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Short Communication

Remifentanil Versus Fentanyl in Mechanically Ventilated Critically Ill Patients: Study Protocol for a Randomized Controlled Study

Yin-Hua Wang[1,2], Yi-Bing Zhu[1], Li Jiang[1], Bin Du[3] and Xiu-Ming Xi[1]*

[1]Department of Critical Care Medicine, Fuxing Hospital, Capital Medical University, Beijing, 100038, China
[2]Department of Critical Care Medicine, North China University of Science and Technology Affiliated Hospital, 73 Jianshe Road, Tangshan, 063000, China
[3]Medical ICU, Peking Union Medical College Hospital, Beijing, 100730, China

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ABSTRACT

Opioids are commonly required to relieve pain in critically ill patients, especially for those under mechanical ventilation (MV). Remifentanil, a potent μ-opioid receptor with a rapid onset and offset, is widely used in anesthesia during surgeries, whereas less commonly administrated in the intensive care unit (ICU). This study is designed as a prospective, randomized, double-blind, controlled, parallel-group trial. Eligible 254 adult patients in ICU requiring MV for more than 24 h and ventilated for less than 48 h at the enrollment are randomly assigned to either the 'remifentanil group' or the 'fentanyl group', in which opioids will be infused for a maximum of 14 days. The primary outcome is the duration of MV. Secondary outcomes include the duration of extubation, costs and length of stay (LOS) in ICU, dose adjustment time, analgesic and sedative agent costs, short-term mortality, and adverse events potentially relevant to the study drugs. Data analysis will adopt an intention-to-treat approach. This trial will demonstrate the probability that remifentanil can reduce the duration of MV in long-term ventilated patients in critically ill patients compared to fentanyl.

Pain and pain-related syndromes are commonly found in critically ill patients. Nearly 50% of ICU survivors recall unpleasant, painful, or stressful events in the ICU (Fraser *et al*., 2000; Breen *et al*., 2005). IPAD recommends that intravenous opioids be considered as the first-line drug class of choice to treat non-neuropathic pain in critically ill patients (Barr *et al*., 2013), while in eCASH concept (Vincent *et al*., 2016). However, there are unsatisfactory aspects. First, fentanyl undergoes extensive hepatic metabolism (Labroo *et al*., 1997); thus, hepatic dysfunctions may lead to insufficiency of metabolism of fentanyl. Second, the half-life of fentanyl is prolonged during the continuous intravenous administration (Kress *et al*., 2000). Remifentanil is a new short-acting selective μ-receptor agonist (Wilhelm and Kreure, 2008), metabolized by tissue nonspecific esterase, insusceptible of hepatic (Dershwitz *et al*., 1996) and renal function (Hoke *et al*., 1997; Pitsiu *et al*., 2004; Glass *et al*., 1999). A meta-analysis indicated that remifentanil was associated with a reduction in duration of mechanical ventilation (MV) (Karabinis *et al*., 2004). However, remifentanil has not yet been extensively accepted by ICU physicians, especially in patients who undergo long-term mechanical ventilation. There is a clear destination to compare the duration of MV and adverse of remifentanil and fentanyl in this RCT. However, there are also disadvantages such as heterogeneity of study objectives, therefore subgroup analysis may be performed according to the patient's APACHE-II score, SOFA score, and disease type.

Materials and methods

The present study proposes a protocol for a registered prospective, multi-center, randomized, double-blind, controlled, two-armed superiority trial. The trial was carried out following the Declaration of Helsinki principles. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. The study has been approved by the local human research ethics committee of the main study site and was registered on the Chinese Clinical Trial Registry (approval number ChiCTR-IPR-17011630). The trial was conducted in 21 ICUs in China.

* Corresponding author: w64237568@163.com
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Subjects were recruited among intubated patients requiring MV for more than 24 h in 21 ICUs in China.

Inclusion criteria included (1) Orotracheal intubated and mechanical ventilated. (2) aged 18 to 85 years old. (3) anticipated mechanical ventilation for more than 24 h.

Exclusion criteria were (i) basic conditions (such as alcohol abuse; (ii) after tranquilizing for more than 2 weeks, analgesia and antipsychotic drug therapy for example) confuse the evaluation of analgesia; requiring deep sedation (Richmond agitation-sedation scale, RASS< -2) for any reason such as prevention of awareness in patients receiving neuromuscular blocking agents, status epilepticus, severe brain injury with intracranial hypertension, for example, P/Fratio ≤100; (iii) severe hepatic insufficiency (Child-pugh>grade C); (iv) contraindication or allergic or history of a previous adverse reaction to any of the study medications; (v) requiring surgical treatment during mechanical ventilation; invasive mechanically ventilated for >48 h; (vi)patient or legal authorizer is not willing to participate in the trial; (vii) known pregnancy or lactating women; (viii) death is deemed imminent and inevitable.

The study applied to stratified randomization. during the enrolment, for reducing the impact on the results from heterogeneity of ventilation and inter-hospital variation as much as possible, stratification was employed according to the investigative center. following written consent, patients of each research center were enrolled into either 'remifentanil group' or 'fentanyl group by subjects' with enrollment order and their random coding were sequence expressed by random coding sequence of investigational drugs. Cases were evenly distributed among the 21 centers. Random sequences were assigned to each center according to the random code of investigative center and investigational drugs (small to large).

Once included in the study, stratified randomization was adopted for the blinding using labeling and sealed envelopes.

For intervention procedure, an intubated patients anticipated mechanical ventilation for more than 24 h and less than 48 h at the enrolment in ICU were randomized (1:1) to remifentanil or fentanyl group. The program was carried following the pain, agitation, and delirium guidelines (Barr *et al*., 2013). Participants received the research medication following a specified protocol as shown in Figure 1. Study medication was administered until extubation, tracheotomy, or up to a maximum of 14 days. As this study was carried out in China, we choose study drug doses referring to the Chinese guideline for the management of pain and sedation in adult patients in the ICU (Branch *et al*., 2018) as well as their medicine specification.

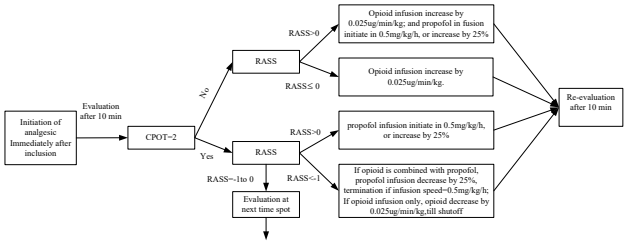

Fig. 1. Protocol for standard treatment phase.

For pharmaceutical solutions of opioids, treatment group received remifentanil (1mg/powder/vial), 2 vials + 40ml 0.9% saline and control group received fentanyl (0.1mg/2ml/ampoule) 20 ampoule. Syringes in each group contained 40ml colorless transparent liquid with equal drug concentration of 0.05mg/ml.

For standard treatment phase, analgesics was started immidiately after enrollment. A dose of 0.025 μg/kg/min of remifentanil (or fentanyl) was administrated intravenously at the initiation of invasive MV. Estimation of pain and sedation level was conducted at every predesigned time point. The increase or decrease in dose of remifentanil or fentanyl was 0.025μg/kg/min at every adjustment, up to 0.15 μg/kg/min at the most. In the case the RASS score was greater than 0, propofol will be used for sedation in both groups at an initial dose of 0.5mg/kg/h. The maximum speed for propofol is 4 mg/kg/h. If the CPOT score is greater than 3, opioids were added first. If the RASS score was less than -1, propofol was reduced or stopped first.

During extubation phase, a daily clock was performed to check weaning screening if patients were ventilated for more than 24 h. The screening was done at 7 am and 2 pm daily. Once weening screening criteria (MacIntyre *et al*., 2001) were completely fulfilled, the 3-min and sequential 30-min spontaneous breathing test (SBT) was carried out.

In case propofol was administrated before SBT, its withdrawal was done under a procedure. It was gradually decreased at a speed of 25% of the original dosage until shutoff before 3-min SBT. If no propofol was used in combination, patients was directly enrolled in the 3-min SBT.

Once the clinical conditions of the patients meet the 3-min SBT, patients were enrolled into 30-min SBT, faded by tramadol hydrochloride tablets in a unit dose of 100mg (maximum dose of 400mg in 24h). Simultaneously, the analgesics were gradually decreased at a speed of 25% of the original dosage to shutoff before extubation. In post-extubation phase if necessary, the open-label midazolam injection (0.01-0.18 mg/kg/h) was instituted for sedation.

For sample size calculation there was a previous study comparing remifentanil with fentanyl in which the

mean duration of MV in remifentanil and fentanyl groups was reported. In which the standard deviation (SD) was 28.5 h vs. 33.6 h.

We planned to conduct two parallel control groups of equal sample size, for a two-sided test.

Based on the formula of $n=((Z1-\alpha/2+Z1-\beta)^2\times(\sigma1^2+\sigma2^2))/\delta^2$. ($\alpha=0.05$; statistical power of 0.2; $1-\beta=0.80$; $\sigma1=28.5$; $\sigma2=33.6$; $\delta=12$) and taking into consideration the attrition bias of 20% at the most, the total number of patients needed in this trial was 254, thus 127 patients in each arm.

For statistical analysis categorical variables were presented as the numbers and percentages and were analyzed by the χ^2- tests or Fisher's exact tests, or when appropriate, as relative risks. Continuous variables were checked for normal distribution by the Kolmogorov-Smirnov test.

Normally distributed variables were expressed by their mean and standard deviation; non-normally distributed variables were expressed by their medians and 95% confidence intervals (95% CI). Comparisons of continuous variables were performed using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Appropriate (linear, logistic, or poisson) regression were generated for the identification of the determinants of outcomes and the correction of baseline covariates.

Duration of MV, duration of extubation, costs and a dose of analgesic and sedative, ICU costs, and ICU-LOS, were tested by Student's t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data. In addition, the primary outcome was stratified according to the length of hospitalization.

All tests of significance were at the 5% significance level and two-sided. Adverse events frequencies, proportions of sedatives, and the 95% CI were used to describe categorical variables. All of the data in this trial were analyzed in IBM SPSS Statistics version 21.0 by an independent statistician before the secondary level unblinding being implemented.

Results

To ensure the majorization and consistency of the data, case report forms (CRF) were included. The primary outcome was the duration of MV, which was measured in hours. Duration of MV was defined as from admission to the last time of SBT before extubation for the first time, whether later reintubation happened or not. Reintubation was included in adverse events (Table I).

Secondary outcomes included (a) duration of extubation: defined as the time from 1st SBT to extubation, which also was the time to extubation after cessation of sedation for the first time; (b) number of times of dose adjustments for study drug: it was a measurement of nursing workload; (c) costs and dosages of analgesic and sedative agent; costs in ICU and ICU-LOS and (d) 28-day mortality.

Table I. Demographic characteristics, Total amount of propofol intraoperatively, Total amount of fentanyl intraoperatively, Therapeutic intervention score, ICU stay and Mechanical ventilation in study groups.

	Remifentanil		Fentanyl		P
Age (years)	28		32		0.37
Female/male (n)	8/3		9/2		0.50
Weight (kg)	30	(14-50)	36	(14-50)	0.69
Duration of operation (min)	225	(60-660)	270	(150-550)	0.88
Total amount of propofol intraoperatively (mg)	1357	(395-1950)	1020	(753-1560)	0.39
Total amount of fentanyl intraoperatively (lg)	100	(50-250)	150	(80-350)	0.22
Therapeutic intervention score	22	(17-31)	24	(16-32)	0.70
ICU stay (days)	3	(2-4)	6	(4-13)	0.04
Mechanical ventilation (min)	1140	(685-1542)	1110	(795-2670)	0.79

we obtained the average dosage per patient per day for every drug. then price was taken into account, costs of analgesic and sedative agent were derived. The costs in ICU, patient expense list mean was taken from the day admission to the trial to discharge from ICU, were derived from the computerized inpatient charging system.

Potentially related side effects of opioids including delirium, hypotension, bradycardia, astriction, chills, vomiting, muscle rigidity, as well as unplanned extubation. Especially, reintubation within 48 h were assessed as an adverse event.

Discussion

We have strengths in our study. First, this study with the prospective, multi-center, randomized, double-blind, controlled design conforming to the CONSORT provided credible data and advanced evidence. Second, there have been limited clinical data of remifentanil in long-term mechanically ventilated patients. We evaluated the patients ventilated for more than two days, thus to evaluate the efficacy and safety the data of remifentanil in long-term ventilated patients was added. Third, seldom clinical studies of remifentanil have reported costs. We especially

took costs into our consideration, to further analyze the cost-effectiveness of remifentanil in comparison to the other less expensive opioids, thus evaluating remifentanil more comprehensively. Fourth, we recorded detailed time points of evaluation of pain and level of sedation and the adjustments of analgesics and sedatives accordingly, thus to analyze and compare the characteristics of analgesic effect of the two opioids, including the way they affect the doses of sedatives. The application of more expensive but shorter-acting remifentanil was rational since it led to faster extubation and shorter ICU-LOS and less morality which resulted into lower total costs.

But there are limitations to our study. First, in comparison to the clinical trials subjected to post-surgical patients, such as clinical trials in coronary artery bypass graft surgery (CABG) patients, for example, the composition of our subjects was of less homogeneity (Schulz *et al*., 2010). Also, we are scheduled to conduct a multi-center clinical trial, hence heterogeneities between centers was the concern. Second, the calculation of sample size was based on the previous studies and also our clinical experience taken into consideration. However, the estimated sample size was of suboptimal precision and confidence.

Ethics and dissemination

Recruitment was commenced in October 2018. The results of this study were expected in October 2020. Results of the trial were reporteded according to the Consolidated Standards of Reporting Trials guidelines (Meng and Young, 2018).

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Statement of conflicts of interest

The authors have declared no conflict of interest.

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