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Research Progress on the Safety of Oliceridine in Perioperative Application

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Abstract

Oliceridine is the first approved biased μ-opioid receptor agonist. It produces analgesia by selectively activating the G protein pathway while minimizing β-arrestin recruitment, a mechanism that theoretically uncouples analgesia from adverse effects. This article systematically reviews the pharmacological basis for the perioperative use of oliceridine, the clinical evidence for its safety, and its value in special patient populations. Studies indicate that at equianalgesic doses, oliceridine is associated with a significantly lower incidence of respiratory depression and better gastrointestinal tolerability compared to conventional opioids. In elderly patients and those with renal or hepatic impairment, no or only mild dose adjustment is required. Cardiovascular and central nervous system adverse effects are manageable, with no risk signals identified beyond those of conventional opioids. Within the framework of multimodal analgesia, oliceridine demonstrates good synergy with other analgesic agents. However, critical questions remain insufficiently addressed, including the risks of long-term tolerance and dependence, as well as its impact on hard endpoints such as postoperative ileus. Future research should focus on long-term follow-up studies and clinical trials centered on bowel function recovery to refine its positioning within Enhanced Recovery After Surgery (ERAS) pathways.

Keywords: oliceridine, perioperative period, opioids, safety, analgesia

1. Introduction

Perioperative pain management is a key component affecting the quality of postoperative recovery in patients. Opioid analgesics, due to their potent analgesic effects, have long served as the cornerstone for the treatment of moderate to severe acute pain. However, while traditional opioids activate the μ-receptor G protein signaling pathway to produce analgesia, they simultaneously activate the β-arrestin pathway to a similar extent, which is closely associated with adverse reactions such as respiratory depression, nausea and vomiting, gastrointestinal dysfunction, and tolerance and dependence (N. Daksla et al., 2023; K. M. Raehal et al., 2005; J. Zhao, 2024). These adverse reactions not only affect patient comfort but may also delay the recovery process and prolong the length of hospital stay, thereby conflicting with the

concept of Enhanced Recovery After Surgery (ERAS) (M. R. Shen & J. F. Waljee, 2019; J. C. Simpson et al., 2019).

How to ensure analgesic efficacy while minimizing the risk of adverse reactions has always been a central challenge in perioperative pain management. In recent years, the development of biased μ-receptor agonists has provided a new approach to addressing this dilemma. Oliceridine, as the first approved biased μ-receptor agonist worldwide, theoretically achieves the decoupling of analgesia and adverse reactions by selectively activating the G protein pathway while attenuating β-arrestin recruitment (J. Piekielna-Ciesielska et al., 2023). Since 2017, multiple phase III clinical trials and real-world studies have been published, providing substantial evidence for its perioperative application.

This article aims to systematically review the pharmacological characteristics of oliceridine, the evidence regarding its perioperative safety, and its application value in special populations, in order to provide a reference for rational clinical use and subsequent research.

2. Pharmacological Characteristics of Oliceridine and the Basis for Its Clinical Application

2.1 Pharmacological Characteristics of Oliceridine

Oliceridine, as the first biased μ-opioid receptor agonist approved for clinical application worldwide, has opened a new pathway for perioperative pain management through its unique mechanism of action (Zhu, C. et al., 2024). At the molecular level, this drug achieves selective regulation of downstream signal transduction of the μ receptor: on the one hand, it efficiently activates the G protein signaling pathway, thereby producing potent analgesic effects; on the other hand, it significantly reduces the recruitment of β-arrestin, thereby minimizing adverse reactions mediated by this pathway (Y. Ni et al., 2024). This selective activation strategy constitutes the pharmacological basis for its differentiated clinical effects. Previous studies have confirmed that classic opioid-related adverse reactions, such as respiratory depression, postoperative nausea and vomiting, and gastrointestinal dysfunction, are mainly closely associated with excessive activation of the β-arrestin pathway (N. Daksla et al., 2023). Therefore, oliceridine theoretically achieves the decoupling of analgesia and adverse reactions.

2.2 Pharmacokinetic and Pharmacodynamic Characteristics of Oliceridine

Oliceridine is a short-acting drug administered intravenously, and its pharmacokinetic characteristics meet the requirements of acute pain management. After intravenous injection, its plasma concentration rapidly reaches peak levels, with a rapid onset of action (approximately 2–5 minutes), enabling rapid relief of moderate to severe pain (E. R. Viscusi et al., 2016). Its elimination half-life is approximately 1.3 to 3 hours. A phase I study conducted in Chinese patients with chronic pain also confirmed that its half-life is approximately 1.85–2.08 hours, showing linear kinetic characteristics (Y. Ni et al., 2024). This indicates that its analgesic effect is predictable and controllable, facilitating titration during the perioperative period according to the intensity of pain stimuli and patient responses.

The most notable feature of its pharmacodynamics is the possibility of a wider therapeutic window. A pharmacodynamic study conducted in elderly volunteers found that, compared with morphine at an equivalent analgesic dose, oliceridine caused a lower degree of respiratory depression and its effect resolved more rapidly (A. Dahan et al., 2018). Utility function-based analysis further showed that, when achieving the same probability of analgesia, the probability of respiratory depression with oliceridine was significantly lower than that with morphine (A. Dahan et al., 2018). This characteristic of "potent analgesia with a low risk of respiratory depression" is one of its most important clinical advantages, which was also verified in a phase IIb study after abdominoplasty (N. Singla et al., 2017).

2.3 Comparison Between Oliceridine and Traditional Opioids

Multiple phase III clinical trials represented by the APOLLO series have systematically evaluated the differences in efficacy and safety between oliceridine and classical opioids in postoperative acute analgesia. A study involving patients undergoing abdominoplasty showed that, compared with morphine, oliceridine met the prespecified non-inferiority standard in analgesic efficacy, confirming its reliable analgesic effectiveness (E. R. Viscusi et al., 2019). However, the core difference between the two is mainly reflected in safety. Compared with the morphine group, the "respiratory safety event"

composite endpoint (such as decreased oxygen saturation) occurred with a significantly lower burden in the oliceridine treatment group, and the proportion of patients forced to discontinue medication due to respiratory function suppression was also significantly reduced (S. D. Bergese et al., 2019). It is worth noting that the safety advantages demonstrated by oliceridine are not limited to the respiratory system. In the large open-label ATHENA study involving a broad surgical population, its adverse event profile showed lower incidences of respiratory depression and gastrointestinal adverse reactions (such as nausea and vomiting) (S. D. Bergese et al., 2019). In addition, a pooled analysis of multiple clinical studies further indicated that while ensuring effective analgesia, oliceridine was associated with a lower incidence of typical opioid-related adverse reactions such as nausea and vomiting compared with traditional drugs (C. Huang et al., 2025).

2.4 Theoretical Basis for the Perioperative Use of Oliceridine

The clinical application of oliceridine is highly consistent with the core concept of Enhanced Recovery After Surgery (ERAS), which aims to promote rapid recovery of postoperative physiological function by reducing complications. In the multimodal analgesia strategy of ERAS, limiting opioid-related adverse effects is a key component of successful implementation, whereas respiratory depression and gastrointestinal dysfunction caused by traditional opioids often become major obstacles to early mobilization and oral intake in patients (A. Beverly et al., 2017). Oliceridine, with its unique biased activation mechanism, retains potent analgesic activity while significantly reducing the risk of respiratory depression and having the potential to alleviate gastrointestinal adverse reactions, which provides a solid pharmacological basis for optimizing perioperative analgesic regimens (L. A. Colvin et al., 2019; H. Yu et al., 2026). The use of this drug enables clinicians managing acute moderate to severe pain to potentially overcome the safety limitations of traditional opioids and achieve effective separation between analgesic efficacy and core adverse reactions. Therefore, the theoretical foundation of its perioperative application lies in selectively regulating signaling pathways at the target level to precisely correct the inherent deficiencies of traditional opioids in the ERAS pathway, thereby creating favorable conditions for stable postoperative transition and accelerated recovery in patients (X. Meng et al., 2025).

3. Clinical Evidence on the Perioperative Safety of Oliceridine

As the first biased μ-opioid receptor agonist applied in clinical practice, the core value of oliceridine lies in its potential safety advantages (E. E. Prommer, 2025). Its unique mechanism of preferentially activating the G protein pathway while minimizing the β-arrestin pathway provides new possibilities for reducing the two major risks of traditional opioids—respiratory depression and addiction dependence—and related clinical research is continuously advancing (Y. Liu et al., 2021).

3.1 Studies on the Role of Oliceridine in Reducing the Risk of Perioperative Respiratory Depression

Respiratory depression induced by opioids is one of the most serious complications during the perioperative period. Oliceridine, due to its biased agonist property, was designed to provide potent analgesia while minimizing this risk to the greatest extent possible.

3.1.1 Mechanism of Respiratory Depression and Risk Assessment

Traditional opioids represented by morphine exert pharmacological effects by binding to μ receptors and non-selectively activating both the downstream G protein signaling pathway and the β-arrestin pathway simultaneously (J. Piekielna-Ciesielska et al., 2020; A. Mafi et al., 2020; A. Manglik et al., 2016). Recent studies indicate that excessive activation of the β-arrestin pathway is closely associated with the mechanisms underlying common clinical adverse reactions such as respiratory depression and gastrointestinal motility disorders (Y. Ni et al., 2024). Based on this pathophysiological basis, the risk assessment of opioid-related respiratory depression in the perioperative period has multidimensional characteristics. In addition to drug dosage as the core variable, individual patient factors also play a crucial role. Advanced age, obesity, a history of obstructive sleep apnea, and concomitant use of other central nervous system depressant drugs can all significantly increase the risk of respiratory depression. However, commonly used clinical monitoring methods, such as respiratory rate, pulse oxygen saturation (SpO_2), and end-tidal carbon dioxide partial pressure ($EtCO_2$), although providing important reference information, still lack a

single early warning indicator with both high sensitivity and specificity, which poses challenges for early identification and timely intervention.

3.1.2 Studies on the Effects of Oliceridine on Respiratory Function

Both basic research and clinical studies suggest that the effect of oliceridine on respiratory function is milder and more transient than that of traditional opioids (D. G. Soergel et al., 2014; P. Simons et al., 2023). A pharmacokinetic-pharmacodynamic study conducted in healthy elderly volunteers showed that, compared with morphine at an equivalent analgesic dose, oliceridine caused less ventilatory depression and a faster recovery from suppression (P. Simons et al., 2023). This more favorable respiratory safety profile has been further verified in clinical studies.

A retrospective analysis based on data from three phase III clinical trials (APOLLO-1, APOLLO-2, and ATHENA) showed that the incidence of opioid-induced respiratory depression (OIRD, defined as decreased respiratory rate or hypoxemia requiring clinical intervention) in patients treated with oliceridine was significantly lower than that in patients treated with traditional intravenous opioids (mainly morphine) (8.0% vs. 30.7%) (S. Bergese et al., 2020). Further subgroup analysis of high-risk populations (including elderly patients, obese patients, and those with obstructive sleep apnea) indicated that oliceridine maintained a significantly lower incidence of adverse events in these patients, suggesting potential advantages in high-risk populations (S. Bergese et al., 2020). This finding was further supported by an independent exploratory analysis of the ATHENA trial. Regardless of whether patients were older than 65 years or had a body mass index (BMI) of ≥30 kg/m², the incidence of OIRD in the oliceridine treatment group remained at a low level, and these traditional risk factors were not observed to significantly increase the risk of respiratory depression (M. Brzezinski et al., 2021). These data provide real-world evidence supporting the clinical value of oliceridine in improving perioperative respiratory safety.

3.1.3 Safety Monitoring Indicators in Clinical Application

To more objectively quantify the respiratory safety risks of opioids, some studies have attempted to evaluate "interruption of patient-controlled analgesia administration due to respiratory safety concerns" as a clinical surrogate endpoint for OIRD. Exploratory analyses of two phase III clinical trials showed that among different dose groups receiving patient-controlled analgesia with oliceridine, the proportion of patients whose administration was interrupted due to respiratory depression (0.1 mg group: 3.2%; 0.35 mg group: 13.9%; 0.5 mg group: 15.1%) was significantly lower than that in the morphine control group (22%), and the mean cumulative interruption time in each dose group also showed a decreasing trend (S. Ayad et al., 2020). This finding provides quantitative reference for indirectly monitoring respiratory function in clinical practice through the administration status of analgesia pumps. In addition, a recent dose-exploration study in outpatient hysteroscopic surgery further expanded its application scenarios. Under conditions of preserved spontaneous respiration, the combination of oliceridine and propofol provided satisfactory anesthetic effects, and no respiratory depression events were observed in any of the participants during the procedure (J. He et al., 2025). This result, from the perspective of a surgical model with low-intensity stimulation, supports the potential of oliceridine to maintain respiratory safety while providing sedation and analgesia.

4. Application Value of Oliceridine in the Safety of Perioperative Medication in Special Populations

Due to significant differences in the metabolism, pharmacological effects, and risk of adverse reactions to opioids in special patients such as the elderly and those with hepatic or renal insufficiency, the use of traditional opioids often faces many limitations (D. L. Chau et al., 2008). The unique pharmacological characteristics of oliceridine provide new possibilities for its application in these special populations.

4.1 Studies on Its Application in Elderly Patients

Elderly patients are significantly more susceptible to adverse reactions caused by opioids, such as respiratory depression and excessive sedation, due to factors such as reduced physiological reserve, altered pharmacokinetic characteristics, and multimorbidity. Existing studies indicate that oliceridine may demonstrate a more favorable safety profile in this high-risk population (Li, Y. et al., 2025).

A prospective randomized controlled study in

elderly patients after colorectal cancer surgery showed that, in a patient-controlled intravenous analgesia regimen, oliceridine combined with sufentanil not only provided better analgesic effects than sufentanil alone, but also significantly reduced the incidence of postoperative nausea and vomiting and respiratory depression (Y. Tian et al., 2025). This result suggests that oliceridine has potential value in multimodal analgesic strategies for elderly patients by enhancing efficacy while reducing adverse reactions. From a pharmacodynamic perspective, a sequential dose study on suppressing hemodynamic responses to tracheal intubation found that the effective dose of oliceridine in elderly patients (≥65 years) (ED95 approximately 50 μg/kg) was slightly lower than that in younger patients (55 μg/kg), and there was no significant difference in hemodynamic fluctuations or incidence of adverse events between the two groups, indicating that its dose-response relationship in the elderly population is predictable and controllable (A. N. Nafziger et al., 2020). Of particular concern is the dimension of respiratory safety. An exploratory analysis of a phase III open-label trial in patients with moderate to severe postoperative pain pointed out that, compared with younger patients, elderly patients (≥65 years) did not show an increased risk of opioid-induced respiratory depression after receiving oliceridine (S. Ayad et al., 2020). This finding was further confirmed in subsequent review literature, providing evidence-based support for the maintenance of respiratory safety of oliceridine in the elderly, a traditionally high-risk population (N. Daksla et al., 2023; D. I. Sessler et al., 2025). Overall, current evidence suggests that in the perioperative use of elderly patients, oliceridine is expected to reduce the burden of common adverse reactions associated with traditional opioids while ensuring analgesic efficacy.

4.2 Application Value in Patients with Hepatic and Renal Insufficiency

Hepatic and renal insufficiency can significantly affect the clearance rate of most opioids and their active metabolites, thereby increasing the risk of drug accumulation and toxicity. Oliceridine, due to its unique metabolic and excretory characteristics, may demonstrate better medication safety in this special population. A phase I pharmacokinetic study in patients with end-stage renal disease (ESRD) and varying degrees of hepatic impairment systematically evaluated the in vivo process of oliceridine after a single intravenous administration. The results showed that, compared with individuals with normal renal function, the clearance rate of oliceridine in patients with ESRD did not change significantly, indicating that its pharmacokinetic characteristics are basically unaffected by renal function, and therefore no dose adjustment is required in clinical use (A. N. Nafziger et al., 2020). In patients with hepatic insufficiency, mild to moderate hepatic impairment also did not significantly affect the clearance rate of oliceridine. Although patients with severe hepatic impairment showed prolonged half-life and increased volume of distribution, their overall clearance rate did not decrease significantly (A. N. Nafziger et al., 2020). Based on the above evidence, relevant reviews and clinical study protocols have pointed out that for patients with mild to moderate hepatic insufficiency, oliceridine can be used at the conventional dose without adjustment; for patients with severe hepatic insufficiency, a strategy of reducing the initial dose and strengthening clinical monitoring is recommended, rather than listing it as an absolute contraindication (B. Goudra & P. M. Singh, 2020; J. C. Luo et al., 2024). This pharmacokinetic characteristic simplifies the clinical medication process to a certain extent and reduces the risk of medication caused by fluctuations in hepatic and renal function.

4.3 Evaluation of the Synergistic Application of Oliceridine in Perioperative Multimodal Analgesia

Multimodal analgesia, as a core strategy for optimizing perioperative pain management and reducing the dose of a single drug and its adverse reactions, has become an important component of the ERAS pathway. Oliceridine, by virtue of its unique safety profile, demonstrates potential value as an opioid component in this strategy. Real-world clinical data have confirmed its good compatibility with other analgesic drugs. In the large phase III ATHENA study, as many as 84% of the subjects received non-opioid analgesics concomitantly while receiving oliceridine analgesia, fully reflecting its high compatibility with multimodal analgesic regimens in clinical practice (S. D. Bergese et al., 2019).

Further exploration of drug synergy has further enriched the above findings. The aforementioned randomized controlled trial in elderly patients showed that when oliceridine was combined

with sufentanil in patient-controlled intravenous analgesia (PCIA), it not only significantly reduced postoperative pain scores, but also reduced the number of analgesia pump presses and the need for rescue analgesia, achieving a synergistic analgesic effect between opioids and effectively controlling the burden of adverse reactions (J. Niu et al., 2023). This study provides new evidence-based support for constructing an "opioid-sparing" analgesic regimen centered on low-dose and multi-target approaches.

Based on existing evidence, the academic community generally believes that future studies should further clarify the optimal positioning and dosing regimen of oliceridine in specific ERAS protocols and multimodal analgesic combinations, in order to maximize its clinical benefits while ensuring analgesic efficacy (B. Hong et al., 2025).

5. Conclusion and Prospects

As a biased μ-opioid receptor agonist, oliceridine, with its unique mechanism of selectively activating the G protein pathway while attenuating β-arrestin recruitment, provides a new approach for perioperative analgesia. Existing evidence shows that, at equianalgesic doses, the incidence of core adverse reactions of traditional opioids, such as respiratory depression, nausea, and vomiting, is significantly reduced, gastrointestinal tolerability is improved, and it has good safety characteristics in elderly patients and patients with hepatic and renal insufficiency. These advantages are highly consistent with the concept of Enhanced Recovery After Surgery, making it a valuable supplementary option in multimodal analgesia.

However, there are still obvious gaps in current research. Most clinical trials have short observation periods, making it difficult to evaluate the risks of tolerance and dependence with long-term use. There is still a lack of prospective data supporting the effect of oliceridine on hard endpoints such as postoperative ileus. Evidence for its application in specific surgical procedures and special pathological conditions is also insufficient. In addition, the lack of pharmacoeconomic evaluation limits the decision-making basis for its clinical promotion.

Future research should focus on the following: conducting long-term follow-up studies to clarify the risk of dependence; designing randomized controlled trials centered on the recovery of intestinal function; exploring its optimal combinations and dosing strategies in different ERAS protocols; accumulating real-world data and completing health economic evaluations. With the improvement of the evidence system, oliceridine is expected to play a more precise clinical role in the dual goals of individualized analgesia and rapid recovery.

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