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# Comparison of oxycodone hydrochloride and flurbiprofen axetil on analgesia in mechanically ventilated patients with respiratory failure in a multicenter study

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**The design of this study is to compare the effectiveness of two analgesic drugs in the intervention of pain events for patients on mechanical ventilation. 414 patients from three hospitals with respiratory failure requiring mechanical ventilation were randomly assigned to oxycodone hydrochloride or flurbiprofen axetil. The primary endpoints is the difference in the proportion of patients with a Behavioral Pain Scale (BPS) score > 5 within 48 h. The secondary endpoints is to compare the dosage of sedative drugs (midazolam, propofol, dexmedetomidine) and to assess the clinical outcomes such as duration of mechanical ventilation. There was no significant difference in BPS scores between the two groups at enrollment, and BPS scores in oxycodone group were significantly lower than those in flurbiprofen axetil group at 24 and 48 h of enrollment. The proportion of patients with BPS less than 5 points in the Oxycodone hydrochloride group was also significantly lower than that in the flurbiprofen axetil group. For patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) score greater than 10, subgroup analysis showed that the mechanical ventilation time of oxycodone hydrochloride group was significantly lower than that of flurbiprofen axetil group with statistical significance, and the dosage of midazolam was significantly lower than that of flurbiprofen axetil group. The length of ICU stay was significantly lower than that of flurbiprofen axetil group. Oxycodone hydrochloride was more potent than flurbiprofen axetil for analgesia for patients with respiratory failure requiring mechanical ventilation.**

**Keywords** Respiratory failure, Analgesia, Oxycodone hydrochloride, Flurbiprofen axetil

Pain in Intensive Care Unit (ICU) patients included pre-existing chronic pain such as chronic neuralgia, acute disease related pain such as surgery, visceral or inflammatory pain, persistent pain associated with ICU treatment such as mechanical ventilation, tracheal intubation, and pain associated with intermittent procedures such as drainage tube placement and tracheotomy[1]. Patients with severe respiratory failure suffer from a variety of pain. If the pain of patients with respiratory failure cannot be well interfered with, it will affect the offline of patients and prolong the hospital stay of patients. Literature reports that more than 1/3 of patients with mechanical ventilation will feel moderate to severe pain, the 28-day mortality of patients with pain increases, and the mechanical ventilation time of patients with pain is prolonged[2]. International guidelines also recommend sedation in addition to pain relief[3]. However, studies have also found that even when analgesia is performed according to international guidelines, the pain control rate is only 80%[2]. The choice of analgesic drugs may be one of the reasons why analgesia is not ideal.

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Current studies have found that oxycodone injection, as an opioid, has similar or better effects on the control of body pain and visceral pain than commonly used morphine and fentanyl, while the incidence of adverse reactions such as nausea and vomiting is low[4,5]. Oxycodone is a μ-opioid receptor agonist, and oral oxycodone is widely used for postoperative analgesia and treatment of cancer pain[6–11]. In China, intravenous (IV) oxycodone was approved for postoperative analgesia in 2013. It has been reported that IV oxycodone can provide satisfactory postoperative analgesia by several studies. There have been no studies of oxycodone in patients with respiratory failure. To this end, this multicenter study envisages better pain control in mechanically ventilated patients with oxycodone.

Meanwhile, we selected flurbiprofen axetil as the control group primarily because our patient population consisted of those with respiratory failure requiring ventilatory support. Flurbiprofen axetil, as a non-steroidal anti-inflammatory drug (NSAID), has minimal sedative effects and negligible respiratory depressant effects, making it a suitable comparator. In our clinical experience, it is effective for managing moderate pain without compromising respiratory function, thus providing a balanced comparison with oxycodone hydrochloride, an opioid known for its potent analgesic effects but also its risk of respiratory depression, which could potentially prolong mechanical ventilation.

## Methods

### Patients and study design

This prospective randomized single-blinded clinical parallel trial, which adhered to CONSORT guidelines, was approved and was performed from May 1st, 2021 to May 1st, 2023, in accordance with the Helsinki Declaration of the World Medical Association. This trial protocol was approved by the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100,021, China, and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient recruitment at chictr.org.cn (ChiCTR2100051176; 15/09/2021; principal investigator: Xuezhong Xing). Research subjects include patients on mechanical ventilation treated in the ICU of the Cancer Hospital of the Chinese Academy of Medical Sciences, Navy General Hospital, Shandong Provincial Hospital from May 2021 to April 2023. Finally, 414 patients were included in the study, including 207 patients in the oxycodone group and 207 patients in the flurbiprofen axetil group. Information was collected from enrolled patients, such as age, sex, hypertension, diabetes, coronary heart disease, shock status, renal insufficiency, Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Table 1).

At the beginning of mechanical ventilation, patients were randomized into in a flurbiprofen axetil group or the oxycodone group. The randomization sequence without stratification was generated by a computer, and sealed with consecutively numbered envelopes.

Patients in Dex group received intravenous oxycodone (2 μg/h·kg; Precedex; AibeininR, Inc., Henrui Pharmaceutical, China). While in the Con group, an initial loading dose of 0.9% sodium chloride was

| Factors | Oxycodone hydrochloride group *N* = 207 | Flurbiprofen axetil group *N* = 207 | *P* |
|---|---|---|---|
| Gender (n, %) | | | 0.843 |
| Male | 93 (44.9%) | 91 (44.0%) | |
| Female | 114 (55.1%) | 116 (56.0%) | |
| Age (year) | 58 ± 15 | 57 ± 16 | 0.972 |
| Hypertension (n, %) | | | 0.227 |
| Yes | 75 (36.2%) | 87 (42.0%) | |
| No | 132 (63.8%) | 120 (58.0%) | |
| Coronary heart disease (n, %) | | | 0.654 |
| Yes | 24 (11.6%) | 27 (13.0%) | |
| No | 183 (88.4%) | 180 (87.0%) | |
| Diabetes (n, %) | | | 0.901 |
| Yes | 41 (19.8%) | 40 (19.3%) | |
| No | 166 (80.2%) | 167 (80.7%) | |
| Shock (n, %) | | | 0.842 |
| Yes | 89 (43.0%) | 87 (42.0%) | |
| No | 118 (57.0%) | 120 (58.0%) | |
| AKI (n, %) | | | 0.128 |
| Yes | 80 (38.6%) | 78 (37.7%) | |
| No | 127 (61.4%) | 129 (62.3%) | |
| APACHE II (median) | 12 (9–16) | 11 (8–16) | 0.339 |
| SOFA (median) | 5 (3–8) | 5 (3–8) | 0.818 |

**Table 1**. Comparison of baseline characteristics between oxycodone hydrochloride group and flurbiprofen axidate group. *AKI* acute kidney injury, *APCHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment.

administered as placebo followed by Intravenous flurbiprofen axetil (50 mg twice daily). The objective of this study is to compare the effectiveness of different analgesic drugs in the intervention of pain events for patients on mechanical ventilation.

**Inclusion criteria:** Expected mechanical ventilation duration > 24 h.

**Exclusion criteria:** (i) The patient has past or current gastrointestinal bleeding. (ii) Age<18 years old; (ii) Patient or family refused to participate the research.

**Primary endpoint:** The difference in the proportion of patients with a BPS score > 5 within 48 h.

**Secondary endpoints:** (i) The dosage of sedative drugs (midazolam, propofol, dexmedetomidine); (ii) Clinical outcomes such as duration of mechanical ventilation, Length of stay in ICU, length of hospital stay.

The BPS score, also known as the Behavioral Pain Scale, includes assessments of facial expression, upper limb movement, and patient-ventilator synchrony, with each part graded from 1 to 4. A score > 5 indicates severe pain necessitating management.

## Statistical analysis

*(a) Type of randomization and randomization sequence generation*

The study is a prospective randomized single-blinded clinical parallel trial. Random number method is used in random method. The random number table was randomly generated by computer, and this experiment adopted a single-blind study design. The doctor in charge assigned the treatment plan to the enrolled patients according to the random number, and the nurse in charge implemented the treatment plan. The subjects did not know the medication plan.

*(b) Sample size calculation*

According to the literature and clinical experience, the current proportion of mechanically ventilated patients with a BPS score > 5 after analgesia is 20%. It is anticipated that this proportion will decrease to 10% following intervention with oxycodone hydrochloride. Setting $\alpha = 0.05$ and $1 - \beta = 0.8$, and using PASS for calculations, 197 cases per group are required. Factoring in a 5% sample attrition rate, each group should consist of 207 cases, making a total of 414 cases.

*(c) Statistical methods*

(i) Categorical data will be described using frequency analysis (number of cases, percentage); continuous data will be described using the mean ± standard deviation.

(ii) For quantitative data, if the data follow a normal distribution, parametric tests such as the *t*-test or analysis of variance will be used. If the data do not follow a normal distribution, non-parametric tests will be chosen. For count data, chi-square tests or exact probability methods will be employed.

## Results

A total of 414 patients were enrolled in this study (Fig. 1). The demographics of enrolled patients are described in a Table 1. There were no significant differences in age, sex, hypertension, diabetes, coronary heart disease, shock state, renal insufficiency, SOFA score and APACHE II score between the two groups ($p > 0.05$ for all). In the oxycodone hydrochloride group, BPS scores were 4.2 ± 1.2 and 3.2 ± 1.3 after 24 h and 48 h, while in the flurbiprofen axetil group, BPS scores were 4.7 ± 1.6 and 3.5 ± 1.7 after 24 h and 48 h, respectively ($p < 0.05$ for both). In the oxycodone hydrochloride group, after 24 h and 48 h, the percentages of BPS scores greater than 5 points were 22.0% and 13.0%, respectively, while in the flurbiprofen axetil group, the percentages of BPS scores greater than 5 points were 34.3% and 34.3%, respectively. In this study, there was no significant difference in BPS scores between the two groups at enrollment, and BPS scores in oxycodone group were significantly lower than those in flurbiprofen axetil group at 24 and 48 h of enrollment ($p < 0.05$ for all, Table 2). The proportion of patients with BPS less than 5 points in the hydroxyl group was also significantly lower than that in the flurbiprofen axetil group ($p < 0.05$ for all, Table 3).

In this study, the mechanical ventilation time, ICU stay and hospital stay of the two groups had no significant statistical significance ($p > 0.05$ for all, Table 4). There was also no significant difference in the dosage of propofol, midazolam and dexmetropil hydrochloride between the two groups ($p > 0.05$ for all, Table 5). In this study, 2 patients in the oxycodone hydrochloride group died during ICU stay and 4 patients died during hospitalization

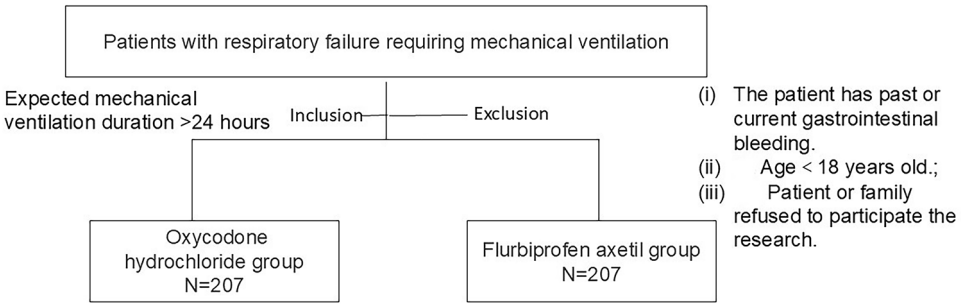


**Fig. 1**. Participant flow diagram of a total of 414 patients were enrolled in this study.

| Group | BPS (0 h) | *P* | BPS (24 h) | *P* | BPS (48 h) | *P* |
|---|---|---|---|---|---|---|
| Oxycodone hydrochloride | 6.1 ± 2.0 | 0.991 | 4.2 ± 1.2 | 0.001 | 3.2 ± 1.3 | 0.001 |
| Flurbiprofen axetil | 6.1 ± 2.0 | | 4.7 ± 1.6 | | 3.5 ± 1.7 | |

**Table 2**. Comparison of BPS scores for analgesic effects of oxycodone hydrochloride and flurbiprofen axidate 24 h and 48 h after administration.

| Group | BPS (0 h) | | BPS (24 h) | | *P* | BPS (48 h) | | *P* |
|---|---|---|---|---|---|---|---|---|
| | ≤ 5 | > 5 | ≤ 5 | > 5 | | ≤ 5 | > 5 | |
| Oxycodone hydrochloride | 0 | 207 (100%) | 161 (78.0%) | 46 (22.0%) | 0.041 | 180 (87.0%) | 27 (13.0%) | 0.047 |
| Flurbiprofen axetil | 0 | 207 (100%) | 135 (65.7%) | 72 (34.3%) | | 138 (66.7%) | 69 (34.3%) | |

**Table 3**. Comparison of percentage of BPS score over 5 for analgesic effects of oxycodone hydrochloride and flurbiprofen axidate 24 h and 48 h after administration.

| Group | Propofol (g) | *P* | Midazolam (mg) | *P* | Dexmetropil hydrochloride (μg) | *P* |
|---|---|---|---|---|---|---|
| Oxycodone hydrochloride | 3.1 ± 5.2 | 0.310 | 16.0 ± 102.8 | 0.440 | 65 ± 339.4 | 0.123 |
| Flurbiprofen axetil | 3.0 ± 4.9 | | 15.8 ± 44.2 | | 60.8 ± 325.0 | |

**Table 4**. Comparison of sedative use between oxycodone hydrochloride group and flurbiprofen axidate group.

| Group | MV (h) | *P* | Los of ICU (day) | *P* | Los of hospital (Day) | *P* |
|---|---|---|---|---|---|---|
| Oxycodone hydrochloride | 61.8 ± 783.1 | 0.639 | 4.9 ± 9.7 | 0.661 | 19.6 ± 14.5 | 0.123 |
| Flurbiprofen axetil | 61.2 ± 126.8 | | 4.7 ± 4.1 | | 18.9 ± 10.3 | |

**Table 5**. Comparison of short-term clinical prognosis between oxycodone hydrochloride group and flurbiprofen axidate group.

| | Oxycodone hydrochloride group | Flurbiprofen axetil group | *P* |
|---|---|---|---|
| Deaths of ICU | 2 | 0 | 0.140 |
| Deaths of hospital | 4 | 5 | 0.832 |
| Nausea and vomiting | 1 | 0 | 0.298 |
| Bloating and abdominal pain | 0 | 0 | – |

**Table 6**. Comparison of adverse reactions between oxycodone hydrochloride group and flurbiprofen axidate group.

because of respiration failure, while in the flurbiprofen axetil group, none of the patients died during ICU stay and 5 patients died during hospitalization because of respiration failure. In terms of side effects, there were 5 cases of evil vomiting in the oxycodone hydrochloride group, and 4 cases of nausea and vomiting in the flurbiprofen axetil group ($p > 0.05$ for all, Table 6).

For patients with APACHE II score greater than 10, subgroup analysis showed that the mechanical ventilation time of oxycodone hydrochloride group was 103.7 ± 80.2 h, which was significantly lower than that of flurbiprofen axetil group (124.3 ± 79.1 h) with statistical significance ($p = 0.027$, Fig. 2), and the dosage of midazolam was significantly lower than that of flurbiprofen axetil group ($p = 0.030$, Fig. 3). The length of ICU stay was significantly lower than that of flurbiprofen axetil group ($p = 0.044$, Fig. 4).

## Discussion

In this prospective single-blind randomized controlled study, the results presented some significant findings. The comparative efficacy of analgesia between oxycodone hydrochloride and flurbiprofen axetil injection for patients with respiratory failure undergoing mechanical ventilation has been a subject of clinical interest. This study indicated that the use of oxycodone hydrochloride may provide a viable alternative to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) like flurbiprofen axetil for pain management in this patient population. Especially for patients who are unable to tolerate NSAIDs due to contraindications, oxycodone hydrochloride

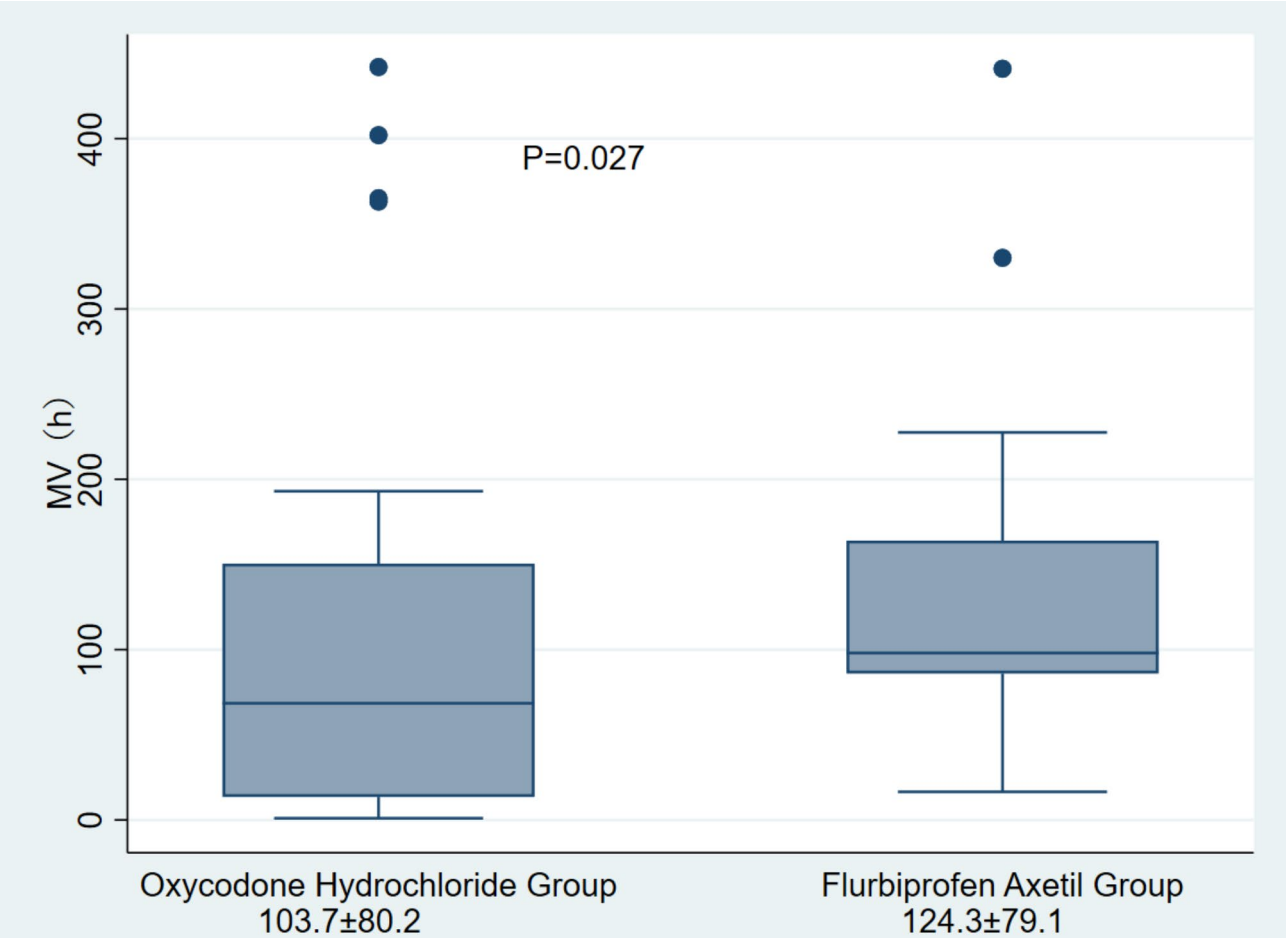


**Fig. 2**. Comparison of mechanical ventilation time between oxycodone hydrochloride and flurbiprofen axidate in patients with APACHE II scores greater than 10.

presents a promising alternative. In our study, we observed a notable interaction between analgesia and sedation protocols, particularly regarding the use of oxycodone hydrochloride and its effects on sedative requirements. Specifically, patients in the oxycodone group required significantly lower doses of midazolam, especially those with higher APACHE II scores. This suggests that oxycodone not only provides effective pain relief but may also enhance sedation, reducing the need for additional sedative medication. This finding is clinically significant as it indicates a potential dual benefit of using oxycodone for critically ill patients: effective analgesia and reduced sedative drug usage, which can minimize the risks associated with high doses of sedatives, such as prolonged sedation or respiratory depression. Moreover, while the difference in propofol requirements between the two groups was not statistically significant, there was a trend suggesting that patients receiving oxycodone might also use less propofol. These interactions highlight the importance of considering analgesic choices in the context of overall sedation management strategies. Future research should further explore these interactions to optimize pain and sedation protocols, ensuring better patient outcomes and resource utilization in the ICU setting.

Oxycodone hydrochloride is a semisynthetic opioid that may be an agonist of the central and peripheral kappa as well as μ-opioid receptors[12], which does not cause significant respiratory depression—a crucial advantage for patients already compromised by respiratory failure. In our study, we observed the effective analgesic properties of oxycodone hydrochloride, which warrant a deeper exploration of its pharmacological profile, specifically its interaction with opioid receptors. Oxycodone is primarily known as a μ-opioid receptor agonist, but importantly, it also exhibits activity at the kappa opioid receptor[12]. This interaction is significant as kappa receptors are implicated in pain modulation, particularly in visceral and neuropathic pain, which are often challenging to manage in clinical settings[6,13,14]. The activation of kappa receptors by oxycodone may contribute to its unique analgesic profile, providing complementary pathways for reducing pain. This comprehensive understanding could pave the way for more targeted and effective analgesic therapies in critically ill patients. No respiratory depression occurred in this experiment. This may be because oxycodone takes pharmacological effects mainly through the kappa receptor, being less sensitive to the u receptor agonism. In addition, opioid analgesics can lead to nausea, vomiting, and other adverse reactions, but this study showed that oxycodone did not increase the incidence of nausea or vomiting. Flurbiprofen axetil, on the other hand, functions through the inhibition of cyclooxygenase, providing effective analgesia but with potential concerns related to its effects on the

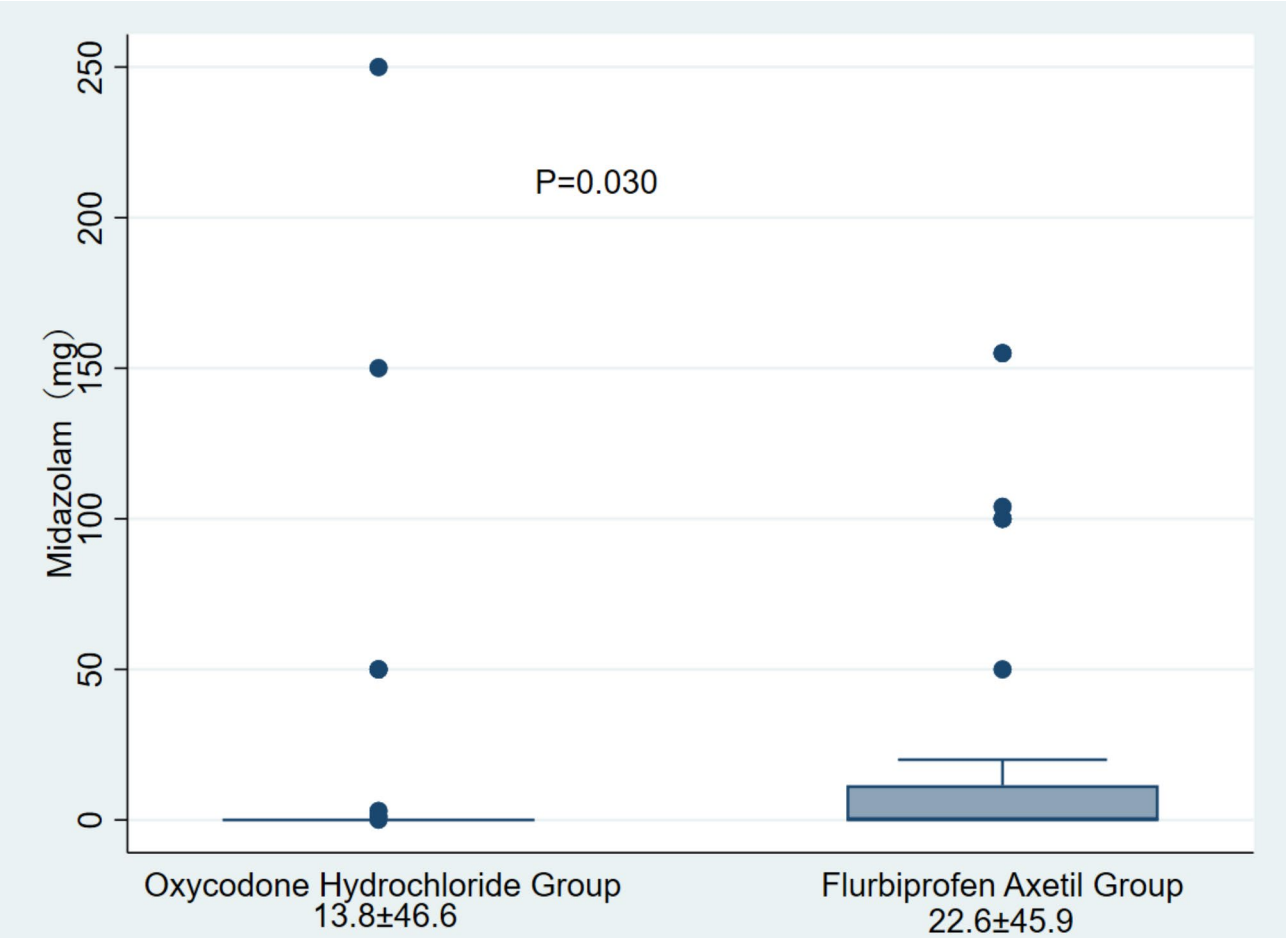


**Fig. 3**. Comparison of midazolam dosage between oxycodone hydrochloride group and flurbiprofen axidate group for patients with APACHE II scores greater than 10.

cardiovascular and gastrointestinal systems[15]. In this study, there was no significant difference in gastrointestinal adverse reactions between the two groups.

Compared with morphine, although oxycodone has lower intrinsic activity with respect to the u type receptor, it has a stronger analgesic effect[16,17]. This is due to the fact that the concentration of unbound oxycodone in the brain is 6 times higher compared with morphine, though concentrations in the blood of both opioid analgesics is comparable. Hence, the oxycodone has a higher safety and efficacy than other opioid analgesics, and minimal immunosuppressive activity[18–20]. Oxycodone has better analgesic effect in patients with mechanical ventilation. Oxycodone can reduce the dose of sedative drugs in critically ill patients (Apache II score greater than 10), shorten the time of mechanical ventilation and ICU stay; oxycodone does not increase occurrence rate of nausea, vomiting and other adverse reactions. The results of this clinical trial are open to further discussion and more precise analysis in the future due to the study limitation of a moderate number of enrolled patients.

Unfortunately, inflammatory molecules were not examined in this study. It was assumed that after the improvement of pain, the levels of inflammatory factors would decrease and the immune function would improve. Additionally, oxycodone hydrochloride has been found to produce fewer side effects and has a lower impact on inflammatory markers, which may suggest a broader therapeutic benefit.

This study has several limitations that must be considered when interpreting the results. First, the single-blinded design was implemented primarily for safety reasons, which may have introduced some bias in the assessment of pain and sedation levels. While this approach ensures that healthcare providers are aware of the treatment being administered, it limits the ability to blind both patients and medical staff. Additionally, patients with a history of gastrointestinal bleeding were excluded from the trial to mitigate potential risks associated with opioid use, which may limit the generalizability of the findings to this subgroup. Furthermore, the short duration of the study 48 h may not fully capture the long-term effects or safety outcomes of the interventions. Future studies with a longer follow-up period and broader inclusion criteria would be beneficial to confirm these findings.

In conclusion, the evidence supports that oxycodone hydrochloride may offer superior pain management with an improved safety profile for mechanically ventilated patients with respiratory failure when compared to flurbiprofen axetil injection. However, further studies are necessary to confirm these findings and to establish standardized protocols for pain management in this critical care setting.

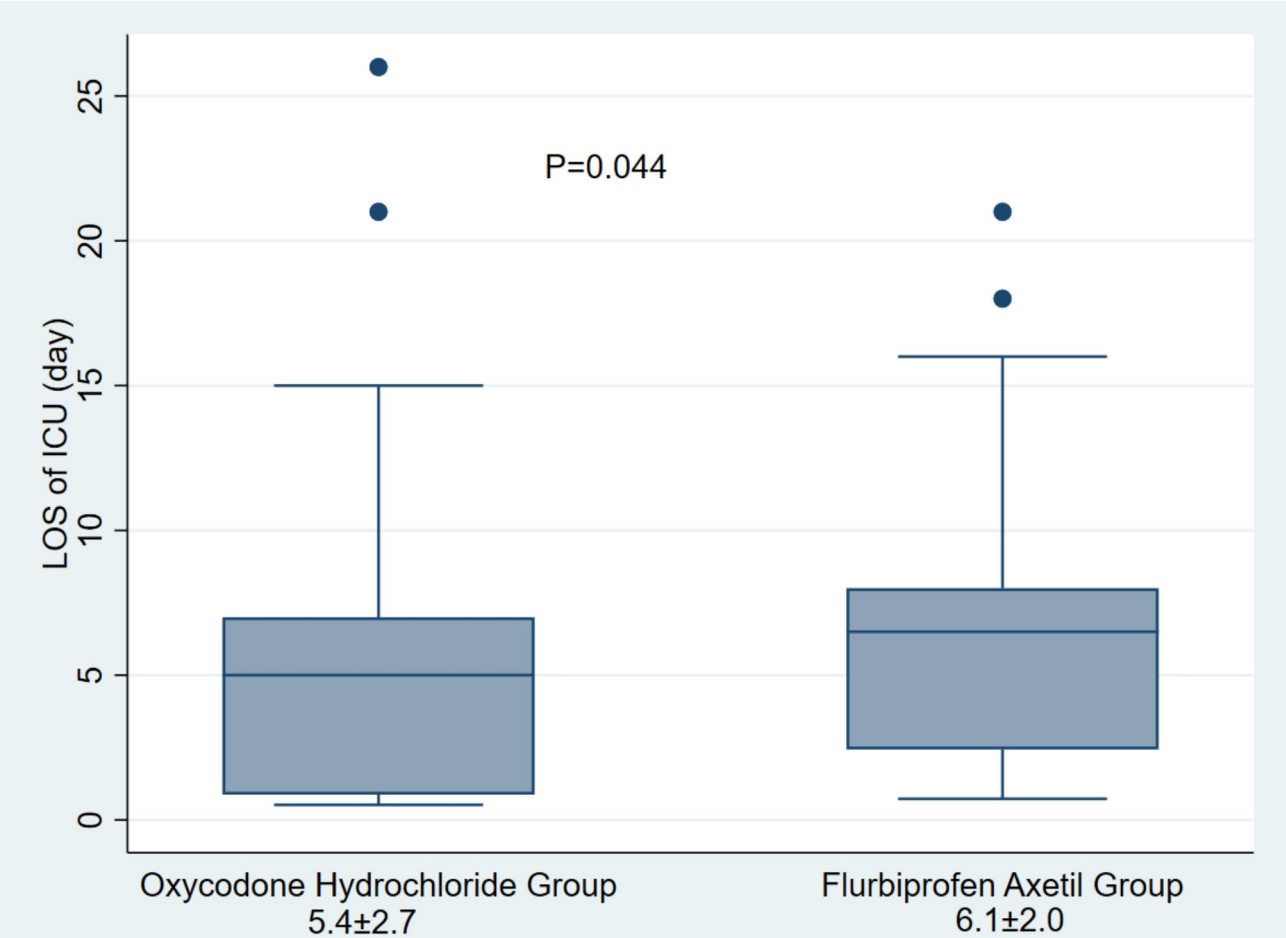


**Fig. 4**. Comparison of length of stay in ICU between oxycodone hydrochloride group and flurbiprofen axidate group for patients with APACHE II score greater than 10.

## Data availability

The data used and/or analysed during the current study are available from corresponding author upon reasonable request.

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## Author contributions
"Zhen-nan Yuan, Yu-juan Xue and Xue-zhong Xing wrote the main manuscript text and Da-wei Li prepared figures and Tables. All authors reviewed the manuscript."

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## Declarations

## Competing interests
The authors declare no competing interests.

## Informed consent and patient details
The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

## Additional information
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