed around 14 mg. Beyond this point, the risk increased (P for non-linearity < 0.05). This non-linear relationship highlights the importance of optimizing oliceridine dosage to minimize the risk of PONV.

Discussion

In this retrospective observational cohort study, we assessed the risk of ORADEs associated with the use of oliceridine and conventional opioids for PCIA using PSM method. Our results demonstrated that the incidence of ORADEs was significantly lower in the oliceridine group compared to the conventional opioids group (24.3% vs 27.8%). Additionally,

the incidence of PONV, was significantly lower in the oliceridine group (15.5% vs 19.7%). This findings suggests that the use of oliceridine in PCIA may potentially reduce the side effect profile compared to conventional opioids. To the best of our knowledge, this is the first study to compare the incidence of ORADEs between oliceridine and conventional opioids via PCIA with sufficient certainty.

To eliminate the potential effects of covariates on the risk of ORADEs, we calculated and balanced the morphine equivalents between the two groups by PSM. We hypothesized that the observed difference could be explained by the mechanism of oliceridine as a biased MOR agonist. Oliceridine selectively agonizes the G-protein-coupled pathway and only weakly activates the β-arrestin-2 pathway, thereby ameliorating ORADEs. Unlike the G-protein pathway, which induces analgesia, the β-arrestin pathway causes ORADEs, particularly respiratory depression and gastrointestinal complications, while diminishing analgesia.[19,20] Preclinical data as early as 2013 demonstrated that TRV130 (Oliceridine) is a biased ligand with differentiated pharmacology, successfully translating evidence that analgesic and adverse MOR signaling pathways are distinct.[21] Other biased opioids such as MEB-1166, MEB-1170, and PZM21 have become the current trend in the development of analgesic drugs.[7,22]

Results from a Phase III study of oliceridine for postoperative analgesia after abdominoplasty showed that the 0.35 mg and 0.5 mg doses of oliceridine demonstrated a favorable safety and tolerability profile in terms of respiratory and gastrointestinal adverse effects when compared to morphine, with equivalent analgesic efficacy. This provides a new therapeutic option for the management of moderate to severe postoperative pain.[11] The ATHENA study similarly showed that oliceridine provided effective postoperative analgesia. However, among the 768 patients treated with oliceridine in the trial, the incidence of adverse reactions leading to early discontinuation and serious adverse reactions were 2% and 3%, respectively. Nausea (31%), constipation (11%) and vomiting (10%) were the most common adverse reactions, with most being mild (37%) or moderate (25%).[12] This findings suggest that clinicians should focus on evaluating and discussing their patients' risk of opioid-related harm.

OIRD and PONV are challenging, resource-intensive, and costly ORADEs. A study by Oderda GM et al analyzed 592,127 hospitalized patients and found that the incidence of respiratory depression ranged from 3% (obstetrics/gynecology) to 17% (cardiothoracic/vascular), and the incidence of nausea/vomiting ranged from 44% (obstetrics/gynecology) to 72% (general surgery/colorectal). The increased odds of OIRD after cardiothoracic surgery were associated with opioid dose.[23] PONV afflict approximately 30% of patients overall, with female patients being at high-risk patients after surgery.[24] In the absence of head-to-head comparative data from randomized controlled trials, an indirect treatment comparison analysis demonstrated that oliceridine was associated with a significant reduction in the incidence of nausea and/or vomiting or the need for antiemetics compared to hydromorphone in orthopedic surgeries.[25] Our study further evaluated the effects of oliceridine on ORADEs in real-world thoracoscopic surgical settings. Furthermore, our study showed that oliceridine doses above 14 mg in PCIA were associated with an increased incidence of PONV.

In our study, there were no statistical differences in the incidence of OIRD and urinary retention. OIRD is a common but often underdiagnosed cause of postoperative respiratory depression. Current methods used to identify and monitor post-operative respiratory safety events have serious limitations, and new tools and techniques are being developed that promise to improve the prediction of respiratory depression.[17] The latest VOLITION study shown that nearly one quarter of patients experienced a respiratory compromise with oliceridine analgesia.[26] In a pharmacokinetic-pharmacodynamic comparison, the authors quantified the effects of oliceridine and morphine on the respiratory system of elderly volunteers. High doses of oliceridine and both doses of morphine cause a rapid onset of respiratory depression, with peak effects reached 0.5 to 1 hour after taking the opioid. After reaching peak, respiratory depression caused by oliceridine returned to baseline more quickly than morphine.[27] These factors may explain why the incidence of ORADEs was higher with traditional opioid than with oliceridine. This was further supported by our results based on restricted cubic spline curves, which allowed for flexibility examining in the association between oliceridine dose and the risk of ORADEs.

In the era of the growing opioid crisis, it is even more important for clinicians to assess and discuss their patients' risk of opioid-related harm. Although data on post-approval use of oliceridine is limited, all clinical evidence collected to date, including the results of exploratory analyses, suggest a lower incidence of opioid-related adverse events associated with oliceridine. Our studies investigating the use of oliceridine or other opioids with different pharmacological profiles for PCIA and focusing on patient outcomes in thoracoscopically assisted lung surgeries, will further add to the clinical evidence in this field.

Limitations

The subjects included in this study were patients undergoing thoracoscopic lung resection; therefore, the generalizability of the results may be constrained by this specific patient population. PSM improves causal inference within the study cohort, but does not inherently increase external validity. While the analgesic regimen implemented in this study comprised three integral components—loading dose, patient-controlled analgesia (PCA), and supplemental dose—the inherent limitations of retrospective studies impede our ability to fully understand the dynamic adjustments of opioids, such as oliceridine. Consequently, the analgesic efficacy of oliceridine in the context of thoracoscopic lung resection surgery requires further validation through subsequent multicenter trials with larger sample sizes.

Secondly, in the referenced literature, the definition of OIRD also included a respiratory rate <10 breaths per minute. However, due to the limitations of the retrospective study design, data on postoperative spontaneous respiratory rates were unavailable. Given that this study relied on a retrospective analysis of electronic medical records, it was not feasible to identify and rectify potential inaccuracies within the data. This limitation underscores the need for caution when interpreting the findings and highlights the importance of prospective studies to ensure data reliability.

Finally, although intraoperative morphine equivalent consumption was not calculated—an important factor in assessing ORADEs and postoperative pain management—this limitation was mitigated by standardized dosing protocols and propensity-matched surgery/anesthesia times between groups.

Conclusion

Oliceridine use in PCIA was associated with a lower incidence of ORADEs, primarily driven by reduced PONV, compared to conventional opioids. However, due to the retrospective nature of this study, these results should be interpreted with caution. Larger prospective randomized controlled trials are needed to confirm these findings.

Data Sharing Statement

The relevant data are available through the corresponding author on request.

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Disclosure

The authors have no conflicts of interest to disclose in this work.

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