ORIGINAL RESEARCH

Remifentanil versus Fentanyl for Analgesia in Mechanically Ventilated Patients: A Multicenter, Prospective, Randomized, Double-Blind, Parallel-Group Clinical Trial

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ABSTRACT

Purpose • Fentanyl is approved for use in many countries as an analgesic for patients requiring mechanical ventilation. However, it redistributes and accumulates easily in the plasma because of its long half-life. Remifentanil is a short context-sensitive half-life analgesic with a lower risk of redistribution and accumulation.

Materials and methods • We conducted a multicenter, randomized, double-blind, non-inferiority trial. Critically ill patients requiring mechanical ventilation were randomly allocated to receive an infusion of either remifentanil or fentanyl for up to 72 h. The primary outcome was the analgesic success rate. A 95% confidence interval lower boundary greater than -8% for the difference between the groups was considered to indicate non-inferiority between the drugs.

Results • A total of 137 patients received remifentanil (69) or fentanyl (68). Remifentanil's non-inferiority to fentanyl concerning its analgesic success rate was established (difference, 5.97%; 95% confidence interval: -3.99% to 16.35%). Mechanical ventilation duration, extubation duration, successful extubation, intensive care unit discharge, intensive care unit length of stay, and adverse events did not differ significantly between the two groups.

Conclusions • Remifentanil was non-inferior to fentanyl regarding the analgesic success rate in critically ill patients requiring mechanical ventilation. (*Altern Ther Health Med.* 2023;29(7):138-147).

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INTRODUCTION

Pain is generally associated with critically ill patients requiring invasive mechanical ventilation (MV).[1,2] Approximately more than 40% of these patients experience moderate to severe pain,[3,4] with pain-induced stress response contributing to dysfunction development.[5] The stress response activates the renin-angiotensin-aldosterone system and the hypothalamic-pituitary-adrenal axis,[6,7] resulting in impaired tissue oxygenation,[8] fluid retention,[9] increased catabolism,[10] impaired wound healing,[11] neuroinflammatory priming,[12] and impaired immune functions[13-16]. The mortality of patients requiring MV can be as high as 51.9% once they develop multiple organ dysfunction syndrome.[17] Analgesics

can relieve the pain and reduce the stress responses in these patients.[18] Stress suppression optimizes impaired tissue oxygenation, decreases catabolism, and suppresses the production and release of inflammatory mediators, thereby preventing or delaying organ dysfunction development and improving the prognosis.[5,18-22]

Fentanyl is considered a first-line analgesic drug for the treatment of non-neuropathic pain in patients requiring invasive MV, principally because of its efficacy in controlling pain and psychological discomfort mitigation.[5,21,23,24] Organ dysfunction may substantially cause fluid shifts, alter protein-binding, change metabolism, and affect the elimination of fentanyl from the body.[25] Significantly, the increased severity of illness is closely associated with these increased pharmacokinetics changes, which predispose patients to fentanyl redistribution and accumulation.[26] Thus, even when administered at the customarily used doses, fentanyl is associated with increased respiratory depression and cardiovascular adverse events (AEs),[18,23,26,27] prolonged duration of MV and weaning,[28-33] and severe intensive care unit (ICU) acquired diaphragm dysfunction.[28,29] Therefore, a new analgesic drug to address these issues would be very desirable in clinical practice.

Remifentanil is a potent, selective, short-acting opioid μ-receptor agonist with clinical analgesic potency similar to fentanyl.[34] Blood-brain balance and analgesia were achieved in healthy adults approximately 1 min after remifentanil administration. Remifentanil has a very short context-sensitive half-life regardless of the dose and duration of the infusion.[35-37] The blood concentration of remifentanil decreases rapidly after the infusion stops, and no accumulation is detected in the body.[37,38] Non-specific esterases rapidly metabolize remifentanil into inactive metabolites.[36,37] Its pharmacokinetic and pharmacodynamic properties are not affected by liver and kidney dysfunction.[39-41] It is also highly suitable for prolonged infusions, with lower redistribution and accumulation risks.[23,27,42,43]

The main reason for this discrepancy is existing studies that evaluated the efficacy and safety of remifentanil in this population of patients were based on single-center, non-blind, and small sample sizes.[44,45] Moreover, the evidence level is low.[5] Evidence-based medical research based on large, multicenter randomized clinical trials (RCTs) evaluating the efficacy and safety of remifentanil analgesia in MV patients is currently lacking. We therefore conducted a multicenter RCT to explore the efficacy and safety of remifentanil compared with fentanyl for analgesia in MV patients.

MATERIAL AND METHODS

Study design

In the present study, a multicenter, prospective, randomized, double-blind, parallel-group, positive-controlled, and non-inferiority clinical trial was conducted. This trial assessed remifentanil versus fentanyl for analgesia in critically ill patients requiring invasive MV. It was performed in 17 Chinese ICUs of Grade III and Class A teaching hospitals (the list of investigators is given in the Supplementary Appendix). NMPA (2016L00132) and the local ethics committees at each trial site approved the trial protocol premise, which was also registered at Clinical Trials (https://clinicaltrials.gov/, NCT05003570). A strict adherence to the Declaration of Helsinki guidelines for experiments on people was maintained throughout the trial. The patients or their representatives provided written informed consent/assent. This study followed CONSORT guidelines.

Study patients

The study patients were eligible if they were between 18 and 80 years old, on MV with endotracheal intubation and expected to continue MV for at least 12 h. Patients with an expected survival period of < 48 h were excluded from the study. Patients were also excluded if they had severe hepatic insufficiency (Child-Turcotte-Pugh [CTP] score > 9), if they had unstable hemodynamics (mean arterial pressure [MAP] ≤ 65 mmHg after administration of 0.5 μg/kg/min norepinephrine), received deep sedation (Richmond Agitation Sedation Scale [RASS] score of -4 to -5),[46] or had received neuromuscular blocking drugs and could not be assessed by RASS.

Randomization and masking

ICU physicians screened all patients requiring invasive MV for eligibility around the clock, 7 days a week. A stratified blocked randomization was used to assign eligible patients to remifentanil or fentanyl group in a 1:1 ratio. Randomization was stratified by the center in a randomization block size of 6.

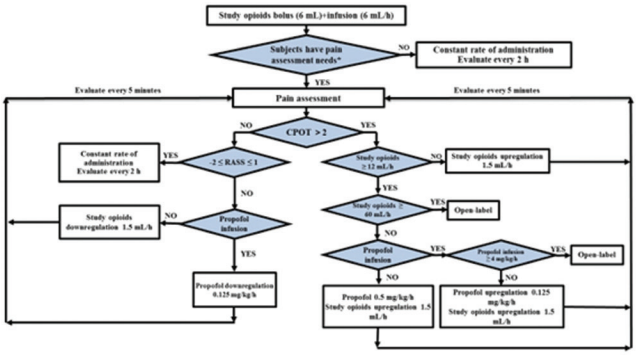
An independent blinded statistician and a person not associated with the trial generated the randomization numbers and drug blinding. Randomization numbers were produced using SAS software (ver. 9.4) and assigned using the electronic interactive web response system (IWRS) for clinical trials. All investigators, ICU staff, clinical research coordinators, data managers, statistical analysts, and patients and their families were blinded to the treatment groupings. Unblinding for individual patients could occur via the IWRS for emergencies, and the patient could withdraw from the study.

Remifentanil (3 mL Vial/1 mg) and fentanyl (50 mcg/mL Fentanyl base/10 mL ampules) were manufactured and provided by Hubei Yichang Humanwell Pharmaceutical Co., Led. We selected fentanyl as the active control since fentanyl was superior to a placebo and was recommended as the standard analgesia by previously published guidelines.[21] In the respective centers, an unblinded nurse with extensive experience in critical care medicine clinical trials prepared bolus syringes identical in appearance, size and weight. The concentrations of remifentanil and fentanyl were determined based on the body weights of individual patients, thereby ensuring that equal infusion rates were equipotent. The fentanyl mimetics were also prepared into the same bolus syringes (the additional methods are given in the Supplementary Appendix).

Study procedures

The screening period was from 72 h before the randomization of patients to enrollment. The investigators reviewed inclusion and exclusion criteria, identified patients, collected baseline data, and collected signed informed consent forms. The treatment period was from the administration of the study opioid to actual extubation, lasting up to 72 h. The patients received the study opioid infusion to maintain optimal analgesia, defined as maintaining an optimal Critical-Care Pain Observation Tool (CPOT) score of 0 to 2 (Supplementary Appendix includes the CPOT scoring details).[47] The investigators collected data on the efficacy and safety of the study opioids and the clinical data of patients. The follow-up period was from the completion of the treatment period until 48 h later. Patients received sedative/analgesic agents according to their clinical needs, followed by the discontinuation of the study drug opioid infusions. The clinical data of the patients and the data on AEs continued to be collected.

Figure 1. The Study Opioids Administration Flow Chart



Abbreviations: CPOT, Critical Care Pain Observation Tool; RASS, Richmond Agitation and Sedation Scale. CPOT and RASS Scores were Assessed Immediately when the Patients Experienced Pain, Discomfort, and Anxiety.

Dosing algorithm during the treatment period

The dosing algorithm during the treatment period was based on the recommendations of the clinical practice guidelines for analgesia and sedation in critically ill patients.[5,21,23] It was also based on the methods setting of previous RCTs,[48,49] including the following five aspects: initial dose of study opioids, dosing adjustment of study opioids, dosing algorithm and adjustment of propofol infusion, dosing algorithm and adjustment of salvage sedation infusion (propofol bolus), and dosing of open-label analgesic/sedative agents. The flowchart of the dosing algorithm is outlined in Figure 1.

Initial dose of the study opioids. The treatment was started in patients with a CPOT score of < 3. An initial infusion of a blinded study opioid was administered to all patients. In the treatment groups given remifentanil-based regimens, the patients received a bolus dose of fentanyl mimetics (placebo) initially (6 mL), followed by a continuous infusion of 6 μg/kg/h (6 mL/h) to maintain optimal analgesia. In the treatment groups given fentanyl-based regimens, the patients received an initial 1 μg/kg fentanyl bolus dose (6 mL) followed by a continuous infusion of 1 μg/kg/h (6 mL/h) to maintain optimal analgesia.

Dosing adjustment of the study opioids. Optimal analgesia was targeted by titrating the infusion in 1.5 mL/h increments (remifentanil group: fentanyl mimetics bolus + remifentanil 1.5 μg/kg/h increments; fentanyl group: fentanyl 1 μg/kg bolus + fentanyl 0.25 μg/kg/h increments). The study opioid infusion rate for patients with pain, discomfort, and anxiety (those with a CPOT score > 2) was increased to 1.5 ml/L/h. Subsequently, the CPOT scores were assessed at 5 min intervals. The increase in the infusion rate of the study opioids was discontinued when optimal analgesia was achieved. The study opioid infusion rate for patients with excessive sedation (those with a RASS score < -2) without pain was decreased to 1.5 mL/h. Then the RASS scores were assessed at 5 min intervals. The decrease in the infusion rate of the study opioids and/or propofol was discontinued when optimal analgesia was achieved.

Dosing algorithm and adjustment of propofol infusion. Propofol was initiated when optimal analgesia was not achieved at a study opioid infusion rate of 12 mL/h (remifentanil group, 12 μg/kg/h; fentanyl group, 2 μg/kg/h). The patients received an initial propofol bolus dose (0.5 mg/kg), followed by a continuous infusion at 0.5 mg/kg/h. They were treated by titrating the propofol infusion rate in 0.125 mg/kg/h increments (25% increase in the rate). The propofol infusion was reduced to treat excessive sedation without pain. Then 5 min interval was used before adjusting the dosage.

Dosing algorithm and adjustment of salvage sedation infusion (propofol bolus). Agitation was treated with a propofol bolus dose (0.5 mg/kg) and increased infusion rates of propofol and study opioids as described earlier.

Dosing of open-label analgesic/sedative agents. If the patients did not achieve optimal analgesia when the study opioid and propofol infusion rates were 60 mL/h (remifentanil, 60 μg/kg/h; fentanyl, 10 μg/kg/h) and propofol 4 mg/kg/h, then the open-label analgesic/sedative drugs were administered according to standard therapy as clinically required, followed by the discontinuation of the study opioid infusions.

Patient data collection and monitoring

Demographical data, surgical history, allergy history, drug or alcohol abuse history, concomitant diseases, pregnancy test (women of childbearing age), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were collected during the screening period. During the screening and follow-up periods, laboratory examinations were conducted; vital signs, concomitant medications, and Sequential Organ Failure Assessment scores were collected and CPOT scores, RASS scores, and AEs were carefully recorded. Vital signs included the following parameters: body temperature, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, respiratory rate, and peripheral blood oxygen saturation (SpO_2). Laboratory examinations included the following tests: routine blood,

serum biochemistry, and clotting functions. Two senior nurses assessed the CPOT and RASS scores. They resolved discrepancies by discussing them with a third senior nurse.

CPOT and RASS scores were routinely assessed every 2 h. In addition, CPOT and RASS scores were assessed immediately when the patients experienced pain, discomfort and/or anxiety. These scores were reassessed 5 min after each study opioid dose adjustment. For the first 2 h following administration of the study opioid, vital signs were recorded every 20 min, then every 2 h for the first 24 h. Finally, they were recorded every 4 h up to 72 h or until actual extubation. These parameters were also recorded immediately upon ICU discharge.

Outcomes

The primary efficacy outcome was the analgesic success rate, defined as the proportion of patients with successful analgesia compared to the number of patients in each group. Successful analgesia was defined as the occurrence of optimal analgesia for more than 70% of the time during the treatment period, typically a CPOT score between 0 and 2.

Secondary efficacy outcomes included CPOT and RASS scores during the treatment period, optimal analgesia duration during the treatment period, analgesia and sedation duration during the treatment period, proportion of optimal analgesia duration during the treatment period, and proportion of optimal analgesia and sedation duration during the treatment period. The secondary outcomes were: study opioids intervention and propofol intervention during the treatment period, MV duration, extubation duration, successful extubation, ICU discharge, ICU mortality, and ICU length of stay (LOS). Safety outcomes included AEs, serious adverse events (SAEs), and hemodynamic stability (MAP and HR) during the treatment period.

Statistical analysis

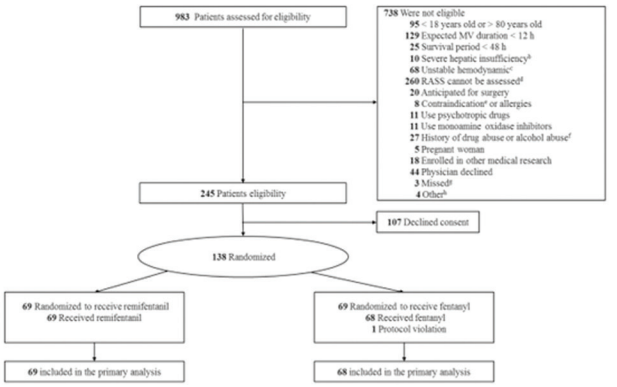
Primary efficacy outcome hypothesis was that remifentanil would be non-inferior to fentanyl based on the analgesic success rate. The analgesic success rate in the control group was expected to be 98%.[50] The clinical non-inferiority margin of -8%, α 0.025 (one-sided), power 0.85, and a 1:1 ratio were set for sample size estimation. The outcome was 55 cases in the experimental group and 55 cases in the control group. Given that approximately 20% of the sample size would likely drop out, 138 patients were included in the study, with 69 in each group.

Three sets of data were analyzed: the full-analysis set (FAS), per-protocol set (PPS), and the safety-analysis set (SS). FAS included all randomized patients who received at least one dose of the study opioids for primary efficacy and baseline characteristics analyses. The secondary outcome data were analyzed according to actual data in the FAS. PPS included all randomized patients who fully adhered to the study protocol for efficacy analysis.

The primary efficacy outcome between the two treatment groups was compared using a non-inferiority test, with a 95% confidence interval (CI) of the differences estimated using the Newcombe-Wilson method. For CPOT and RASS scores, optimal analgesia duration, optimal analgesia and sedation duration, the proportion of optimal analgesia duration, the proportion of optimal analgesia and sedation duration, the number of propofol infusion, and the dosage of the propofol were used, and the two groups were compared using a Wilcoxon rank sum test.[51] A chi-squared test was employed to compare the two groups for the proportion of patients using propofol, successful extubation, ICU discharge, ICU mortality, and AEs during the treatment period. A log-rank test was used to compare the two groups for MV duration, extubation duration, duration of the treatment period, and ICU LOS. The Kaplan-Meier method was used to draw curves.

We used SAS ver. 9.4 for all summarized statistical computations. The significance test was conducted at the 5% level and was two-sided.

Figure 2. Screening, Selection, and Flow of Patients[a]



[a]No Data were collected on ineligible patients. Four patients in the remifentanil group and 9 in the fentanyl group had consent withdrawn for the study drugs but were followed-up for outcomes and were included in the primary analysis (full-analysis set).
[b]Child-Turcotte-Pugh [CTP] score > 9.
[c]Unstable hemodynamics (MAP ≤65 mmHg) after administration of 0.5 μg/kg/min norepinephrine.
[d]Received deep sedation (Richmond Agitation Sedation Scale [RASS] score of -4 to -5) 46 or had received neuromuscular blocking drugs and could not be assessed by RASS (i.e., patients experiencing mental disease or coma).
[e]Myasthenia gravis, bronchial asthma, or abdominal compartment syndrome.
[f]Alcoholism: drinking more than 14 times/week (1 time = 150 mL wine, 360 mL beer or 45 mL spirits).
[g]Missed patients included those admitted to the ICU on weekends or holidays or at other times when the research coordinators or pharmacists were unavailable.
[h]Other reasons included non-residents, incarcerated patients or family members who were not approached due to extreme stress.

RESULTS

Trial population

Of the 983 patients who received invasive MV and underwent screening from September 2021 to August 2022, 138 were enrolled in the trial and received the investigational opioids. Of these 138 patients, 125 (90.58%) completed the trial. Four patients in the remifentanil group and 9 in the fentanyl group withdrew from the study due to personal reasons or because of SAEs. Among the fentanyl group patients, 1 received a prohibited medication (meperidine hydrochloride injection) during the trial. Finally, 137 patients (69 remifentanil and 68 fentanyl) were evaluable for FAS and SS. The PPS included 124 patients (65 remifentanil and 59 fentanyl) (Figure 2).

Two groups had similar baseline characteristics of FAS (Table 1). The proportion of patients admitted to the ICU postoperatively reached approximately 70%. Moreover, the remifentanil group and the fentanyl group comprised 48 (69.57%) and 49 (70.06%) postoperative patients, respectively. The remaining ~30% of the patients were medical patients admitted to the ICU. The median CPOT scores at baseline were 0 [interquartile range (IQR) 0.0, 1.0] in the remifentanil group and 0 (IQR 0.0, 1.0) in the fentanyl group. In comparison, the remifentanil and fentanyl groups median scores were 12.5 (IQR 8.5, 16.0) and 12 (IQR 9.0, 18.0), respectively, on APACHE II.

Primary efficacy outcome

The primary endpoint analysis in FAS showed that 65 of the 69 patients (94.20%) in the remifentanil group achieved successful analgesia; in the fentanyl group, 60 of the 68 patients (88.24%) achieved successful analgesia. The difference (remifentanil vs. fentanyl) was 5.97% (95% CI: -3.99% to 16.35%). The lower boundary of the 95% CI for the difference between the groups was > -8%. Thus, remifentanil showed non-inferiority to fentanyl based on this finding.[52] However, we could not unambiguously determine the superiority of remifentanil compared to fentanyl because the upper boundary of the 95% CI for the difference between the groups was greater than 0 (Table 2).

Secondary efficacy outcomes

The analgesia and sedation levels at the optimum level were not substantially different between the groups. During the treatment period, the median CPOT score of the remifentanil group was 0.29 (IQR 0.20, 0.35) and the fentanyl group was 0.22 (IQR 0.13, 0.34). In comparison, the median RASS score of the remifentanil group during the treatment period was -0.60 (IQR -0.73, -0.45) and the fentanyl group was -0.50 (IQR -0.58, -0.38) (P = .01) (Figure 3).

Other secondary outcomes

Recovery parameters. Recovery parameters did not remarkably differ statistically between the groups (Table 3). The median MV and extubation durations were 19.17 h (IQR 14.60, 43.40) and 0.96 h (IQR 0.45, 1.42), respectively, in the remifentanil group. In the remifentanil and fentanyl groups, 22 (31.88%) and 23 (33.82%) patients, respectively were discharged from the ICU. One patient in each group died in the ICU from cardiac arrest (remifentanil group) and cardiogenic shock (fentanyl group).

Table 1. Patient Demographics and Baseline Clinical Characteristics (Full-Analysis Set)

Variable	Remifentanil (n = 69)	Fentanyl (n = 68)	*P* value
Demographics, No. (%)			
Age (years)	60.0 (48.0, 70.0)	58.5 (47.0, 71.5)	.76
Male	42 (60.87)	49 (72.06)	.17
Female	27 (39.13)	19 (27.94)	.17
Han ethnicity	63 (91.30)	63 (92.65)	.77
Other ethnicity	6 (8.70)	5 (7.35)	.77
Height (cm)	167.5 (160.0, 171.5)	165.0 (160.0, 170.0)	.76
Weight (kg)	65.0 (56.0, 78.0)	65.5 (55.0, 72.0)	.40
BMI (kg/cm^2)	23.9 (21.7, 26.1)	23.6 (21.4, 26.2)	.41
Surgical history	62 (89.86)	59 (86.76)	.57
Other past medical history[a]	0 (0.00)	1 (1.47)[b]	.32
ICU admission category, No. (%)			
Medical	21 (30.43)	19 (27.94)	.75
Surgical	48 (69.57)	49 (70.06)	.75
ICU admitting diagnostic category, No. (%)			
Neurological	10 (14.49)	8 (11.76)	.64
Respiratory	7 (10.14)	6 (8.82)	.79
Cardiovascular	7 (10.14)	6 (8.82)	.79
Gastrointestinal	13 (18.84)	13 (19.12)	.97
Urinary	1 (1.45)	1 (1.47)	.99
Trauma	7 (10.14)	10 (14.71)	.42
Other medical	4 (5.80)	3 (4.41)	.71
Other surgical	20 (28.99)	21 (30.88)	.81
Pre-existing illness at ICU admission, No. (%)			
Neurological	24 (34.78)	28 (41.17)	.44
Respiratory	34 (49.28)	36 (52.94)	.67
Cardiovascular	35 (50.72)	36 (52.94)	.80
Gastrointestinal	26 (37.68)	28 (41.17)	.68
Urinary	23 (33.33)	26 (38.24)	.55
Tumor	20 (28.99)	13 (19.12)	.18
Other surgical and medical	14 (20.29)	22 (32.35)	.11
Clinical characteristics			
APACHE II (score)	12.5 (8.5, 16.0)	12.0 (9.0, 18.0)	.74
SOFA (score)	5.0 (3.0, 6.0)	5.0 (3.0, 7.0)	.78
Body temperature (°C)	36.7 (36.5, 37.4)	36.7 (36.4, 37.5)	.91
MAP (mmHg)	85.0 (76.0, 95.0)	87.0 (81.0, 96.0)	.64
HR (bpm)	84.0 (71.0, 100.0)	88.5 (75.0, 107.5)	.07
RR (bpm)	15.0 (15.0, 18.0)	16.0 (14.0, 18.0)	.87
S_pO_2 (%)	99.0 (98.0, 100.0)	99.0 (98.0, 100.0)	.94
CL (mL/min)	82.2 (52.2, 108.4)	83.6 (47.2, 123.5)	.38
CTP (score)	6.0 (6.0, 7.0)	6.00 (5.25, 7.0)	.53
CPOT (score)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	.99
RASS (score)	-1.0 (-1.5, 0.0)	0.0 (-1.0, 0.0)	.97
Patients received NE, No. (%)	30 (43.47)	34 (50.00)	.44
NE dose (μg/min)	8.0 (2.0, 12.0)	8.0 (3.0, 16.0)	.43

[a]This includes a history of alcohol or drug abuse in last 2 years, long-term neuropsychiatric medications use, gestation, or lactation.
[b]The fifth patient has a long-term neuropsychiatric medication use.

Note: All continuous variables were reported as medians (interquartile range).

Study opioid intervention during the treatment period. Both groups of patients included in the FAS had similar exposure to the study opioids during the treatment period. The treatment period had a median duration of 16.48 h (IQR 13.15, 23.52) for remifentanil and 16.49 h (IQR 13.38, 22.70) for fentanyl. Forty-one patients received the study opioid infusion for more than 24 h, 20 patients received remifentanil and 21 received fentanyl. The median total study opioid dosage and weighted median study opioid infusion rate in the remifentanil group were 6.95 mg (IQR 5.11, 11.46)

Table 2. Efficacy Outcomes (Full-Analysis Set)

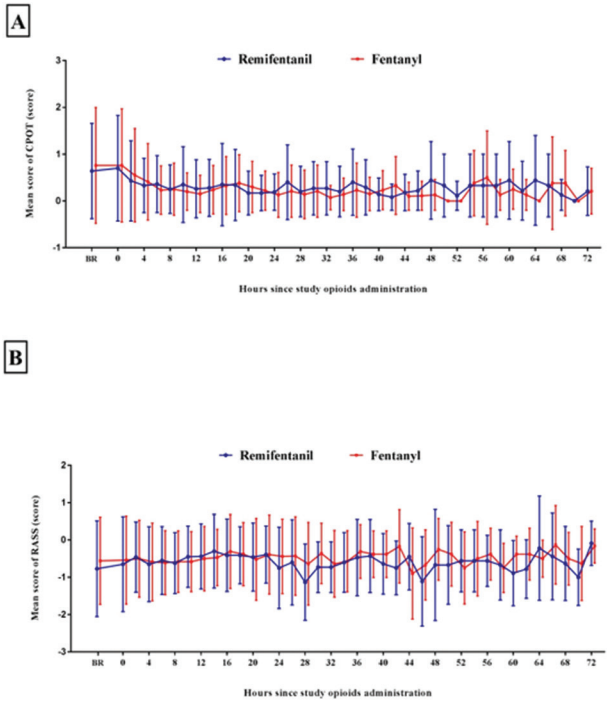
Variable	Remifentanil (n = 69)	Fentanyl (n = 68)	*P* value
Primary efficacy outcome			
Analgesic success[a], No. (%)	65 (94.20)	60 (88.24)	NA
Between-group difference (remifentanil versus fentanyl), (95% CI)[b]		5.97 (-3.99~16.35)	
Secondary outcomes			
CPOT score during study opioids infusion (score)	0.29 (0.20, 0.35)	0.22 (0.13, 0.34)	.07
Optimal analgesia[c] duration (h)	16.48 (12.73, 23.52)	16.36 (12.19, 22.79)	.93
Proportion of optimal analgesia[c] duration (%)	99.29 (97.04, 100.00)	99.38 (96.28, 100.00)	.62
RASS score during study opioids infusion (score)	-0.60 (-0.73, -0.45)	-0.50 (-0.58, -0.38)	.01
Optimal analgesia and sedation[d] duration (h)	15.67 (12.57, 23.43)	16.09 (12.19, 22.33)	.97
Proportion of optimal analgesia and sedation[d] duration (%)	97.89 (92.73, 99.93)	98.67 (95.01, 100.00)	.50
MV duration (h)	19.17 (14.60, 43.40)	18.71 (14.46, 41.76)	.69
Extubation duration (h)	0.96 (0.45, 1.42)	0.87 (0.49, 2.20)	.27
Successful extubation, No. (%)	57 (82.61)	46 (67.65)	.05
ICU LOS (h)	54.83 (41.46, 79.47)	53.75 (44.57, 66.51)	.57
ICU discharge, No. (%)	22 (31.88)	23 (33.82)	.81
ICU mortality, No. (%)	1 (1.45)	1 (1.47)	.99

[a]Defined as > 70% of the time during the treatment period with optimal analgesia (a CPOT score of 0 to 2).
[b]95% CI adopted the NewCombe-Wilson.
[c]Patients with a CPOT score of 0 to 2.
[d]Patients with a CPOT score of 0 to 2 and a RASS score of -2 to 1.

Note: All continuous variables were reported as medians (Q_1, Q_3).

Abbreviations: CI, confidence interval; CPOT, Critical Care Pain Observation Tool; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; NA, not applicable; RASS, Richmond Agitation and Sedation Scale.

Figure 3. CPOT and RASS scores during the treatment period**.**



[a]Shown is CPOT score curve for patients in the remifentanil and fentanyl groups.
[b]The RASS score curve in the remifentanil and fentanyl groups. The score curves show the means, and the I bars indicate ± SD (95% of the observations are within the error bars).

and 6.00 µg/kg/h (IQR 5.96, 7.41), respectively. The corresponding vales for the fentanyl group were 1.31 mg (IQR 0.93, 1.90) and 1.00 µg/kg/h (IQR 1.00, 1.63), respectively. The results in the PPS were similar to those in the FAS. The data of FAS and PPS exposure to study opioids are summarized in Table 3.

Propofol intervention during the treatment period. During the treatment period, the propofol intervention included patients receiving a propofol infusion, patients receiving a salvage sedation infusion (propofol bolus), and patients receiving both treatment modalities. Both groups of patients in the FAS had similar exposure to the propofol intervention (Table 3).

Propofol infusion. A total of 23 patients in the FAS (remifentanil group: 9 patients; fentanyl group: 14 patients) received a propofol infusion. The median duration of the propofol infusion and the median time from the start of the opioid infusion to the start of the propofol infusion were similar in both groups. In particular, the median duration of the propofol infusion was 14.47 h (IQR 7.02, 23.88) in the remifentanil group and 12.66 h (IQR 9.57, 20.96) in the fentanyl group. In comparison, the median time from the start of the opioid infusion to the start of the propofol infusion was 7.38 h (IQR 3.86, 33.72) in the remifentanil group and 2.01 h (IQR 0.87, 6.48) in the fentanyl group. Remifentanil patients received a median total propofol dosage of 565.20 mg (IQR 305.54, 1144.04), while fentanyl patients received 529.16 mg (IQR 323.03, 883.14). The weighted median propofol infusion in the remifentanil group was 0.59 µg/kg/h (IQR 0.48, 0.73). The corresponding value for the fentanyl group was 0.65 µg/kg/ (IQR 0.54, 0.85). The rate of increase and decrease were similar in both groups in terms of the propofol dose adjustment.

Table 3. Study Opioids and Propofol Used During the Treatment Period (Full-Analysis Set)

Variable	Remifentanil (n = 69)	Fentanyl (n = 68)	*P* value
Study opioids			
Duration of study opioids infusion (h)	16.48 (13.15, 23.52)	16.49 (13.38, 22.70)	0.50
Patients receiving the study drug infusion for > 24 h	20 (28.99)	22 (32.35)	0.67
Total study opioids dosage (mg)	6.95 (5.11, 11.46)	1.31 (0.93, 1.90)	NA
Weighted study opioids infusion rate (µg/kg/h)	6.00 (5.96, 7.41)	1.00 (1.00, 1.63)	NA
Propofol infusion			
Patients received a propofol infusion, No. (%)	9 (13.04)	14 (20.59)	.24
Time from starting the opioid infusion to starting the propofol infusion (h)	7.38 (3.86, 33.72)	2.01 (0.87, 6.48)	.26
Duration of propofol infusion (h)	14.47 (7.02, 23.88)	12.66 (9.57, 20.96)	.86
Total propofol dosage (mg)	565.20 (305.54, 1144.04)	529.16 (323.03, 883.14)	.95
Weighted propofol infusion rate (µg/kg/h)	0.59 (0.48, 0.73)	0.65 (0.54, 0.85)	. 77
Patients who received the following numbers of propofol rate increases, No. (%)			
1–3	6 (66.67)	5 (35.71)	.15
≥ 4	3 (33.33)	9 (64.29)	.15
Patients who received the following numbers of propofol rate decreases, No. (%)			
0	6 (66.67)	7 (50.00)	.43
1–3	3 (33.33)	5 (35.71)	.91
≥ 4	0 (0.00)	2 (14.29)	.14
Salvage sedation infusion (propofol bolus)			
Patients who received the salvage sedation infusion, No. (%)	18 (26.09)	12 (17.65)	.23
Salvage sedation infusion number (times)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	.28
Total salvage sedation dosage (mg)	41.25 (30.00, 170.63)	63.50 (40.18, 183.38)	.58
Patients who received the following numbers of salvage sedation, No. (%)			
1–3	12 (66.67)	9 (75.00)	.50
≥ 4	6 (33.33)	3 (25.00)	.31
Propofol infusion and salvage sedation infusion			
Patients who received propofol, No. (%)	22 (31.88)	19 (27.94)	.61
Total propofol dosage (mg)	163.75 (40.00, 389.56)	430.88 (60.00, 911.70)	.10

Salvage sedation infusion (propofol bolus). Salvage sedation infusion was administered to 30 patients in the FAS (remifentanil group: 18 patients; fentanyl group: 12 patients). The median numbers of salvage sedation infusions were 0 times (IQR 0.0, 1.0) in the remifentanil group and 0 times (IQR 0.0, 1.0) in the fentanyl group. Remifentanil patients received a median salvage sedation dosage of 41.25 mg (IQR 30.00, 170.63), while fentanyl patients received 63.50 mg (IQR 40.18, 183.38).

Propofol infusion and salvage sedation infusion. Propofol infusion and salvage sedation infusion was administered to 41 patients in the FAS (remifentanil group: 22 patients; fentanyl group: 19 patients). Remifentanil patients received median total propofol dosages of 163.75 mg (IQR 40.00, 389.56), while fentanyl patients received 430.88 mg (IQR 60.00, 911.70).

Safety outcomes

During the treatment period, the patients who received remifentanil exhibited similar AEs to those who received fentanyl (81.16% vs. 82.35%); similar grade 3 to 5 AEs (13.04% vs. 11.76%) were also reported (Table 4). There were 5 SAEs (acute coronary syndrome, acute myocardial infarction, cardiac arrest, respiratory acidosis, and acute respiratory failure) exhibited by 3 patients who received remifentanil and 3 SAEs (acute kidney injury, cardiogenic shock, and gastrointestinal bleeding) exhibited by 2 patients in the fentanyl group. None of the 8 SAEs were considered to be related to the study opioids. No obvious significant difference were found in the hemodynamic status between the two groups of patients.

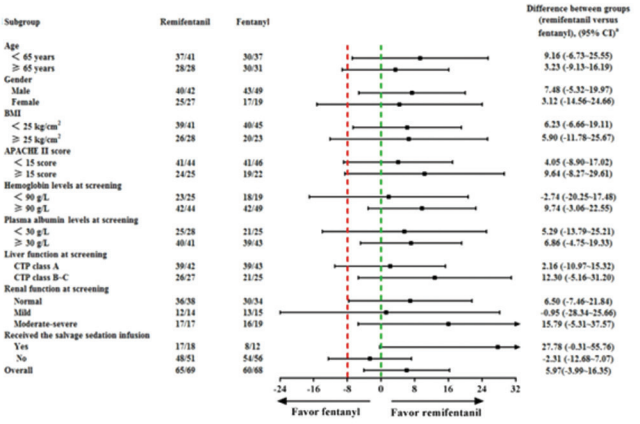
Table 4. Safety Outcomes (Safety Population)

Variable	Remifentanil (n = 69)	Fentanyl (n = 68)	*P* value
AEs overall[a], No. (%)			
Any AEs	56 (81.16)	56 (82.35)	.86
AEs with maximum grade of ≥ 3[b]	9 (13.04)	8 (11.76)	.82
SAEs[c]	3 (4.35)	2 (2.94)	.67
AEs leading to discontinuation of study opioids	1 (1.45)	2 (2.94)	.62
AEs leading to dose adjustment of study opioids[d]	8 (11.59)	3 (4.41)	.21
AEs related to the assigned regimen[a], No. (%)			
Any AEs	24 (34.78)	22 (32.35)	.76
SAEs[c]	0 (0)	0 (0)	NA
MAP			
Overall weighted MAP (mmHg)	84.11 (76.89, 91.84)	85.38 (79.44, 92.25)	.40
Proportion of time within 10% of mean MAP baseline value (%)	51.84 (37.06, 75.30)	51.42 (33.82, 68.41)	.95
MAP ≤ 50 mmHg, No. (%)	1 (1.40)	0 (0.00)	.32
MAP ≥ 100 mmHg, No. (%)	47 (68.11)	47 (69.12)	.90
HR			
Overall weighted HR (bpm)	86.96 (76.32, 96.76)	90.88 (76.10, 102.92)	.12
Proportion of time within 10% of mean HR baseline value (%)	49.94 (28.44, 81.13)	48.78 (23.51, 100.00)	.56
HR ≤ 60 bpm, No. (%)	14 (20.29)	11 (16.18)	.53
HR ≥ 100 bpm, No. (%)	46 (66.67)	48 (70.59)	.62

[a]Shown are results for all the adverse events as coded according to the Medical Dictionary for Regulatory Activities, ver. 25.0, during the treatment period. Patients were those who received at least one dose of remifentanil or fentanyl as grouped according to actual intervention.
[b]Severity grades were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.
[c]Serious adverse events included acute coronary syndrome, acute myocardial infarction, cardiac ion, or temporary discontinuation of trial regimen.

Note: All continuous variables were reported as medians (interquartile range).

Figure. 4. Subgroup analyses for primary outcome. Estimates of the differences in effect between the remifentanil and fentanyl groups (%) are presented along with the 95% confidence interval (CI). The green dotted line (0%) is the clinical superiority margin and the red dotted line (-8%) is the clinical non-inferiority margin. The lower limit of a 95% CI > 0% shows clinically significant superiority and necessarily non-inferiority of remifentanil. The upper limit of a 95% CI < 0% demonstrates clinically significant inferiority (or superiority of fentanyl). The lower limit of the 95% CI > -8% but < 0% shows clinically significant non-inferiority, but the superiority of remifentanil is uncertain (e.g., subgroup younger than 65 years old). The lower limit of the 95% CI < -8% and the upper limit of the 95% CI > 0% failed to demonstrate the clinical non-inferiority of remifentanil (e.g., subgroup over 65 years old). Renal function was assessed by predicting the patient's creatinine clearance (CL_{cr}). Normal renal function was defined as a predicted CL_{cr} > 80 mL/min. Mild renal impairment was defined as a predicted CL_{cr} of 51–80 mL/min. The difference between the remifentanil and fentanyl groups was evaluated using the NewCombe-Wilson test.



Subgroup analyses for the primary outcome

The subgroup analyses for the primary outcome defined according to baseline characteristics were not prespecified in the trial. The results indicated that the non-inferiority of remifentanil to fentanyl was established in males, patients younger than 65 years old, patients with a body mass index (BMI) < 25 kg/cm^2, patients with hemoglobin levels ≥ 90 g/L, patients with CTP class B-C, patients with normal and moderate to severe renal function, and in patients who received a salvage sedation infusion. We could not clearly determine the superiority of remifentanil to fentanyl in any other subgroups (Figure 4).

DISCUSSION

In this multicenter, double-blind, randomized, and non-inferiority clinical trial, we assessed remifentanil versus fentanyl for analgesia in patients requiring invasive MV. Overall, remifentanil maintained the patients' optimal analgesia during the treatment period. The non-inferiority of remifentanil to fentanyl was also established. Moreover, remifentanil was found to offer better successful analgesia, decreased propofol exposure, successful extubation, and hemodynamic stability.

Our results were consistent with previous studies that proved that remifentanil is particularly advantageous in general postsurgical patients,[53-55] neurotrauma patients,[49,50,56,57] patients with respiratory complications,[58,59] and patients with renal dysfunction.[49,60,61]

We found that CPOT and RASS scores in the remifentanil group remained in the optimal range during the treatment period, with no remarkable difference from the fentanyl group. However, the analgesic success of the remifentanil group was nearly six percent higher than that of the fentanyl group. We also found that the number of patients who received a propofol infusion, salvage sedation infusion, and the total propofol dosage in the remifentanil group was less than those in the fentanyl group. Moreover, the time from the initiation of study opioid infusion to the initiation of propofol infusion for the remifentanil group was longer than that for the fentanyl group. These differences suggested that patients in the remifentanil group had a lower demand for sedatives than those in the fentanyl group.

A non-inferiority trial was the subject of the present study. The sample size limited our exploration of the efficacy of remifentanil to some extent. Hence, we have interpreted the data and presented the above views with caution. However, it should be recognized that although the above differences were not statistically substantial, the impact of these differences on the efficacy and prognosis of patients should not be ignored. The optimal analgesia was associated with a low incidence of the stress response, organ dysfunction, prolonged MV duration, and critical complications. In comparison the lower demand for propofol was associated with little exposure to fat emulsions and a low incidence of over sedation, respiratory depression, deep vein thrombosis, and diaphragm dysfunction. Hence, we believe that the superiority of remifentanil should be explored in the future using RCTs with a large sample size to support these conclusions.

Our results showed that the MV duration, extubation duration, successful extubation, ICU LOS, ICU discharge, and ICU mortality between the two groups were not remarkably different. Remifentanil did not reduce the duration of MV. As for ICU LOS, ICU discharge, and ICU mortality, our results were consistent with previous studies.[45,48-50,62] Moreover, the two opioids exhibited no remarkable differences in their actions.

The analysis results were consistent with the primary outcome in the subgroups of males, patients younger than 65 years old, patients with BMI < 25 kg/cm^2, and with hemoglobin levels ≥ 90 g/L. Age, gender, and BMI affected the analgesic effect of remifentanil.[63] This scenario may be related to the difference in the proportion of lean body mass among the groups, possibly affecting the distribution of remifentanil.[64] The explanation for the hypoproteinemia subgroup was likely derived from a similar mechanism. These subgroup analyses were not originally prespecified in the study. Hence, the above results may introduce bias and should be interpreted with a degree of caution.

The strengths of the research are as follows. First, this multicenter, double-blind RCT assessed the efficacy and safety of remifentanil for maintaining optimal analgesia in patients requiring MV. And, the CPOT scores of 0 to 2 and the RASS scores of -2 to 1 used in this trial are consistent with the latest strategies for analgesia-based sedation and for targeting light levels of sedation, which permits a better evaluation of the efficacy and safety of the study opioid drugs.

The trial had a number of limitations. First, further stratified randomization by factors (gender, age, and disease severity) that may have affected the efficacy of the opioids was limited by the sample size. Second, nearly 70% of all included patients were surgical cases. Thus, the ability to generalize the findings to medical patients with more complex conditions is limited. Third, we did not record drug-related respiratory depression because respiratory support made the measurements relatively insensitive and limited the power of determining the drug's accumulation. Lastly, we did not measure the pharmacokinetic parameters of the drugs. Hence, the efficacy and safety related to pathophysiological changes were not fully explored.

CONCLUSIONS

With fewer major safety concerns, remifentanil was non-inferior to fentanyl with respect to the analgesic success rate in critically ill patients requiring MV. These findings support the use of remifentanil for maintaining optimal analgesia in patients requiring invasive MV.

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AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest.

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