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CLINICAL TRIAL REPORT

A Comparison of Oliceridine versus Sufentanil for Patient-Controlled Analgesia After Total Knee Arthroplasty in Elderly Patients: A Double-Blinded Randomized Controlled Study

Xi Liu[1,*], Suna Wang[2,*], Xiaoxiao Chen[1,*], Yuanyuan Tian[1], Junli Sun[1], Aizhong Wang[1], Qi Li[1], Hui Zhang[1]

[1]Department of Anesthesiology, Shanghai Sixth People's Hospital Affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [2]Department of Clinical Research Center, Shanghai Sixth People's Hospital Affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hui Zhang; Qi Li, Shanghai Sixth People's Hospital Affiliated with Shanghai Jiao Tong University School of Medicine, No. 600, Yishan Road, Xuhui District, Shanghai, People's Republic of China, Tel +86 18930173683; +86 18930173681, Email zhanghui@sjtu.edu.cn; niki77@sjtu.edu.cn

Purpose: Oliceridine is a G protein-biased μ-opioid receptor agonist, maintaining potent analgesic effects and simultaneously lessening disadvantageous reactions. This study is intended to compare Oliceridine and sufentanil patient-controlled analgesia (PCA) for postoperative analgesia in elderly patients suffering from knee arthroplasty.

Patients and Methods: A total of 138 patients scheduled for knee arthroplasty were randomized to receive postoperative PCA with either Oliceridine (2 μg kg^{-1} mL^{-1}) or sufentanil (0.02 μg kg^{-1} mL^{-1}). To preserve blinding, identical volume-based settings (mL) were used for both groups. The PCA regimen comprised a 1 mL loading dose (equivalent to 2 μg kg^{-1} Oliceridine or 0.02 μg kg^{-1} sufentanil), a background infusion of 2 mL h^{-1}, and a 2 mL bolus dose with a 10-minute lockout interval. Outcomes for systematic assessment included the sum of pain intensity difference (SPID), numeric rating scale (NRS) scores, and the incidence of postoperative nausea, vomiting and respiratory depression.

Results: Subjects in this research were 71.5 years on average, and 83% were female. Throughout 48 h postoperatively, the mean difference between Group Oliceridine and Group sufentanil was −7.13 (95% CI: −24.26 to 10.00); the upper bound of the 95% CI did not exceed the pre-specified non-inferiority margin of 10, thereby meeting the non-inferiority criterion. Aside from that, nausea (33.33% vs. 50.72%; P = 0.039) and vomiting (14.49% vs. 34.78%; P = 0.006) presented much lower incidence in Group Oliceridine within 48 h postoperative.

Conclusion: Oliceridine may have non-inferior analgesic efficacy to sufentanil and is associated with a lowered incidence of nausea and vomiting within 48 h.

Plain Language Summary: Many older adults need strong pain relief after knee replacement surgery. While common opioid pain medications work well, they often cause bothersome side effects like nausea and vomiting. Finding a pain control option that is both effective and easier to tolerate is an important goal. Our research team compared a newer pain medication, oliceridine (also known as TRV130), with a commonly used opioid, sufentanil. We studied 138 older patients who used a patient-controlled pump to manage their pain for two days after knee surgery. We tracked how their pain was controlled and recorded any side effects. We found that pain relief with oliceridine was non-inferior to sufentanil. The key difference was in side effects: significantly fewer patients who received oliceridine experienced nausea or vomiting. This means that for older adults recovering from knee surgery, oliceridine offers a potentially better-tolerated choice for effective pain control, with less of the stomach-related side effects that can make recovery unpleasant.

Keywords: patient-controlled analgesia, oliceridine, pain measurement, postoperative nausea and vomiting, PONV, TRV130

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Introduction

Total knee arthroplasty (TKA) is the primary treatment for elderly patients with end-stage knee osteoarthritis.[1] These patients normally experience moderate to severe pain after surgery, which considerably impedes recovery, compromises satisfaction, and adversely affects overall outcomes.[2,3] Notwithstanding the fundamental fact that regional nerve blocks are extensively employed for postoperative pain management in our clinical daily, a multitude of patients still report moderate to severe pain within the first 24 to 48 hours (h) after surgery. At present, the mainstream clinical regimen is dependent upon sufentanil delivered via patient-controlled analgesia (PCA) pumps in conjunction with nonsteroidal anti-inflammatory drugs. Nonetheless, opioid-related adverse events (ORAEs) remain principal concerns attributable to the activation of the β-arrestin pathway.[4,5] And elderly patients are particularly vulnerable to ORAEs due to factors such as declining organ function, reduced physiological reserve, increased comorbidity burden, frailty, and age-related pharmacokinetic and pharmacodynamic changes.[6,7]

Oliceridine serves as a G protein-biased μ-opioid receptor agonist,[8,9] first reported in 2013 and approved by the U.S. Food and Drug Administration in 2020.[10,11] As the first novel analgesic that selectively activates G protein signaling while limiting β-arrestin recruitment, Oliceridine not only maintains potent analgesic effects, but also substantially lowers the risk of unfavorable reactions.[12–14] As indicated by preclinical and early clinical studies, Oliceridine optimizes μ-opioid receptor function through its G protein-biased mechanism, demonstrating advantages in both maintaining analgesic efficacy and improving safety profile.[13–17] It is even well-tolerated in special populations such as the elderly and obese patients.[18]

Existing studies have commonly used the conventional opioid morphine as a control. Nonetheless, sufentanil has been universally employed in clinical practice on account of its higher therapeutic index and shorter plasma-to-central nervous system equilibrium half-life (t½ke0),[19] which contribute to a superior safety profile. This phenomenon is more striking in postoperative PCA pumps. In such cases, sufentanil gains progressively extensive application scopes in contrast to morphine. Considering its prominent status as a dominant analgesic, a question arises from the public and the academic society: how is the novel agent Oliceridine comparable with sufentanil?

As a consequence, this study seeks to evaluate the efficacy and side effects of Oliceridine for postoperative analgesia of the elderly undergoing TKA in contrast to sufentanil.

Materials and Methods

Trial Design and Ethics Approval

This was a single-center, prospective, double-blinded, randomized controlled, non-inferiority study with a 1:1 allocation ratio. The study was approved by the Ethical Committee of Shanghai Sixth People's Hospital, affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, China (Chairperson: Prof. Weiping Jia) on September 23, 2024 (approval number: 2024–169-(1)) and registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx, registration number: ChiCTR2500099271; principal investigator: HZ; registration date:2025–03-20). All participants provided written informed consent before their inclusion in the study. This manuscript adheres to the principles of the Helsinki Declaration and complies with the Consolidated Standards of Reporting Trials guidelines.

Participants

Eligible patients were aged 65 years or older, had an ASA physical status of I or II, and a body mass index (BMI) ranging from 19.0 to 30.0 kg m^{-2} at screening. They were recruited to undergo elective knee arthroplasty. The exclusion criteria were as follows: refusal to participate; participation in other drug trials within 30 days before enrollment; contraindications to the study medications; history of opioid addiction; chronic analgesic use; severe hepatic or renal dysfunction; history of vestibular disorders or presence of dizziness, nausea, retching, or vomiting within one week prior to enrollment; history of obstructive sleep apnea syndrome; history of alcohol, drug, or medication withdrawal within the past three years; and postoperative detection of nerve injury or other serious complications. All participants were recruited from Shanghai Sixth People's Hospital, affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, China. The recruitment was completed from March 21, 2025, to

August 6, 2025. All the participants underwent follow-up from March 21, 2025, to August 8, 2025. After the predetermined sample size was reached, the trial would be terminated accordingly.

Randomisation and Blinding

Allocation concealment was ensured by an independent researcher. This researcher generated a 1:1 computer-based randomization schedule using Microsoft Excel. The allocation sequence was then kept strictly concealed in a password-protected electronic file, accessible only to this individual. On the day of surgery, after a patient was enrolled, the same independent researcher would open this file, prepare the PCA pump with Oliceridine (2 μg kg^{-1} mL^{-1}) (Nhwa Pharma. Corporation, Jiangsu, China) or sufentanil (0.02 μg kg^{-1} mL^{-1}) (Humanwell Healthcare (Group). Corporation, Jiangsu, China) according to the next assignment on the concealed list, and then provide it to the attending anesthesiologist. To preserve blinding, identical volume-based pump settings (mL) were used for both groups. The PCA regimen comprised a 1 mL loading dose (equivalent to 2 μg kg^{-1} Oliceridine or 0.02 μg kg^{-1} sufentanil), a background infusion of 2 mL,$^{-1}$ and a 2 mL bolus dose (equivalent to 4 μg kg^{-1} Oliceridine or 0.04 μg kg^{-1} sufentanil) with a 10-minute lockout interval. Everyone else involved, like patients, surgeons, and post-anesthesia care unit (PACU) nurses, did not know which group each participant was in.

Intervention

All participants adhered to the usual preoperative fasting rule (6 h no solids, 2 h no colored fluids) and took no premeds. Once in the operating room, regular ASA monitors were put on, and an intravenous access was started. General anesthesia was induced intravenously using dexamethasone (5 mg), propofol (2 mg kg^{-1}), sufentanil (0.3 μg kg^{-1}), and rocuronium (0.6 mg kg^{-1}). Mechanical ventilation was started by using 6–8 mL kg^{-1} tidal volume and 10–12 breaths each minute. The anesthesia was sustained by using propofol, sufentanil, and sevoflurane, aiming for a bispectral index of 40–60. Three investigators, each with over five years' clinical experience, handled all anesthetic tasks, while four skilled surgeons performed the surgeries.

Patients underwent monitoring in the PACU one hour subsequent to surgery. When leaving, all patients were awake and could clearly tell the investigator how much pain they felt. A prepared PCA electronic pump was subsequently initiated for postoperative pain control, and both patients and their family members were instructed on its appropriate use. Follow-up assessments were conducted at 3, 8, 24, and 48 h postoperatively. Pain intensity was assessed by employing the numeric rating scale (NRS, ranging from 0 to 10). Subjects with an NRS score > 4 received 40 mg parecoxib sodium as rescue analgesia, with additional doses administered as needed.[20,21] If ineffective, 100 mg tramadol was administered. Severe nausea and vomiting were treated with 5 mg tropisetron. All interventions and observations were accurately recorded, and any other adverse reactions were promptly managed with appropriate symptomatic treatment and documented.

Outcomes and Data Collection

The primary outcome of this study was the sum of pain intensity difference (SPID) of NRS at rest state during 48 h postoperatively. Secondary outcomes included: (a) SPIDs and NRS at rest state during 3 h, 8 h, and 24 h postoperatively; (b) SPIDs and NRS at active state during 3 h, 8 h, 24 h and 48 h postoperatively; (c) the incidence of nausea and vomiting within 48 h; and (d) the incidence of respiratory depression (SPO_2 <90% or respiratory rate of <8 breaths/min) within 48 h. All unfavorable events were recorded. The SPID for a given time interval (t) is calculated as follows: $SPID_t = \Sigma(NRS_{ti} - NRS_{baseline}) \times (t_i - t_{i-1})$.

Demographic and baseline characteristics of the patients were systematically recorded, encompassing age, sex, height, weight, ASA physical status, and duration of surgery. Additionally, intraoperative sufentanil consumption and other analgesic medications administered on the ward were also documented.

Sample Size

We assumed a mean difference of −12.77 and a pooled standard deviation of 36.37 for the primary endpoint between the Oliceridine and sufentanil groups according to previous study and our pretrial.[20] Subsequently, a two-sample non-inferiority *t*-test was carried out by using a one-sided alpha of 0.025, power of 90%, a non-inferiority margin of 10, and

a 1:1 allocation ratio. The margin of Δ=10 was determined by applying a 60% retention factor to the 48-hour SPID difference between morphine and placebo (M1 = −27.7) reported in prior evidence.[20] The calculation, performed with PASS software, indicated a requirement of 55 subjects per group. To account for a potential 20% dropout rate, the total sample size was increased to 138 subjects, with 69 allocated to each group.

Statistical Analysis

Baseline characteristics and all outcomes were summarised as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables, and count (percentage) for categorical variables. With regard to primary outcome, non-inferiority was declared if the upper bound of the two-sided 95% confidence interval (CI) for the mean difference in the primary outcome did not exceed the pre-specified non-inferiority margin of 10 in the intent-to-treat set. With respect to secondary outcomes, continuous variables with a normal distribution were compared by carrying out the independent samples *t*-test. Those with a non-normal distribution were compared by conducting the Mann–Whitney *U*-test. Categorical variables, including secondary and safety outcomes, were analyzed by performing the Chi-square test or Fisher's exact test, as appropriate. A post hoc sensitivity analysis was performed using a linear regression model to adjust for the intraoperative dose of sufentanil. Statistical significance was defined as a two-sided P value < 0.05 and all analyses were performed using R software (version 4.4.2).

Results

After screening 186 patients, 138 subjects were enrolled in this study ultimately, and then randomly assigned to Group Oliceridine (n=69) and Group sufentanil (n=69) (Figure 1). No participants were lost to follow-up. The intention-to-treat set and per-protocol set comprised the same 138 participants. The mean age of subjects was 71.5 (SD 4.8) years, and 83% were female. There were no significant differences in the baseline characteristics of patients, types of surgery and postoperative medication between these two groups. Nevertheless, Group sufentanil had a lower dose of sufentanil during the surgery period (Table 1).

For primary outcome, the rest state SPID during 48 h postoperatively ($rSPID_{48h}$) was 135.36 (47.63) in Group Oliceridine versus 142.49 (53.91) in Group sufentanil (Figure 2). The mean difference between these two group was −7.13 (95% CI: −24.26 to 10.00). The upper bound of the 95% CI did not exceed the pre-specified non-inferiority margin of 10, which confirmed non-inferiority (P for non-inferiority: 0.025). The SPIDs at other time points including rest or active state displayed no conspicuous distinction between Group Oliceridine and Group sufentanil. Given the significant

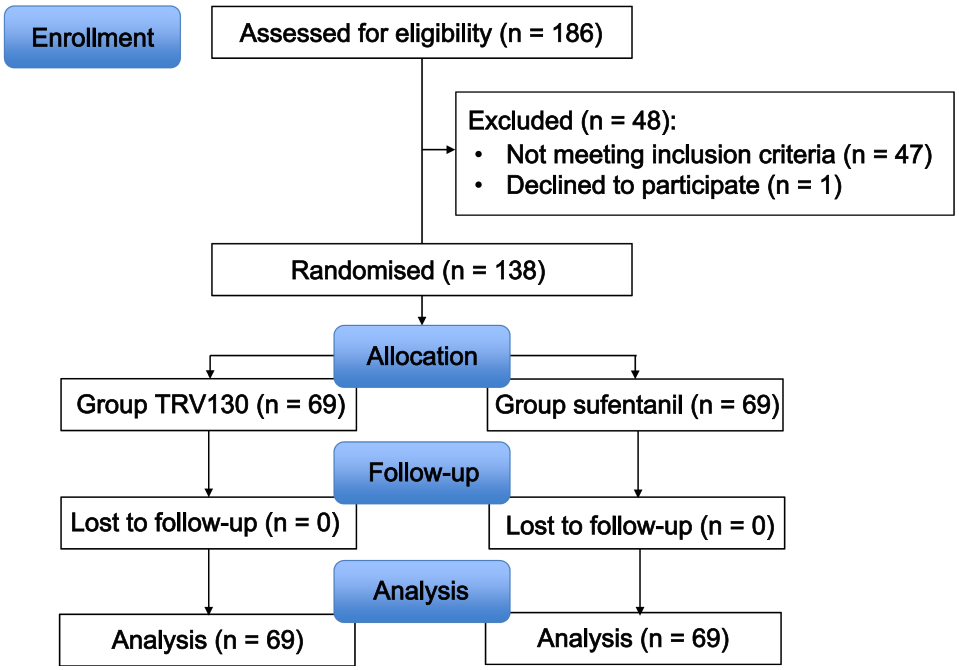

Figure 1 The Study flow diagram.

Table 1 Basic Characteristics

Characteristics	Oliceridine (n=69)	Sufentanil (n=69)	P value[a]
Sex			0.110
Male	8 (11.59%)	15 (21.74%)	
Female	61 (88.41%)	54 (78.26%)	
Age (year)	71.99 (4.98)	70.97 (4.54)	0.234
Weight (kg)	64.45 (8.76)	65.38 (9.48)	0.548
Height (cm)	159.17 (6.13)	159.43 (7.11)	0.512
ASA physical status			
1 (Healthy)	0 (0)	0 (0)	
2 (Mild systemic disease)	69 (100%)	69 (100%)	
Duration of surgery (min)	83.12 (19.67)	80.72 (21.66)	0.304
The dose of sufentanil during the surgery period (μg)	49.34 (2.43)	46.23 (5.58)	<0.001
Surgery type			0.401
Bicompartmental knee arthroplasty with robot-assisted	39 (56.52%)	33 (47.83%)	
Unicompartmental knee arthroplasty with robot-assisted	11 (15.94%)	8 (11.59%)	
Bicompartmental knee arthroplasty without robot-assisted	17 (24.64%)	26 (37.68%)	
Unicompartmental knee arthroplasty without robot-assisted	2 (2.90%)	2 (2.90%)	

Notes: The data was presented as n (%) or mean (standard deviation). [a]Pearson's Chi-squared test; Two Sample *t*-test; Fisher's exact test.
Abbreviation: ASA, American Society of Anesthesiologists,

difference between the two groups in intraoperative sufentanil dose, a post hoc analysis adjusting for this confounder showed that the mean difference for $rSPID_{48h}$ failed to meet the non-inferiority criterion (mean difference, −2.45; 95% CI, −20.60 to 15.70) (Supplemental Table 1).

Consistent with the SPID results, NRS scores at rest and during activity showed no significant difference between the Oliceridine and Sufentanil groups at any time point. As illustrated by our observations, while the vast majority of patients

	TRV130 (n=69) Mean (SD)	Sufentanil (n=69) Mean (SD)	Mean difference (95%CI)	P value[b]
Primary outcome				
$rSPID_{48h}$	135.36 (47.63)	142.49 (53.91)	−7.13 (−24.26 to 10.00)[a]	0.412
Secondary outcome				
$rSPID_{24h}$	69.28 (27.34)	71.88 (28.71)	−2.61 (−12.05 to 6.83)	0.586
$rSPID_{8h}$	12.00 (8.08)	11.83 (6.73)	0.17 (−2.33 to 2.68)	0.891
$rSPID_{3h}$	0.84 (1.80)	1.10 (1.48)	−0.26 (−0.81 to 0.29)	0.353
$rSPID_{24-48h}$	66.09 (26.16)	70.61 (29.93)	−4.52 (−13.99 to 4.94)	0.346
$rSPID_{8-24h}$	57.28 (23.02)	60.06 (27.08)	−2.78 (−11.25 to 5.68)	0.517
$aSPID_{48h}$	185.59 (54.75)	193.00 (60.23)	−7.41 (−26.79 to 11.97)	0.451
$aSPID_{24h}$	95.51 (27.73)	97.35 (31.51)	−1.84 (−11.84 to 8.15)	0.716
$aSPID_{8h}$	19.22 (9.57)	17.58 (7.77)	1.64 (−1.30 to 4.57)	0.272
$aSPID_{3h}$	1.97 (2.69)	1.86 (2.12)	0.12 (−0.70 to 0.93)	0.779
$aSPID_{24-48h}$	90.09 (34.29)	95.65 (33.81)	−5.57 (−17.03 to 5.90)	0.339
$aSPID_{8-24h}$	76.29 (23.79)	79.77 (30.12)	−3.48 (−12.62 to 5.66)	0.453

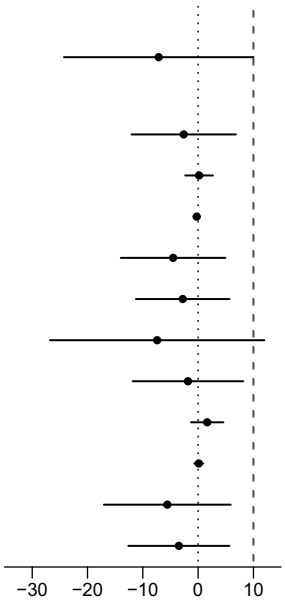

Figure 2 Comparison of SPIDs between treatment groups. Data are mean (SD) or mean difference (95% CI). [a]The upper bound of the 95% confidence interval for $rSPID_{48h}$ was 9.9977, which is less than the non-inferiority margin of 10 that had been pre-specified. The P value for the non-inferiority test was 0.02498. [b]Two-sided independent *t*-test.
Abbreviations: rSPID, resting summed pain intensity difference; aSPID, active summed pain intensity difference; CI, confidence interval.

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were pain-free at 1 h postoperative (The median (first quartile, third quartile)) of both groups were 0.00 (0.00, 0.00) no matter at rest or active), pain intensity increased thereafter. This trend was most pronounced during activity, with a marked rise after 8 h postoperative ($aNRS_{8h}$: 4.00 (2.00, 4.00) vs. 3.00 (2.00, 4.00), $aNRS_{24h}$: 5.00 (4.00, 6.00) vs. 5.00 (4.00, 6.00), $aNRS_{48h}$: 4.00 (3.00, 4.00) vs. 4.00 (3.00, 5.00)) (Table 2).

For safety outcome, nausea occurred in 23 (33.33%) participants in Group Oliceridine and 35 (50.72%) participants in Group sufentanil within 48 h postoperatively; vomiting occurred in 10 (14.49%) participants in Group Oliceridine and 24 (34.78%) participants in Group sufentanil. The incidence of nausea and vomiting within 48 hours postoperatively was much lower in the Oliceridine group than in the sufentanil group (P = 0.039 and P = 0.006, respectively). No cases of respiratory depression were observed in either group (Table 3).

Discussion

To our knowledge, we report the first randomized trial comparing a Oliceridine-based patient-controlled analgesia (PCA) pump with a sufentanil-based PCA pump in elderly patients. The results demonstrate that Oliceridine provides non-inferior analgesic efficacy to sufentanil while yielding a significantly lower incidence of nausea and vomiting within the first 48 hours postoperatively.

As a G protein-biased μ-opioid receptor agonist, oliceridine preferentially activates G-protein signaling and reduces β-arrestin recruitment, which was a mechanism recommended for the preservation of potent analgesia and the mitigation of undesirable effects simultaneously.[22] This biased signaling profile not only differentiates it from morphine in vitro, but also underscores its ameliorated safety outcomes in animals. However, this profile gives rise to less respiratory depression and gastrointestinal dysfunction at equianalgesic doses.[5,8,9,23,24] In humans, Oliceridine exhibited remarkable,

Table 2 The Numeric Rating Scale of Each Time-Point at Rest or Active State

Measurements	Oliceridine (n=69)	Sufentanil (n=69)	P value[a]
$rNRS_{1h}$	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.173
$rNRS_{3h}$	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.145
$rNRS_{8h}$	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	0.410
$rNRS_{24h}$	4.00 (3.00, 4.00)	3.00 (3.00, 4.00)	0.876
$rNRS_{48h}$	3.00 (2.00, 3.00)	3.00 (2.00, 4.00)	0.611
$aNRS_{1h}$	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.283
$aNRS_{3h}$	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.787
$aNRS_{8h}$	4.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.201
$aNRS_{24h}$	5.00 (4.00, 6.00)	5.00 (4.00, 6.00)	0.687
$aNRS_{48h}$	4.00 (3.00, 4.00)	4.00 (3.00, 5.00)	0.236

Notes: The data was presented as Median (first quartile, Third quartile). [a]Wilcoxon rank sum test.

Table 3 The Other Secondary Outcomes

Measurements	Oliceridine (n=69)	Sufentanil (n=69)	P value[a]
Nausea	23 (33.33%)	35 (50.72%)	0.039
Vomiting	10 (14.49%)	24 (34.78%)	0.006
Oxygen saturation < 90%	0	0	
Respiratory rate ≤ 8 breaths/min	0	0	
Postoperative medication			
Parecoxib sodium	66 (95.65%)	69 (100.00%)	0.245
Tramadol	14 (20.29%)	8 (11.59%)	0.163
Tropisetron	14 (20.29%)	8 (11.59%)	0.163

Notes: The data was presented as n (%). [a]Chi-square test.

dose-related drug behavior and gives strong pain relief in both healthy volunteers and post-surgery pain tests, suggesting that it is comparable to morphine but with fewer side effects.[14–16] Proof also shows it's useful in tough medical cases, like giving quick and lasting pain relief to burn patients.[17,25]

Our results match earlier studies showing that Oliceridine PCA works was comparable to regular opioid PCA for pain relief.[26] Unlike previous studies that mainly compared Oliceridine with morphine, a classic opioid, our study is the first to test Oliceridine against sufentanil, a commonly used opioid in Chinese clinics. As one of the fentanyls, sufentanil is a synthetic μ-opioid receptor agonist, which is 50 to 100 times stronger than morphine in the body, but its effects are similar, including pain relief, drowsiness, slowed breathing, constipation, euphoria, and the risk of tolerance and addiction.[27] In everyday use, sufentanil PCA works better for pain relief than morphine, with fewer side effects. However, some patients still feel sick and vomit, and doctors still worry about breathing problems, especially in older people. The Oliceridine PCA dosage was selected on the basis of our previous studies,[11,28] and the lockout interval was determined in line with the Expert Consensus on Postoperative Pain Management in Adults (2017) issued by the Chinese Society of Anesthesiology. As found before, fewer patients in the Oliceridine group felt sick and vomited. In particular, the nausea rate (33.33%) stayed similar, while the vomiting rate (14.49%) rose slightly.[29] This outcome might stem from more women in our group. Compared to SHR8554, another type of μ-opioid drug, our Oliceridine group had more nausea but similar vomiting rates.[20] In contrast, our Oliceridine group saw fewer cases of both nausea and vomiting than in a past study.[30] This phenomenon may be the result of differences in surgical type The reason is that abdominal procedures are bound up with a more striking risk of postoperative nausea and vomiting. And the application of dexamethasone used in our study also lead to a lower incidence of nausea and vomiting. Importantly, our study witnessed no breathing problems, which was dissimilar from earlier reports.[28] Differences in surgery type and postoperative analgesic dosing may be the primary reason why the above phenomena occurred. Abdominal surgeries often bring about breathing issues, but our study included patients having knee replacements, which do not usually affect breathing. Moreover, using both general anesthesia and ultrasound-guided nerve block in our plan cut down opioid needs. The Oliceridine PCA regimen also had a slow basal rate, with just 0.2 mg per bolus (for a 50 kg patient). Follow-up records show not every patient needed extra doses. And, we acknowledge that several earlier studies have indicated a significant influence of intraoperative sufentanil dosage on postoperative morphine consumption, pain levels, and hyperalgesia.[31–33] Therefore, to ensure the robustness of our findings, we performed a sensitivity analysis of the analgesic scores at each follow-up time point. However, after adjustment for the intraoperative dose of sufentanil, the mean difference of $rSPID_{48h}$ failed to meet the non-inferiority criterion, which suggested that our results are not robust. This sensitivity analysis reveals that the apparent non-inferiority in the primary analysis could be partially attributed to, or confounded by, differences in intraoperative analgesic management. These findings should be interpreted with caution and warrant further research for confirmation.

In this study, in contrast to studies using a standardized fixed-dose regimen, our protocol individualized the analgesic pump dosage based on patient body weight, thereby prioritizing inter-individual variation and delivering a truly personalized analgesic regimen. Nevertheless, we should note several limitations. First, this was a trial at one center. As a top orthopedic hospital, our study's surgery and anesthesia methods are commonly used for quick recovery. Second, we only included patients with ASA I–II status and BMI in a set range. Thus, patients with serious health risks like severe chronic illnesses, obesity, or sleep apnoea were not included. While the utility of oliceridine in such risky groups requires dedicated proof, its mechanistic profile suggests the observed safety benefits might be particularly beneficial for, and could be extrapolated to, frail elderly patients with reduced physiologic reserve (eg., ASA ≥III), pending confirmatory studies. Third, owing to the inclusion of elderly patients and associated clinical safety concerns, a conservative, lower-dose PCA pump regimen was deliberately chosen. This approach, however, likely led to increased consumption of supplemental analgesics on the ward, which may have compromised the interpretation of the primary outcome by introducing a potential confounding variable. Nevertheless, our non-inferiority conclusion likely applies to this overall, multimodal analgesic strategy, which aligns with recommended practice for elderly patients.[34,35] This showed that within such a safety-oriented protocol, an oliceridine-based regimen is not inferior to one based on sufentanil. Finally, while this study focused on analgesic efficacy and select disadvantageous effects, it did not address economic implications. As noted by Simpson et al,[36] using Oliceridine instead of morphine for 1000 patients cost $96,623 more on pain drugs.

Nonetheless, this cost could be balanced by fewer ORAEs: managing ORAEs with oliceridine costs $528,424, while morphine costs $852,429, saving $324,005. Moreover, using Oliceridine just for high-risk patients and morphine for others could boost savings to $363,944.[37] In other words, it remains ambiguous about the cost difference between Oliceridine and sufentanil.

Nevertheless, the findings of this study indicate that with the assistance of regional nerve blocks, most patients reported satisfactory analgesia within the first 3 h postoperatively, with the majority exhibiting NRS scores below 4. Nonetheless, pain levels began to increase by the 8 h mark. These observations underline the imperative for continued exploration of analgesic strategies following total knee arthroplasty, which is a research priority that aligns with two ongoing carried out by our research group at present.

Conclusion

Our study suggests that Oliceridine may have a non-inferior analgesic to sufentanil for PCA pump subsequent to knee arthroplasty in the elderly. And the advantage of Oliceridine at the aspect of lessening nausea and vomiting in elderly patients has been confirmed. Future research is necessary to determine whether they could potentially supplement or even replace traditional opioids, particularly cost-effective options like fentanyl.

Abbreviations

TKA,Total knee arthroplasty; patient-controlled analgesia, PCA; ORAEs, opioid-related adverse events; BMI, body mass index; PACU, post-anesthesia care unit; NRS, numeric rating scale; SPID, sum of pain intensity difference; SD, standard deviation; IQR, interquartile range; CI, confidence interval.

Data Sharing Statement

Subject to the policies of the Ethics Committee, the anonymized dataset from this study can be accessed by submitting a reasonable academic request to the corresponding author, along with a research protocol approved by the applicant's local ethics committee.

Ethics Approval and Informed Consent

All procedures performed on the patients were in accordance with the 1964 helsinki declaration and its later amendments. The study was approved by the Ethical Committee of Shanghai Sixth People's Hospital, affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, China (approval number: 2024-169-(1)).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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