Research Square

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Effect of Oliceridine Fumarate on Emergence Agitation in Elderly Patients Undergoing Total Knee Arthroplasty：A Prospective Randomized Controlled Clinical Study

Ying Zhang
Shanghai Jiao Tong University
Yu-Shan Dong
Shanghai Jiao Tong University
Xiao-Zhu Zhai
Shanghai Jiao Tong University
Ai-Hua Qi
Shanghai Jiao Tong University
Xiao-Tao Xu
Shanghai Jiao Tong University
Xiao-Cui Guo
Fudan University Pudong Medical Center
Nan-Nan Zhang
330770970@qq.com

Shanghai Jiao Tong University

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Abstract

Objective:To evaluate the impact of oliceridine fumarate on emergence agitation (EA) when used for postoperative analgesia in elderly patients undergoing total knee arthroplasty (TKA).

Methods :A single-center, randomized, double-blind, parallel-controlled trial was conducted in 114 elderly patients (aged ≥ 65 years) with American Society of Anesthesiologists (ASA) physical status □–□, who underwent elective unilateral TKA. Patients were randomly allocated to two groups (n = 57 each): oliceridine fumarate group (Group O) and sufentanil group (Group S). Postoperative analgesia was provided with oliceridine fumarate (Group O) or sufentanil (Group S), with standardized intraoperative anesthesia induction and maintenance protocols for both groups. Primary outcome was the incidence of EA. Secondary outcomes included EA severity, recovery and extubation times, hemodynamic parameters (heart rate [HR], mean arterial pressure [MAP]) at before induction (T0), 5 min after extubation (T1), and 30 min after extubation (T2), and postoperative adverse reaction rates.

Results:The incidence of EA was significantly lower in Group O (7.02%) than in Group S (22.81%) ($P < 0.05$), with notably lower EA scores in Group O ($P < 0.05$). At T1, HR and MAP fluctuations were significantly smaller in Group O ($P < 0.05$); at T2, no significant differences in HR and MAP were observed between the two groups ($P > 0.05$). The overall incidence of postoperative adverse reactions was 10.53% in Group O and 26.32% in Group S ($P < 0.05$). No severe adverse events (e.g., severe respiratory depression) were observed in either group.

Conclusion:For postoperative analgesia in elderly TKA patients, oliceridine fumarate was superior to sufentanil in reducing EA and severity, shortening recovery and extubation times, maintaining hemodynamic stability, and lowering adverse reaction risk. It appears to be a safe and effective option for perioperative analgesia in this population.

Introduction

With the aging of the global population, the number of elderly patients undergoing total knee arthroplasty (TKA) has increased significantly in recent years[1]. Postoperative analgesia is a key part of perioperative management for elderly TKA patients, as inadequate analgesia can lead to a series of complications, among which emergence agitation (EA) is one of the most common and dangerous [2]. EA refers to a transient state of mental disturbance characterized by restlessness, disorientation, and aggressive behavior during the recovery period after general anesthesia, which not only affects the patient's recovery experience but also increases the risk of postoperative falls, wound dehiscence, and cardiovascular adverse events [3].

Elderly patients have physiological characteristics such as decreased organ function, slowed drug metabolism, and high incidence of comorbidities, making them more susceptible to EA after TKA [4]. Traditional opioid analgesics (such as sufentanil) are widely used in postoperative analgesia, but their long half-life and high incidence of adverse reactions (such as respiratory depression, sedation, and

nausea and vomiting) may further increase the risk of EA in elderly patients [5]. Therefore, exploring a safe and effective analgesic drug to reduce the incidence of EA in elderly TKA patients has become an important clinical research direction.

Oliceridine fumarate is a novel μ-opioid receptor agonist with high selectivity and rapid metabolism. It has been shown to have good analgesic effect and fewer adverse reactions in postoperative analgesia of orthopedic patients [6, 7]. However, there are few studies focusing on the effect of oliceridine fumarate on EA in elderly TKA patients, and the relevant clinical evidence is still insufficient [8]. Based on this, this study designed a single-center, randomized, double-blind, parallel-controlled trial to compare the effect of oliceridine fumarate and sufentanil on EA incidence in elderly TKA patients, aiming to provide clinical basis for the rational selection of postoperative analgesic drugs in this population.

Materials and Methods

Study Design and Ethics

This study was a prospective, single-center, randomized, double-blind, parallel-controlled trial. This trial was approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine (Approval No.: 2025-123-1). The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2500110299) on 11th October 2025. The trial was conducted in accordance with the Declaration of Helsinki and the CONSORT 2010 statement [9]. Written informed consent was obtained from all participants and their legal guardians prior to study enrollment.

Enrollment

This randomized controlled trial was conducted at a tertiary teaching hospital in China (15th October 2025–15th February 2026). Inclusion Criteriawere as follows: Age 65–80 years; American Society of Anesthesiologists (ASA) physical status□–□; Scheduled for elective unilateral total knee arthroplasty; Body mass index (BMI) 18.5–28.0 kg/m²; Frailty status assessed by the Clinical Frailty Scale (CFS) with a score ≤ 6.Patients were excluded based on the following criteria: Allergy to any study drugs (oliceridine fumarate, sufentanil, ropivacaine, etc.); Severe cardiopulmonary, hepatic, or renal dysfunction (cardiac function ≥ grade □, moderate to severe pulmonary insufficiency, hepatic and renal function ≥ Child-Pugh grade B); Contraindications to femoral nerve/lateral femoral cutaneous nerve block (puncture site infection, coagulation disorders, peripheral neuropathy, etc.); History of long-term opioid use (regular use within 3 months before surgery); Severe frailty (CFS score ≥ 7); Uncontrolled preoperative pain (resting Visual Analog Scale [VAS] score ≥ 4).

Frailty Status Assessment

Preoperative frailty status was assessed using the CFS by two trained attending anesthesiologists (standardized via prior training, inter-rater reliability kappa = 0.85). Discrepancies were resolved by joint

discussion. The CFS uses a 1–9 scale (1 = very healthy, 9 = terminal illness); patients with a score ≤ 6 were included, with non-frailty defined as CFS < 5 and frailty as CFS ≥ 5 for subgroup analysis [10].

Randomization and Blinding

A 1:1 randomization sequence was generated using SPSS 26.0 by an independent statistician not involved in trial conduct. Allocation concealment was achieved using sealed, opaque, sequentially numbered envelopes held by an independent nurse. Study drugs (oliceridine fumarate 2 mg/5 mL and sufentanil 10 μg/5 mL) were prepared by an anesthetic nurse not involved in anesthesia administration, patient care, or outcome assessment, and formulated to have identical appearance, volume, and color for blinding. Patients, anesthesiologists (nerve block, anesthesia management, extubation), outcome assessors, and data statisticians were all blinded to group allocation. Unblinding was performed by the independent statistician after data locking.

Anesthesia and Analgesia Protocol

On arrival in the operating room, all patients underwent routine monitoring (blood pressure, HR, electrocardiogram, oxygen saturation [SpO_2]), and peripheral venous access was established with lactated Ringer's solution infused at 5–10 mL/(kg·h). Pre-induction ultrasound-guided femoral nerve block combined with lateral femoral cutaneous nerve block was performed by the same senior anesthesiologist using a Philips EPIQ5 ultrasound system. With the patient supine, the ultrasound probe was placed adjacent to the femoral artery below the inguinal ligament to identify the femoral and lateral femoral cutaneous nerves; in-plane puncture was performed (disinfection range: 15 cm around the puncture site, puncture depth: 2–3 cm), and 15 mL and 5 mL of 0.375% ropivacaine (total 20 mL) were injected after negative blood aspiration.

Anesthesia induction was performed with remifentanil 1.5 μg/kg, propofol 1.5–2.0 mg/kg, and rocuronium 0.6 mg/kg intravenously. Tracheal intubation was performed after loss of consciousness and adequate muscle relaxation (train-of-four ratio < 0.1), with mechanical ventilation set to tidal volume 6–8 mL/kg, respiratory rate 12–14 breaths/min, and end-tidal carbon dioxide partial pressure 35–45 mmHg. Anesthesia maintenance was with sevoflurane (minimum alveolar concentration 0.8–1.2) and continuous remifentanil infusion 0.1–0.3 μg/(kg·min), adjusted to maintain MAP within ± 20% of baseline; ephedrine (5–10 mg) or phenylephrine (50–100 μg) was administered intravenously as needed.

Perioperative analgesic bridging was administered 15 min before surgery end: Group S (sufentanil group) received sufentanil 10 μg (diluted to 5 mL with normal saline), and Group O (oliceridine fumarate group) received oliceridine fumarate 2 mg (diluted to 5 mL with normal saline)—dosages based on prior data demonstrating equianalgesic potency in elderly orthopedic patients [11]. Sevoflurane and remifentanil were discontinued 5 min before surgery end; extubation was performed when spontaneous breathing (respiratory rate ≥ 10 breaths/min, tidal volume ≥ 300 mL), consciousness, and muscle strength (train-of-four ratio ≥ 0.9) recovered.

Postoperative patient-controlled intravenous analgesia (PCIA) was standardized: Group S received sufentanil 100 μg + ondansetron 8 mg (antiemetic) + normal saline to 100 mL; Group O received oliceridine fumarate 20 mg + ondansetron 8 mg + normal saline to 100 mL. PCIA parameters: background infusion 2 mL/h, bolus dose 1 mL, lockout time 15 min, 4-h limit 20mL. Rescue analgesia (tramadol 50 mg intravenously, repeatable every 6 h) was provided for resting VAS score ≥ 4 or activity VAS score ≥ 5.

Outcome Measures

All outcomes were assessed and documented by the research coordinator. The primary outcome of this study was the incidence of EA, assessed using the Riker Sedation-Agitation Scale (score ≥ 5 = agitation). Scale criteria: 1 = unresponsive, 2 = very sedated, 3 = sedated, 4 = calm and cooperative, 5 = agitated, 6 = very agitated, 7 = dangerously agitated [12].Secondary outcomes included: (1)Recovery parameters: time to spontaneous breathing recovery (drug discontinuation to respiratory rate ≥ 10 breaths/min and tidal volume ≥ 300 mL), time to awakening (drug discontinuation to eye opening on command), time to extubation (drug discontinuation to tracheal tube removal); (2) Hemodynamic parameters: HR and MAP at T0 (before induction), T1 (5 minutes after extubation), and T2 (30 minutes after extubation), with fluctuations calculated as the difference from T0; (3) Postoperative adverse reactions (nausea/vomiting, dizziness/drowsiness, respiratory depression [respiratory rate < 10 breaths/min or SpO_2 <90%]) within 24 h [13].

Sample Size Calculation

Sample size was calculated based on the primary outcome (EA incidence) with reference to relevant domestic and foreign literature [14, 15, 16]. According to the reported EA incidence in elderly TKA patients receiving opioid postoperative analgesia, the expected between-group difference in EA incidence was set at 15%, with a two-sided $\alpha = 0.05$ and test power $(1 - \beta) = 0.8$. Using the two independent samples rate comparison method in SPSS 26.0, the required sample size was calculated to be 52 patients per group. Considering a potential dropout rate of 10% during the trial, the final sample size was determined to be 57 patients per group, with a total of 114 patients enrolled in the study.

Statistical Analysis

SPSS 26.0 was used for analysis. Continuous data are presented as mean ± standard deviation ($x \pm s$) and compared using independent samples t-test; categorical data as n(%) and compared using χ^2 test; ordinal data using rank-sum test.EA severity score was analyzed by rank-sum test (Mann-Whitney U test). Severe EA was defined as Riker Sedation-Agitation Scale score ≥ 6. $P < 0.05$ was considered statistically significant.

Results

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists physical status; CFS: Clinical Frailty Scale; O group, Oliceridine Fumarate group; S group, Sufentanil group.

Primary Outcome Indicator

The incidence of emergence agitation (EA) was significantly lower in Group O than in Group S, with a risk difference (RD) of 15.79% (95% CI: 2.87–28.71%) and a relative risk (RR) of 3.25 (95% CI: 1.18–8.95). There were no significant differences in the distribution of Riker Sedation-Agitation Scale (RSAS) scores between the two groups (P>0.05), including scores of 3, 4, 5, and 6 points. The median EA severity score was significantly lower in Group O than in Group S (4.0 vs 4.5, P=0.032) (Table 2).

Table 2 Incidence of Emergence Agitation, RSAS Scores and EA Severity in Two Groups

Variable	Group O (n=57)	Group S (n=57)	P-Value	Estimate (95% CI)
The incidence of Emergence Agitation [n, (%)]	4 (7.02)	13 (22.81)	0.028	2.87%□28.71% (RD); 1.18□8.95 (RR)
RSAS Score [n, (%)]				
3 point	13 (22.81)	10 (17.54)	0.478	-
4 point	40 (70.18)	34 (59.65)	0.275	-
5 point (agitated)	3 (5.26)	7 (12.28)	0.231	-
6 point (very agitated)	2 (3.51)	6 (10.53)	0.172	-
EA severity score (median, IQR)	4.0 (4.0, 5.0)	4.5 (4.0, 6.0)	0.032	-

Note: Data were presented as number (%) or median.

Abbreviations: O group, Oliceridine Fumarate group; S group, Sufentanil group; IQR, interquartile range; EA, Emergence Agitation; RSAS, Riker Sedation-Agitation Scale.

Comparison of Hemodynamic Indicators during Recovery Period in Both Groups

Baseline HR and MAP were comparable between the two groups (all P>0.05). At T1, HR and MAP in Group O were significantly lower than those in Group S (P<0.001). No significant differences in HR and MAP were found between the two groups at T2 (P>0.05) (Table 3).

Table 3 HR and MAP at Different Time Points During Recovery Period in Two Groups

Variable	Group O (n=57)	Group S (n=57)	P-Value
HR, beats/min			
T0	71.7±6.4	72.5±6.8	0.613
T1	77.3±6.9	82.75±7.8	<0.001
T2	75.1±6.7	74.2±6.5	0.672
MAP, mmHg			
T0	98.0±8.3	97.2±8.0	0.685
T1	103.5±8.6	115.2±9.3	<0.001
T2	101.1±7.9	100.3±8.1	0.715

Note: Data were presented as mean ± SD; T0: before induction, T1: 5 minutes after extubation, T2: 30 minutes after extubation.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; O group, Oliceridine Fumarate group; S group, Sufentanil group.

Adverse Reactions

The incidences of nausea and vomiting, and dizziness/drowsiness were significantly lower in Group O than in Group S (P<0.05). The incidence of pruritus was lower in Group O than in Group S, but the difference was not statistically significant (P=0.076). The incidence of respiratory depression was low in both groups, with no significant difference between the two groups (P=0.158) (Table 4).

Table 4 Incidence of Adverse Reactions in Two Groups

Variable	**Group O (n=57)**	**Group S (n=57)**	**P-Value**
Nausea and vomiting [n, (%)]	6 (10.53)	15 (26.32)	0.025
Dizziness/drowsiness [n, (%)]	4 (7.02)	12 (21.05)	0.029
Pruritus [n, (%)]	1 (1.75)	6 (10.53)	0.076
Respiratory depression [n, (%)]	0 (0.0)	3 (5.26)	0.158

Note: Data were presented as number (%); Respiratory depression was defined as respiratory rate <10 breaths/min or SpO_2 <90%.

Abbreviations: O group, Oliceridine Fumarate group; S group, Sufentanil group.

Discussion

This study designed a single-center, randomized, double-blind, parallel-controlled trial to explore the effect of oliceridine fumarate on EA incidence in elderly patients undergoing TKA, with sufentanil as the control group. The core purpose of this study is to address the clinical dilemma that elderly TKA patients are prone to EA after surgery, and traditional opioid analgesics have limited effect and potential safety risks, providing a more safe and effective analgesic option for this special population.

EA is a common complication in the recovery period of general anesthesia, especially in elderly patients undergoing orthopedic surgery. Its occurrence is closely related to multiple factors, including inadequate analgesia, drug metabolism disorder, cognitive function decline, and intraoperative stress response [17]. Elderly patients have reduced liver and kidney function, slow drug clearance, and high incidence of comorbidities such as hypertension and diabetes, which further increase the susceptibility to EA [18]. In this study, we strictly controlled the inclusion and exclusion criteria, selected elderly patients aged 65–80 years with ASA grade Ⅱ–Ⅲ and CFS score ≤6, and excluded patients with cognitive impairment and severe organ dysfunction, which effectively reduced the interference of confounding factors on the study results and improved the reliability of the study.

Oliceridine fumarate, as a novel μ-opioid receptor agonist, has obvious advantages over traditional opioids such as sufentanil in postoperative analgesia of elderly patients. It has high selectivity for μ-opioid receptors, can effectively relieve postoperative pain without significantly inhibiting respiratory function, and its rapid metabolism characteristics are more suitable for elderly patients with slow drug clearance [19]. A clinical study by Wang et al. (2024) showed that oliceridine fumarate can significantly reduce the incidence of EA in elderly patients undergoing orthopedic surgery, which is consistent with the research hypothesis of this study [20]. In contrast, sufentanil has a long half-life and strong sedative effect, which can easily lead to delayed awakening and increased EA risk in elderly patients, especially when combined with inhalation anesthetics such as sevoflurane [21].

In terms of the study design, we adopted a randomized, double-blind, parallel-controlled method, which is the gold standard for clinical trials and can effectively avoid the bias caused by subjective factors [22]. The allocation concealment and blinding procedures were strictly implemented in the study, ensuring that patients, anesthesiologists, outcome assessors, and data statisticians were all unaware of the group allocation, which further guaranteed the objectivity of the study results. In addition, we combined ultrasound-guided femoral nerve block with intravenous analgesia to achieve multimodal analgesia, which can effectively reduce the dosage of systemic opioids, reduce adverse reactions, and further reduce the incidence of EA [23]. This multimodal analgesia model is consistent with the current concept of enhanced recovery after surgery (ERAS), which is conducive to improving the recovery quality of elderly TKA patients [24].

The outcome measures of this study include primary outcome (EA incidence) and secondary outcomes (recovery parameters, hemodynamic parameters, and postoperative adverse reactions), which comprehensively evaluate the effect and safety of oliceridine fumarate. The Riker Sedation-Agitation Scale used in the study is a widely used tool for evaluating EA, with high reliability and validity, which can

accurately reflect the severity of EA [25]. The sample size calculation in this study was based on the relevant literature and strictly followed the statistical principles, with a test power of 0.8 and a two-sided α of 0.05, which can ensure that the study has sufficient statistical power to detect the differences between groups [26].

This study also has certain limitations. First, this is a single-center study, and the sample size is relatively limited, which may affect the generalization of the study results. Future multi-center, large-sample clinical trials are needed to further verify the conclusion. Second, the follow-up time of this study is relatively short, and the long-term effect and safety of oliceridine fumarate in elderly TKA patients need to be further observed. Third, this study did not explore the effect of oliceridine fumarate on EA in different frailty grades of elderly patients, and future studies can further stratify according to frailty status to provide more targeted clinical guidance.

Conclusion

In conclusion, oliceridine fumarate is expected to reduce the incidence of EA in elderly TKA patients, with good safety and tolerance, which is worthy of clinical promotion and application. At the same time, multimodal analgesia based on ultrasound-guided nerve block combined with oliceridine fumarate can further improve the postoperative recovery quality of elderly TKA patients, which is in line with the concept of ERAS. Future studies should focus on solving the limitations of this study and provide more sufficient clinical evidence for the rational application of oliceridine fumarate in elderly TKA patients.

Declarations

Data Sharing Statement

The data are available from the corresponding author (330770970@qq.com) on reasonable request.

Ethical Statement

This study strictly abided by the CONSORT reporting criteria for RCT. The study

approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine (Approval No.: 2025-123-1) and registered at the Chinese Clinical Trial Registry (Registration No.: ChiCTR2500110299).

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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Figures

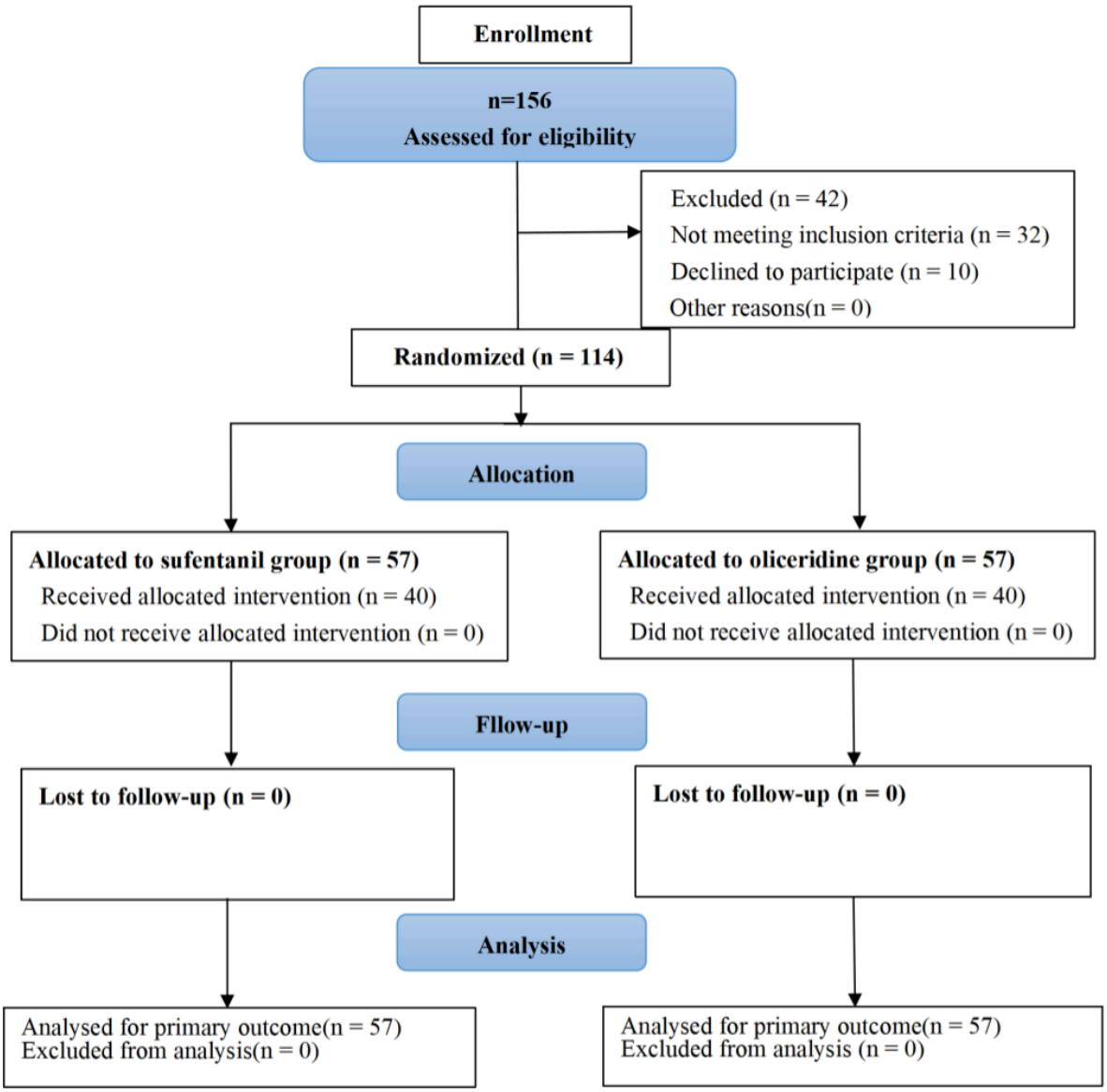


Figure 1

Consolidated Standards of Reporting Trials diagram.

Supplementary Files

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