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# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial



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| | |

# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial

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## ABSTRACT

**Introduction:** Acute pain is common during endotracheal extubation period, and is related to complications and adverse outcomes. Patients with delayed extubation after craniotomy are vulnerable to pain and complications of extubation. However, pain control during extubation is still inadequate. Remifentanil, a new opioid with rapid onset and short duration of action, provides adequate analgesia during procedures with minimal effect of respiratory depression.

**Methods and analysis:** The study is a prospective, randomized, double-blinded, controlled, parallel-group design. Patients with delayed extubation after intracranial surgery are screened daily. Adult patients ready for extubation are enrolled and assigned randomly to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Pain intensity is measured by visual analog scale (VAS) pain score. Adverse events during drug infusion are documented and reported. Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Incidence of re-intubation and re-operation within 72 hours after extubation, length of stay in intensive care unit and hospital and mortality are collected. The primary endpoint is the incidence of severe pain (defined as VAS pain score more than 5 cm) during peri-extubation period (defined as the period of time from immediately before extubation to 20 minutes after

extubation).

**Ethics and dissemination:** The study was approved by the IRB of Beijing Tiantan Hospital, Capital Medical University. Study findings will be disseminated through peer-reviewed publications and conference presentations.

**Trial Registration:** ClinicalTrials (NCT): ChiCTR-PRC-13003879.

**Main strengths and limitations of the study**

Pain is common during extubation period, and related to complications and adverse outcome. Adequate analgesia is needed in this situation. The main strength of the study is that we will provide the evidence of a new opioid (remifentanil) with minimal respiratory depression effect and a rapid onset and short duration of action, for prophylactic analgesia during extubation in patients after craniotomy.

Other opioids may be suitable for prophylactic analgesia during extubation. The main limitation of the study is that we do not use other opioids, such as morphine or fentanyl, as control groups.

## INTRODUCTION

Clinical epidemiology studies have shown that critically ill patients in intensive care unit (ICU) are at high-risk of pain, and inadequate treatment of pain is associated with adverse outcomes [1,2]. Appropriate analgesia, not only attenuates stress response resulted from pain, but also reduces the incidence of iatrogenic complications, shorten the duration of mechanical ventilation and length of stay (LOS) in ICU [3-5]. In addition to pain at rest, pain related to procedures is common in ICU patients, and inadequate treatment of procedural pain remains a significant problem for many patients [6]. The revised clinical practice guidelines for management of pain, agitation, and delirium from Society of Critical Care Medicine (SCCM) also recommend that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to chest tube removal and other types of potentially painful procedures, and suggest that intravenous opioids should be considered as the first-line drug class of choice [7]. Manipulation of artificial airway, especially endotracheal extubation is among the high pain-intensity procedures in ICU. By using the patient's self-report pain scale as pain evaluation method, Gacouin et al. found that 45% of patients experienced severe pain at the time of endotracheal extubation [8]. Acute pain during extubation is associated with sympathetic nervous system activation, which could result in respiratory and circulatory instability [9]. Therefore, it is reasonable to control pain and stress responses at the time of endotracheal extubation in some high-risk patients, such as those after intracranial surgery. It has been reported that the proportion of patients who underwent delayed extubation after craniotomy is about 10% to 50% [10,11]. These

patients are vulnerable to pain and complications of extubation [12]. On the other hand, despite a greater awareness of pain during endotracheal extubation, clinicians remain reluctant to administer opioids in patients following craniotomy. The major concern is the side effects of respiratory depression and influence on consciousness of these drugs. To our knowledge, up to now, no study has been published for adequate management of pain during extubation in patients with delayed extubation after craniotomy.

Remifentanil is a potent synthetic selective μ-opioid receptor agonist with a rapid onset and short duration of action, regardless of the duration of its administration [13,14]. Remifentanil differs from other synthetic opioids in its metabolism by non-specific plasma and tissue esterases. Study in human volunteers has shown that the respiratory depression of remifentanil by bolus injection is mild and easily treated with requests to breathe or the administration of oxygen [15]. These pharmacological properties suggest that remifentanil could be a potentially safe and effective analgesic in clinical situations requiring a brief period of intense control of pain, such as painful procedures in ICU [16]. There have been reported remifentanil used as prophylactic analgesia during removal of chest drain [17], insertion and removal of long-term central venous access [18], dressing change [19], and endotracheal suctioning [20]. However, although a plenty of studies have shown that the remifentanil facilitates emergency in general anesthesia and weaning process in mechanical ventilation [14,16,21], study for prophylactic use of remifentanil in endotracheal extubation is limited.

There has been increased interest in use of remifentanil in brain injured patients. In patients with traumatic brain injury, it has been demonstrated that remifentanil has no

significant changes in systematic and cerebral hemodynamics, such as intracranial pressure, mean blood pressure, cerebral perfusion pressure, and cerebral blood flow velocity [22]. Several studies also compared remifentanil with fentanyl or morphine as analgesic in neurologic ICU patients. A randomized multicenter study in patients with brain injury showed that mean neurologic assessment times were significantly shorter with remifentanil than with fentanyl or with morphine, and patients were extubated significantly faster after remifentanil than after morphine [23]. Another retrospective study investigated patients with delayed extubation after brain tumor surgery, and found that mean extubation times were significantly shorter after remifentanil/propofol than after fentanyl/midazolam, and LOS in ICU was significantly reduced [24]. These results indicate that the rapid metabolism and lack of accumulation of remifentanil facilitate faster waking and neurological assessment, and suggest that remifentanil might be a better choice of analgesic in patients with brain injury.

In present study, remifentanil is used as prophylactic analgesics in patients with delayed extubation after craniotomy. The aim is to evaluate the efficacy and safety of remifentanil for control of pain and stress responses due to extubation. The primary hypothesis is that prophylactic use of remifentanil will reduce the incidence of severe pain during endotracheal extubation.

## METHODS AND ANALYSIS

### Study design overview

The present study is a prospective, single-center, randomized, double-blinded, placebo-controlled, two-arm trial in patients with delayed extubation after craniotomy. Trial schematic diagram is shown in Figure 1.

### Study setting and population

The study setting is neurosurgical ICU (30 beds), Beijing Tiantan Hospital (1100 beds), Capital Medical University, Beijing, China.

All patients after intracranial surgery with delayed extubation admitted to our ICU are screened daily for study eligibility.

Inclusion criteria are:

1) Age between 18-65 years-old;
2) Within 72 hours after operation;
3) Awaken and able to cope with the assessment of visual analog scale (VAS) pain score;
4) Ready for extubation after evaluated by neurosurgeon and ICU physician in charge.

Exclusion criteria are:

1) Operation relating to medulla oblongata region;
2) Hepatic Insufficiency;

3) Renal insufficiency;

4) Pregnant or lactating women;

5) Need continuous infusion of vasopressor before the start of study drug infusion;

6) Chronic opioid use over three months;

7) Known opioids allergy;

8) Readmitted to ICU after randomization to the study;

9) Enrolled in another trial.

Patient's endotracheal tube is extubated at the discretion of neurosurgeon and ICU physician in charge of the patient. Neurosurgeon and ICU physician discuss the patient's status and evaluate the patient by a screen checklist (Table 1) [10]. When answers of all items in checklist are "yes", the patient is ready for extubation. At this time, a 24-hour on-call study coordinator will be informed immediately, and patient's eligibility for the study is evaluated and confirmed.

**Randomization, double-blind and allocation concealment**

The study has a prospective, randomized, double-blinded, controlled, parallel-group design. Consecutive patients are randomly assigned to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'. Randomization is based on computer generated random digits table and follows a concealed process using sealed and numbered envelopes that allocate the patient to either of the two arms of the study. Patients may be randomized into this study only once unless they were discharged from the hospital and were re-admitted beyond 180 days of the first enrollment. The study

does not allow cross-over and, if any occur, they will be reported as protocol violations. Experimental drug and placebo with the same character are prepared by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.

**Data collected at study entry**

At baseline, data on demographic, history of past illness characteristics and diagnosis of the patients are obtained. The surgical site, operation time, use of sedatives and analgesics during anesthesia and ICU stay, time of mechanical ventilation, formulation and dose of postoperative patient-control-analgesia (PCA) pump, and time between end of operation and study drug infusion are recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II) is calculated.

**Trial interventions**

All patients are randomized 1:1 to receive remifentanil (Remi group) or placebo (Saline group) infusion. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Study drugs are administered by using syringe pump.

Immediately after drug infusion, ICU physician evaluate the patient by using extubation screen checklist shown in Table 1. If the patient passes the evaluation, endotracheal extubation will be carried out immediately by registered ICU nurses. The patient will be labeled as "failing to pass extubation test after drug administration" if he or she does not pass the evaluation. The reason of test failure will be documented. The patient will be re-evaluated every hour thereafter, and data about extubation will be documented.

Vital signs, which including heart rate (HR), respiratory rate (RR), non-invasive blood pressure (BP) and pulse oxygen saturation ($SpO_2$), are continuously monitored. VAS pain score is used to measure the pain intensity by the study investigator [25]. Each patient is instructed and asked to point to a mark on a 10-cm horizontal line labelled with descriptors of pain intensity ('No pain' at the 0 cm point and 'Extreme pain' at the 10 cm point). VAS and vital signs (HR, RR, BP and $SpO_2$) are documented at four time points: before drug infusion (baseline), immediately before extubation, immediately to 3 minutes after extubation and 20 minutes after extubation.

Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Following data are collected: incidence of re-intubation within 72 hours after extubation, incidence of re-operation due to intracranial hemorrhage or edema within 72 hours after extubation, LOS in ICU and hospital and mortality.

**Adverse events management and emergency stop of the study drug**

Patients are closely monitored during study drug infusion. Taking into account the potential adverse effects of remifentanil, experimental drugs must be immediately terminated when the following occurs:

1) Unresponsive to calling and patting on the shoulder;
2) RR less than 8 respirations per minute and $SpO_2$ less than 92%;
3) HR less than 50 beats per minute after atropine in 0.25 mg bolus;
4) Systolic BP less than 90 mmHg;
5) Serious allergic reaction such as throat swelling, bronchospasm or skin rash.

These data will be documented and reported as adverse events.

**Study endpoints**

The primary endpoint of present study is the incidence of severe pain during peri-extubation period. Peri-extubation is defined as the period of time from immediately before extubation to 20 minutes after extubation. Severe pain is defined as one of the VAS pain scores is more than 5 cm.

Secondary endpoints include:

1) VAS pain score and vital signs (HR, RR, BP and $SpO_2$) during peri-extubation period;
2) Incidence of failing to pass extubation evaluation after experimental drug infusion;
3) Incidence of re-intubation within 72 hours after extubation;
4) Incidence of re-operation due to intracranial hemorrhage or edema within 72

hours after extubation;

5) Incidence of adverse events during experimental drug infusion;

6) LOS in ICU and hospital;

7) Mortality.

**Current sample size justification**

Primarily, we expect the incidence of severe pain during peri-extubation period to decrease after remifentanil infusion in delayed extubation patients after craniotomy. Previous investigation showed that severe peri-extubation pain was occurred in 45% of patients [8]. It is expected that the incidence of severe pain would decrease to 30% after remifentanil infusion. Using the Power and Sample Size Calculation program, we will need to study 74 experimental subjects and 74 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability with testing this null hypothesis is 0.05.

**Statistical analysis**

All analyses will be according to the intention-to-treat principle, that is, all randomized patients will be analyzed in the groups to which they were originally allocated and will be blinded to treatment assignment.

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the $\chi^2$-test.

Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

We use repeated measure of analysis of variance (ANOVA) for comparing VAS pain score and vital signs (HR, RR, BP and $SpO_2$) across different time points (before drug infusion and during peri-extubation period) between the two groups.

All tests of significance will be at the 5% significance level, and two-sided. Analyses are conducted by using SPSS 17.0.

## ETHICS AND DISSEMINATION

### Ethical aspects and informed consent

Patients with delayed extubation after craniotomy are often unable to provide consent before extubation. After patient's eligibility for the study is confirmed, the ICU physician will introduce the family to the study coordinator. The physician will make sure the family knows the credentials of the study coordinator, and says that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that the patient may experience pain during extubation and, if so, the patient could become worse. The coordinator will say that a new opioid drug, remifentanil provides adequate analgesia with minimal respiratory depression. He (or she) will explain that in a small percentage of patients, remifentanil could cause bradycardia, hypotension and respiratory depression. The potential advantages of using or not using remifentanil will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study

coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

A register is kept of all patients evaluated for inclusion and of patients who withdraw from the study. The latter are clinically followed up without their data being analyzed in the study.

The study protocol and consent forms were approved on November 1, 2013 by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (approval number KY2013-002-01). The study was registered on November 8, 2013 at the Chinese Clinical Trial Registry (ChiCTR-PRC-13003879).

**Dissemination plan**

Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.

## TRIAL STATUS

The first patient was enrolled on January 06, 2014. The study will be completed in December 2014.

## SUMMARY

Endotracheal extubation is a critical step during post-operative care in neurosurgical patients [9]. Pain is common during extubation period, and related to complications and adverse outcome [8]. Adequate analgesia is needed in this situation. Although revised Clinical Practice Guidelines from SCCM have recommended that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to potentially painful procedures [7], study for analgesia during endotracheal extubation is still limited. As a new opioid with minimal respiratory depression effect and a rapid onset and short duration of action, remifentanil seems suitable for prophylactic analgesia during extubation in patients after craniotomy [13-16]. We want to provide such evidence in present study. Even a neutral result will provide important insight, as this would mean that more studies are needed to explore a safe and effective way of pain management during endotracheal extubation.

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**Authors' contributions**

YXW and JXZ participated in the design of the study and drafted the manuscript. HC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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The study was funded by Beijing Health Bureau (No: 2009-3-28). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

**Competing interests**

The authors declare that they have no competing interests.

**Table 1: Screening checklist used to determine the patient's suitability for extubation**

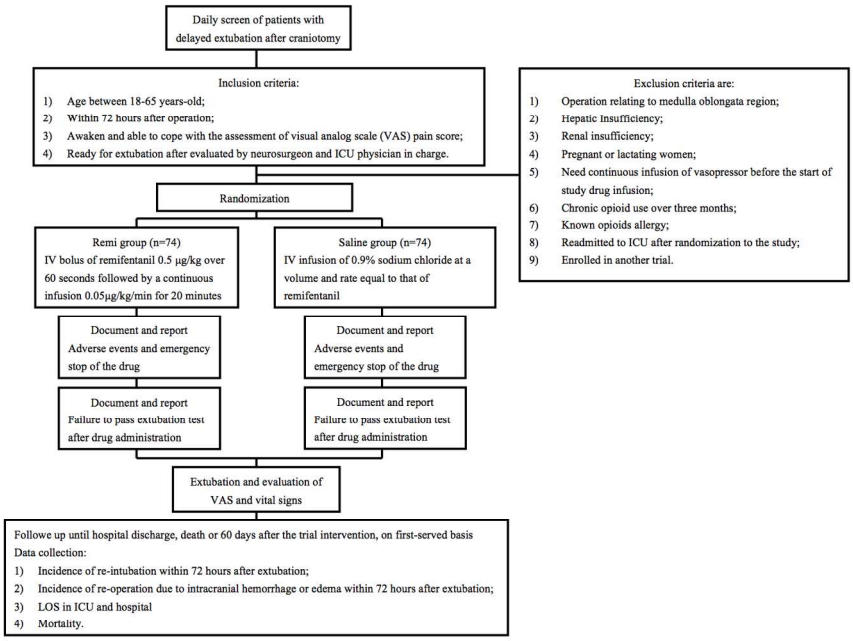
| Question | Answer |
|---|---|
| 1. Awake and alert with cerebral function adequate for patient co-operation or equivalent preoperative state of consciousness? | Yes/No |
| 2. Hemodynamic stability (lack of vasopressor support and mean arterial pressure within 10-15% of baseline)? | Yes/No |
| 3. Adequate recovery of muscle strength? | Yes/No |
| 4. Normal tidal volumes, normocapnia (end-tidal carbon dioxide 30-45 mmHg), minimum pulse oximetry > 95% with $FiO_2$ 0.5? | Yes/No |
| 5. Intact gag reflex and swallow function (presence of clearly audible cough during suctioning)? | Yes/No |

The answer to all questions must be "yes" in order for extubation to be approved.

$FiO_2$: fraction of inspired oxygen

**Figure legend**

Figure 1: Trial schematic diagram




309x249mm (150 x 150 DPI)

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-6 |
| | 2b | Specific objectives or hypotheses | 6 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 7, 9 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | Not applicable |
| Participants | 4a | Eligibility criteria for participants | 7 |
| | 4b | Settings and locations where the data were collected | 7 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9-11 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11-12 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | Not applicable |
| Sample size | 7a | How sample size was determined | 12 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | Not applicable |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 8-9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 8-9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 8-9 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 8-9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 8-9 |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | 8-9 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 12-13 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | Not applicable |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Not applicable in items 13a to 22 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | |
| | 14b | Why the trial ended or was stopped | |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | ChiCTR-PRC-13003879 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | Not applicable |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | The study was supported by Beijing Health |

| | |
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| | Bureau (No: 2009-3-28). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial



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# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial

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Keywords: remifentanil, analgesia, prophylactic, extubation, craniotomy

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## ABSTRACT

**Introduction:** Acute pain is common during endotracheal extubation period, and is related to complications and adverse outcomes. Patients with delayed extubation after craniotomy are vulnerable to pain and complications of extubation. However, pain control during extubation is still inadequate. Remifentanil, a new opioid with rapid onset and short duration of action, provides adequate analgesia during procedures with minimal effect of respiratory depression.

**Methods and analysis:** The study is a prospective, randomized, double-blinded, controlled, parallel-group design. Patients with delayed extubation after intracranial surgery are screened daily. Adult patients ready for extubation are enrolled and assigned randomly to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Pain intensity is measured by visual analog scale (VAS) pain score. Adverse events during drug infusion are documented and reported. Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Incidence of re-intubation and re-operation within 72 hours after extubation, length of stay in intensive care unit and hospital and mortality are collected. The primary endpoint is the incidence of severe pain (defined as VAS pain score more than 5 cm) during peri-extubation period (defined as the period of time from immediately before extubation to 20 minutes after

extubation).

**Ethics and dissemination:** The study was approved by the IRB of Beijing Tiantan Hospital, Capital Medical University. Study findings will be disseminated through peer-reviewed publications and conference presentations.

**Trial Registration:** ClinicalTrials (NCT): ChiCTR-PRC-13003879.

**Main strengths and limitations of the study**

Pain is common during extubation period, and related to complications and adverse outcome. Adequate analgesia is needed in this situation. The main strength of the study is that we will provide the evidence of a new opioid (remifentanil) with minimal respiratory depression effect and a rapid onset and short duration of action, for prophylactic analgesia during extubation in patients after craniotomy.

Other opioids may be suitable for prophylactic analgesia during extubation. The main limitation of the study is that we do not use other opioids, such as morphine or fentanyl, as control groups. Because there is no proven dose of remifentanil which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator, the dose of remifentanyl used in present study is arbitrary.

## INTRODUCTION

Clinical epidemiology studies have shown that critically ill patients in intensive care unit (ICU) are at high-risk of pain, and inadequate treatment of pain is associated with adverse outcomes [1,2]. Appropriate analgesia, not only attenuates stress response resulted from pain, but also reduces the incidence of iatrogenic complications, shorten the duration of mechanical ventilation and length of stay (LOS) in ICU [3-5]. In addition to pain at rest, pain related to procedures is common in ICU patients, and inadequate treatment of procedural pain remains a significant problem for many patients [6]. The revised clinical practice guidelines for management of pain, agitation, and delirium from Society of Critical Care Medicine (SCCM) also recommend that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to chest tube removal and other types of potentially painful procedures, and suggest that intravenous opioids should be considered as the first-line drug class of choice [7]. Manipulation of artificial airway, especially endotracheal extubation is among the high pain-intensity procedures in ICU. By using the patient's self-report pain scale as pain evaluation method, Gacouin et al. found that 45% of patients experienced severe pain at the time of endotracheal extubation [8]. Acute pain during extubation is associated with sympathetic nervous system activation, which could result in respiratory and circulatory instability [9]. Therefore, it is reasonable to control pain and stress responses at the time of endotracheal extubation in some high-risk patients, such as those after intracranial surgery. It has been reported that the proportion of patients who underwent delayed extubation after craniotomy is about 10% to 50% [10,11]. These

patients are vulnerable to pain and complications of extubation [12]. On the other hand, despite a greater awareness of pain during endotracheal extubation, clinicians remain reluctant to administer opioids in patients following craniotomy. The major concern is the side effects of respiratory depression and influence on consciousness of these drugs. To our knowledge, up to now, no study has been published for adequate management of pain during extubation in patients with delayed extubation after craniotomy.

Remifentanil is a potent synthetic selective μ-opioid receptor agonist with a rapid onset and short duration of action, regardless of the duration of its administration [13,14]. Remifentanil differs from other synthetic opioids in its metabolism by non-specific plasma and tissue esterases. Study in human volunteers has shown that the respiratory depression of remifentanil by bolus injection is mild and easily treated with requests to breathe or the administration of oxygen [15]. These pharmacological properties suggest that remifentanil could be a potentially safe and effective analgesic in clinical situations requiring a brief period of intense control of pain, such as painful procedures in ICU [16]. There have been reported remifentanil used as prophylactic analgesia during removal of chest drain [17], insertion and removal of long-term central venous access [18], dressing change [19], and endotracheal suctioning [20]. However, although a plenty of studies have shown that the remifentanil facilitates emergency in general anesthesia and weaning process in mechanical ventilation [14,16,21], study for prophylactic use of remifentanil in endotracheal extubation is limited.

There has been increased interest in use of remifentanil in brain injured patients. In patients with traumatic brain injury, it has been demonstrated that remifentanil has no

significant changes in systematic and cerebral hemodynamics, such as intracranial pressure, mean blood pressure, cerebral perfusion pressure, and cerebral blood flow velocity [22]. Several studies also compared remifentanil with fentanyl or morphine as analgesic in neurologic ICU patients. A randomized multicenter study in patients with brain injury showed that mean neurologic assessment times were significantly shorter with remifentanil than with fentanyl or with morphine, and patients were extubated significantly faster after remifentanil than after morphine [23]. Another retrospective study investigated patients with delayed extubation after brain tumor surgery, and found that mean extubation times were significantly shorter after remifentanil/propofol than after fentanyl/midazolam, and LOS in ICU was significantly reduced [24]. These results indicate that the rapid metabolism and lack of accumulation of remifentanil facilitate faster waking and neurological assessment, and suggest that remifentanil might be a better choice of analgesic in patients with brain injury.

In present study, remifentanil is used as prophylactic analgesics in patients with delayed extubation after craniotomy. The aim is to evaluate the efficacy and safety of remifentanil for control of pain and stress responses due to extubation. The primary hypothesis is that prophylactic use of remifentanil will reduce the incidence of severe pain during endotracheal extubation.

## METHODS AND ANALYSIS

### Study design overview

The present study is a prospective, single-center, randomized, double-blinded, placebo-controlled, two-arm trial in patients with delayed extubation after craniotomy. Trial schematic diagram is shown in Figure 1.

### Study setting and population

The study setting is neurosurgical ICU (30 beds), Beijing Tiantan Hospital (1100 beds), Capital Medical University, Beijing, China.

All patients after intracranial surgery with delayed extubation admitted to our ICU are screened daily for study eligibility.

Inclusion criteria are:

1) Age between 18-65 years-old;
2) Within 72 hours after operation;
3) Awaken and able to cope with the assessment of visual analog scale (VAS) pain score;
4) Ready for extubation after evaluated by neurosurgeon and ICU physician in charge.

Exclusion criteria are:

1) Operation relating to medulla oblongata region;
2) Hepatic Insufficiency;

3) Renal insufficiency;

4) Pregnant or lactating women;

5) Need continuous infusion of vasopressor before the start of study drug infusion;

6) Chronic opioid use over three months;

7) Known opioids allergy;

8) Readmitted to ICU after randomization to the study;

9) Enrolled in another trial.

Patient's endotracheal tube is extubated at the discretion of neurosurgeon and ICU physician in charge of the patient. Neurosurgeon and ICU physician discuss the patient's status and evaluate the patient by a screen checklist (Table 1) [10]. When answers of all items in checklist are "yes", the patient is ready for extubation. At this time, a 24-hour on-call study coordinator will be informed immediately, and patient's eligibility for the study is evaluated and confirmed.

**Randomization, double-blind and allocation concealment**

The study has a prospective, randomized, double-blinded, controlled, parallel-group design. Consecutive patients are randomly assigned to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'. Randomization is based on computer generated random digits table and follows a concealed process using sealed and numbered envelopes that allocate the patient to either of the two arms of the study. Patients may be randomized into this study only once unless they were discharged from the hospital and were re-admitted beyond 180 days of the first enrollment. The study

does not allow cross-over and, if any occur, they will be reported as protocol violations. Experimental drug and placebo with the same character are prepared by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.

**Data collected at study entry**

At baseline, data on demographic, history of past illness characteristics and diagnosis of the patients are obtained. The surgical site, operation time, use of sedatives and analgesics during anaesthesia and ICU stay, time of mechanical ventilation, formulation and dose of postoperative patient-control-analgesia (PCA) pump, and time between end of operation and study drug infusion are recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II) is calculated.

**Trial interventions**

All patients are randomized 1:1 to receive remifentanil (Remi group) or placebo (Saline group) infusion. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Study drugs are administered by using syringe pump.

Immediately after drug infusion, ICU physician evaluate the patient by using extubation screen checklist shown in Table 1. If the patient passes the evaluation, endotracheal extubation will be carried out immediately by registered ICU nurses. The patient will be labeled as "failing to pass extubation test after drug administration" if he or she does not pass the evaluation. The reason of test failure will be documented. The patient will be re-evaluated every hour thereafter, and data about extubation will be documented.

Vital signs, which including heart rate (HR), respiratory rate (RR), non-invasive blood pressure (BP) and pulse oxygen saturation ($SpO_2$), are continuously monitored. VAS pain score is used to measure the pain intensity by the study investigator [25]. Each patient is instructed and asked to point to a mark on a 10-cm horizontal line labelled with descriptors of pain intensity ('No pain' at the 0 cm point and 'Extreme pain' at the 10 cm point). VAS and vital signs (HR, RR, BP and $SpO_2$) are documented at four time points: before drug infusion (baseline), immediately before extubation, immediately to 3 minutes after extubation and 20 minutes after extubation.

Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Following data are collected: incidence of re-intubation within 72 hours after extubation, incidence of re-operation due to intracranial hemorrhage or edema within 72 hours after extubation, LOS in ICU and hospital and mortality.

**Adverse events management and emergency stop of the study drug**

Patients are closely monitored during study drug infusion. Taking into account the potential adverse effects of remifentanil, experimental drugs must be immediately terminated when the following occurs:

1) Unresponsive to calling and patting on the shoulder;
2) RR less than 8 respirations per minute and $SpO_2$ less than 92%;
3) HR less than 50 beats per minute after atropine in 0.25 mg bolus;
4) Systolic BP less than 90 mmHg;
5) Serious allergic reaction such as throat swelling, bronchospasm or skin rash.

These data will be documented and reported as adverse events.

**Study endpoints**

The primary endpoint of present study is the incidence of severe pain during peri-extubation period. Peri-extubation is defined as the period of time from immediately before extubation to 20 minutes after extubation. Severe pain is defined as one of the VAS pain scores is more than 5 cm.

Secondary endpoints include:

1) VAS pain score and vital signs (HR, RR, BP and $SpO_2$) during peri-extubation period;
2) Incidence of failing to pass extubation evaluation after experimental drug infusion;
3) Incidence of re-intubation within 72 hours after extubation;
4) Incidence of re-operation due to intracranial hemorrhage or edema within 72

hours after extubation;

5) Incidence of adverse events during experimental drug infusion;

6) LOS in ICU and hospital;

7) Mortality.

**Current sample size justification**

Primarily, we expect the incidence of severe pain during peri-extubation period to decrease after remifentanil infusion in delayed extubation patients after craniotomy. Previous investigation showed that severe peri-extubation pain was occurred in 45% of patients [8]. It is expected that the incidence of severe pain would decrease to 30% after remifentanil infusion. Using the Power and Sample Size Calculation program, we will need to study 74 experimental subjects and 74 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability with testing this null hypothesis is 0.05.

**Statistical analysis**

All analyses will be according to the intention-to-treat principle, that is, all randomized patients will be analyzed in the groups to which they were originally allocated and will be blinded to treatment assignment.

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the $\chi^2$-test.

Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

We use repeated measure of analysis of variance (ANOVA) for comparing VAS pain score and vital signs (HR, RR, BP and $SpO_2$) across different time points (before drug infusion and during peri-extubation period) between the two groups.

All tests of significance will be at the 5% significance level, and two-sided. Analyses are conducted by using SPSS 17.0.

## ETHICS AND DISSEMINATION

### Ethical aspects and informed consent

Patients with delayed extubation after craniotomy are often unable to provide consent before extubation. After patient's eligibility for the study is confirmed, the ICU physician will introduce the family to the study coordinator. The physician will make sure the family knows the credentials of the study coordinator, and says that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that the patient may experience pain during extubation and, if so, the patient could become worse. The coordinator will say that a new opioid drug, remifentanil provides adequate analgesia with minimal respiratory depression. He (or she) will explain that in a small percentage of patients, remifentanil could cause bradycardia, hypotension and respiratory depression. The potential advantages of using or not using remifentanil will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study

coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

A register is kept of all patients evaluated for inclusion and of patients who withdraw from the study. The latter are clinically followed up without their data being analyzed in the study.

The study protocol and consent forms were approved on November 1, 2013 by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (approval number KY2013-002-01). The study was registered on November 8, 2013 at the Chinese Clinical Trial Registry (ChiCTR-PRC-13003879).

**Dissemination plan**

Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.

## TRIAL STATUS

The patient recruitment began on January 6, 2014, and the first patient was enrolled on the same day. The study will be completed in December 2014.

## SUMMARY

Endotracheal extubation is a critical step during post-operative care in neurosurgical patients [9]. Pain is common during extubation period, and related to complications and adverse outcome [8]. Adequate analgesia is needed in this situation. Although revised Clinical Practice Guidelines from SCCM have recommended that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to potentially painful procedures [7], study for analgesia during endotracheal extubation is still limited. As a new opioid with minimal respiratory depression effect and a rapid onset and short duration of action, remifentanil seems suitable for prophylactic analgesia during extubation in patients after craniotomy [13-16]. We want to provide such evidence in present study. Even a neutral result will provide important insight, as this would mean that more studies are needed to explore a safe and effective way of pain management during endotracheal extubation. This is the main strength of present study. There are some limitations to our study protocol. First, because there is no proven dose of remifentanil which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator, the dose of remifentanyl used in present study is arbitrary. Second, we assumed a 15% reduction in severe pain after the administration of remifentanil in the calculation of sample size. There are no previous studies to support this. However, an effectivity of 15% is generally adopted in clinical studies.

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## Authors' contributions

YXW and JXZ participated in the design of the study and drafted the manuscript. HC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

## Funding statement

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## Competing interests

The authors declare that they have no competing interests.

**Table 1: Screening checklist used to determine the patient's suitability for extubation**

| Question | Answer |
|---|---|
| 1. Awake and alert with cerebral function adequate for patient co-operation or equivalent preoperative state of consciousness? | Yes/No |
| 2. Hemodynamic stability (lack of vasopressor support and mean arterial pressure within 10-15% of baseline)? | Yes/No |
| 3. Adequate recovery of muscle strength? | Yes/No |
| 4. Normal tidal volumes, normocapnia (end-tidal carbon dioxide 30-45 mmHg), minimum pulse oximetry > 95% with $FiO_2$ 0.5? | Yes/No |
| 5. Intact gag reflex and swallow function (presence of clearly audible cough during suctioning)? | Yes/No |

The answer to all questions must be "yes" in order for extubation to be approved.

$FiO_2$: fraction of inspired oxygen

**Figure legend**

Figure 1: Trial schematic diagram

# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial

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**ABSTRACT**

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## INTRODUCTION

Clinical epidemiology studies have shown that critically ill patients in intensive care unit (ICU) are at high-risk of pain, and inadequate treatment of pain is associated with adverse outcomes [1,2]. Appropriate analgesia, not only attenuates stress response resulted from pain, but also reduces the incidence of iatrogenic complications, shorten the duration of mechanical ventilation and length of stay (LOS) in ICU [3-5]. In addition to pain at rest, pain related to procedures is common in ICU patients, and inadequate treatment of procedural pain remains a significant problem for many patients [6]. The revised clinical practice guidelines for management of pain, agitation, and delirium from Society of Critical Care Medicine (SCCM) also recommend that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to chest tube removal and other types of potentially painful procedures, and suggest that intravenous opioids should be considered as the first-line drug class of choice [7]. Manipulation of artificial airway, especially endotracheal extubation is among the high pain-intensity procedures in ICU. By using the patient's self-report pain scale as pain evaluation method, Gacouin et al. found that 45% of patients experienced severe pain at the time of endotracheal extubation [8]. Acute pain during extubation is associated with sympathetic nervous system activation, which could result in respiratory and circulatory instability [9]. Therefore, it is reasonable to control pain and stress responses at the time of endotracheal extubation in some high-risk patients, such as those after intracranial surgery. It has been reported that the proportion of patients who underwent delayed extubation after craniotomy is about 10% to 50% [10,11]. These

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patients are vulnerable to pain and complications of extubation [12]. On the other hand, despite a greater awareness of pain during endotracheal extubation, clinicians remain reluctant to administer opioids in patients following craniotomy. The major concern is the side effects of respiratory depression and influence on consciousness of these drugs. To our knowledge, up to now, no study has been published for adequate management of pain during extubation in patients with delayed extubation after craniotomy.

Remifentanil is a potent synthetic selective μ-opioid receptor agonist with a rapid onset and short duration of action, regardless of the duration of its administration [13,14]. Remifentanil differs from other synthetic opioids in its metabolism by non-specific plasma and tissue esterases. Study in human volunteers has shown that the respiratory depression of remifentanil by bolus injection is mild and easily treated with requests to breathe or the administration of oxygen [15]. These pharmacological properties suggest that remifentanil could be a potentially safe and effective analgesic in clinical situations requiring a brief period of intense control of pain, such as painful procedures in ICU [16]. There have been reported remifentanil used as prophylactic analgesia during removal of chest drain [17], insertion and removal of long-term central venous access [18], dressing change [19], and endotracheal suctioning [20]. However, although a plenty of studies have shown that the remifentanil facilitates emergency in general anesthesia and weaning process in mechanical ventilation [14,16,21], study for prophylactic use of remifentanil in endotracheal extubation is limited.

There has been increased interest in use of remifentanil in brain injured patients. In patients with traumatic brain injury, it has been demonstrated that remifentanil has no

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significant changes in systematic and cerebral hemodynamics, such as intracranial pressure, mean blood pressure, cerebral perfusion pressure, and cerebral blood flow velocity [22]. Several studies also compared remifentanil with fentanyl or morphine as analgesic in neurologic ICU patients. A randomized multicenter study in patients with brain injury showed that mean neurologic assessment times were significantly shorter with remifentanil than with fentanyl or with morphine, and patients were extubated significantly faster after remifentanil than after morphine [23]. Another retrospective study investigated patients with delayed extubation after brain tumor surgery, and found that mean extubation times were significantly shorter after remifentanil/propofol than after fentanyl/midazolam, and LOS in ICU was significantly reduced [24]. These results indicate that the rapid metabolism and lack of accumulation of remifentanil facilitate faster waking and neurological assessment, and suggest that remifentanil might be a better choice of analgesic in patients with brain injury.

In present study, remifentanil is used as prophylactic analgesics in patients with delayed extubation after craniotomy. The aim is to evaluate the efficacy and safety of remifentanil for control of pain and stress responses due to extubation. The primary hypothesis is that prophylactic use of remifentanil will reduce the incidence of severe pain during endotracheal extubation.

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## METHODS AND ANALYSIS

### Study design overview

The present study is a prospective, single-center, randomized, double-blinded, placebo-controlled, two-arm trial in patients with delayed extubation after craniotomy. Trial schematic diagram is shown in Figure 1.

### Study setting and population

The study setting is neurosurgical ICU (30 beds), Beijing Tiantan Hospital (1100 beds), Capital Medical University, Beijing, China.

All patients after intracranial surgery with delayed extubation admitted to our ICU are screened daily for study eligibility.

Inclusion criteria are:

1) Age between 18-65 years-old;
2) Within 72 hours after operation;
3) Awaken and able to cope with the assessment of visual analog scale (VAS) pain score;
4) Ready for extubation after evaluated by neurosurgeon and ICU physician in charge.

Exclusion criteria are:

1) Operation relating to medulla oblongata region;
2) Hepatic Insufficiency;

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3) Renal insufficiency;

4) Pregnant or lactating women;

5) Need continuous infusion of vasopressor before the start of study drug infusion;

6) Chronic opioid use over three months;

7) Known opioids allergy;

8) Readmitted to ICU after randomization to the study;

9) Enrolled in another trial.

Patient's endotracheal tube is extubated at the discretion of neurosurgeon and ICU physician in charge of the patient. Neurosurgeon and ICU physician discuss the patient's status and evaluate the patient by a screen checklist (Table 1) [10]. When answers of all items in checklist are "yes", the patient is ready for extubation. At this time, a 24-hour on-call study coordinator will be informed immediately, and patient's eligibility for the study is evaluated and confirmed.

**Randomization, double-blind and allocation concealment**

The study has a prospective, randomized, double-blinded, controlled, parallel-group design. Consecutive patients are randomly assigned to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'. Randomization is based on computer generated random digits table and follows a concealed process using sealed and numbered envelopes that allocate the patient to either of the two arms of the study. Patients may be randomized into this study only once unless they were discharged from the hospital and were re-admitted beyond 180 days of the first enrollment. The study

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does not allow cross-over and, if any occur, they will be reported as protocol violations. Experimental drug and placebo with the same character are prepared by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.

**Data collected at study entry**

At baseline, data on demographic, history of past illness characteristics and diagnosis of the patients are obtained. The surgical site, operation time, use of sedatives and analgesics during anaesthesia and ICU stay, time of mechanical ventilation, formulation and dose of postoperative patient-control-analgesia (PCA) pump, and time between end of operation and study drug infusion are recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II) is calculated.

**Trial interventions**

All patients are randomized 1:1 to receive remifentanil (Remi group) or placebo (Saline group) infusion. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Study drugs are administered by using syringe pump.

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Immediately after drug infusion, ICU physician evaluate the patient by using extubation screen checklist shown in Table 1. If the patient passes the evaluation, endotracheal extubation will be carried out immediately by registered ICU nurses. The patient will be labeled as "failing to pass extubation test after drug administration" if he or she does not pass the evaluation. The reason of test failure will be documented. The patient will be re-evaluated every hour thereafter, and data about extubation will be documented.

Vital signs, which including heart rate (HR), respiratory rate (RR), non-invasive blood pressure (BP) and pulse oxygen saturation ($SpO_2$), are continuously monitored. VAS pain score is used to measure the pain intensity by the study investigator [25]. Each patient is instructed and asked to point to a mark on a 10-cm horizontal line labelled with descriptors of pain intensity ('No pain' at the 0 cm point and 'Extreme pain' at the 10 cm point). VAS and vital signs (HR, RR, BP and $SpO_2$) are documented at four time points: before drug infusion (baseline), immediately before extubation, immediately to 3 minutes after extubation and 20 minutes after extubation.

Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Following data are collected: incidence of re-intubation within 72 hours after extubation, incidence of re-operation due to intracranial hemorrhage or edema within 72 hours after extubation, LOS in ICU and hospital and mortality.

**Adverse events management and emergency stop of the study drug**

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Patients are closely monitored during study drug infusion. Taking into account the potential adverse effects of remifentanil, experimental drugs must be immediately terminated when the following occurs:

1) Unresponsive to calling and patting on the shoulder;
2) RR less than 8 respirations per minute and $SpO_2$ less than 92%;
3) HR less than 50 beats per minute after atropine in 0.25 mg bolus;
4) Systolic BP less than 90 mmHg;
5) Serious allergic reaction such as throat swelling, bronchospasm or skin rash.

These data will be documented and reported as adverse events.

**Study endpoints**

The primary endpoint of present study is the incidence of severe pain during peri-extubation period. Peri-extubation is defined as the period of time from immediately before extubation to 20 minutes after extubation. Severe pain is defined as one of the VAS pain scores is more than 5 cm.

Secondary endpoints include:

1) VAS pain score and vital signs (HR, RR, BP and $SpO_2$) during peri-extubation period;
2) Incidence of failing to pass extubation evaluation after experimental drug infusion;
3) Incidence of re-intubation within 72 hours after extubation;
4) Incidence of re-operation due to intracranial hemorrhage or edema within 72

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hours after extubation;

5) Incidence of adverse events during experimental drug infusion;

6) LOS in ICU and hospital;

7) Mortality.

**Current sample size justification**

Primarily, we expect the incidence of severe pain during peri-extubation period to decrease after remifentanil infusion in delayed extubation patients after craniotomy. Previous investigation showed that severe peri-extubation pain was occurred in 45% of patients [8]. It is expected that the incidence of severe pain would decrease to 30% after remifentanil infusion. Using the Power and Sample Size Calculation program, we will need to study 74 experimental subjects and 74 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability with testing this null hypothesis is 0.05.

**Statistical analysis**

All analyses will be according to the intention-to-treat principle, that is, all randomized patients will be analyzed in the groups to which they were originally allocated and will be blinded to treatment assignment.

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the $\chi^2$-test.

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Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

We use repeated measure of analysis of variance (ANOVA) for comparing VAS pain score and vital signs (HR, RR, BP and $SpO_2$) across different time points (before drug infusion and during peri-extubation period) between the two groups.

All tests of significance will be at the 5% significance level, and two-sided. Analyses are conducted by using SPSS 17.0.



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## ETHICS AND DISSEMINATION

### Ethical aspects and informed consent

Patients with delayed extubation after craniotomy are often unable to provide consent before extubation. After patient's eligibility for the study is confirmed, the ICU physician will introduce the family to the study coordinator. The physician will make sure the family knows the credentials of the study coordinator, and says that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that the patient may experience pain during extubation and, if so, the patient could become worse. The coordinator will say that a new opioid drug, remifentanil provides adequate analgesia with minimal respiratory depression. He (or she) will explain that in a small percentage of patients, remifentanil could cause bradycardia, hypotension and respiratory depression. The potential advantages of using or not using remifentanil will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study

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coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

A register is kept of all patients evaluated for inclusion and of patients who withdraw from the study. The latter are clinically followed up without their data being analyzed in the study.

The study protocol and consent forms were approved on November 1, 2013 by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (approval number KY2013-002-01). The study was registered on November 8, 2013 at the Chinese Clinical Trial Registry (ChiCTR-PRC-13003879).

**Dissemination plan**

Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.



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## TRIAL STATUS

The patient recruitment began on January 6, 2014, and ~~T~~the first patient was enrolled on ~~January 06, 2014~~the same day. The study will be completed in December 2014.

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**SUMMARY**

Endotracheal extubation is a critical step during post-operative care in neurosurgical patients [9]. Pain is common during extubation period, and related to complications and adverse outcome [8]. Adequate analgesia is needed in this situation. Although revised Clinical Practice Guidelines from SCCM have recommended that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to potentially painful procedures [7], study for analgesia during endotracheal extubation is still limited. As a new opioid with minimal respiratory depression effect and a rapid onset and short duration of action, remifentanil seems suitable for prophylactic analgesia during extubation in patients after craniotomy [13-16]. We want to provide such evidence in present study. Even a neutral result will provide important insight, as this would mean that more studies are needed to explore a safe and effective way of pain management during endotracheal extubation. This is the main strength of present study. There are some limitations to our study protocol. First, because there is no proven dose of remifentanil which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator, the dose of remifentanyl used in present study is arbitrary. Second, we assumed a 15% reduction in severe pain after the administration of remifentanil in the calculation of sample size. There are no previous studies to support this. However, an effectivity of 15% is generally adopted in clinical studies.

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**Authors' contributions**

YXW and JXZ participated in the design of the study and drafted the manuscript. HC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

**Funding statement**

The study was funded by Beijing Health Bureau (No: 2009-3-28). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

**Competing interests**

The authors declare that they have no competing interests.



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**Table 1: Screening checklist used to determine the patient's suitability for extubation**

| Question | Answer |
|---|---|
| 1. Awake and alert with cerebral function adequate for patient co-operation or equivalent preoperative state of consciousness? | Yes/No |
| 2. Hemodynamic stability (lack of vasopressor support and mean arterial pressure within 10-15% of baseline)? | Yes/No |
| 3. Adequate recovery of muscle strength? | Yes/No |
| 4. Normal tidal volumes, normocapnia (end-tidal carbon dioxide 30-45 mmHg), minimum pulse oximetry > 95% with $FiO_2$ 0.5? | Yes/No |
| 5. Intact gag reflex and swallow function (presence of clearly audible cough during suctioning)? | Yes/No |

The answer to all questions must be "yes" in order for extubation to be approved.

$FiO_2$: fraction of inspired oxygen



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**Figure legend**

Figure 1: Trial schematic diagram



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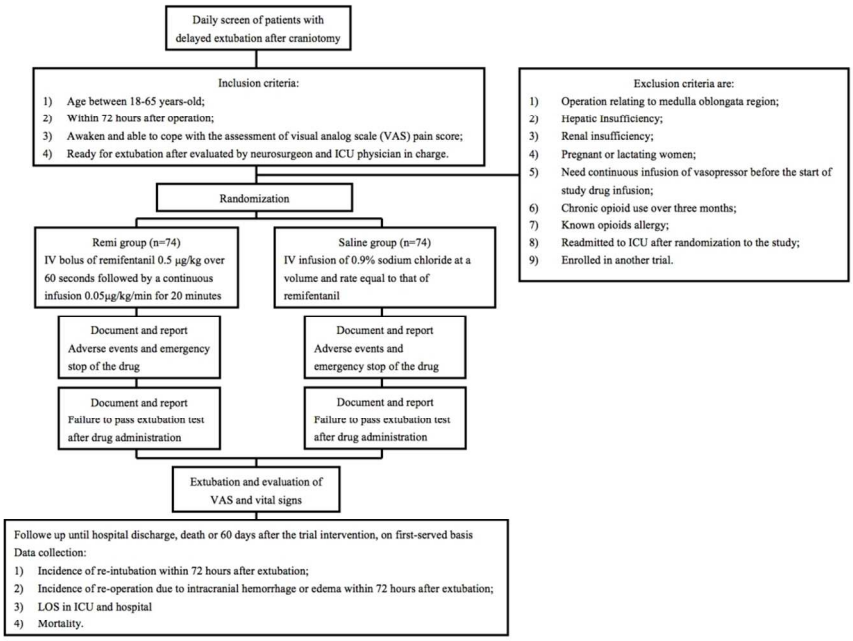


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# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-6 |
| | 2b | Specific objectives or hypotheses | 6 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 7, 9 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | Not applicable |
| Participants | 4a | Eligibility criteria for participants | 7 |
| | 4b | Settings and locations where the data were collected | 7 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9-11 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11-12 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | Not applicable |
| Sample size | 7a | How sample size was determined | 12 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | Not applicable |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 8-9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 8-9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 8-9 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 8-9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 8-9 |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | 8-9 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 12-13 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | Not applicable |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Not applicable in items 13a to 22 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | |
| | 14b | Why the trial ended or was stopped | |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | ChiCTR-PRC-13003879 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | Not applicable |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | The study was supported by Beijing Health |

| | |
|---|---|
| | Bureau (No: 2009-3-28). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial



| | |
|---|---|
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| Secondary Subject Heading: | Intensive care, Neurology |
| Keywords: | Anaesthesia in neurology < ANAESTHETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS |
| | |

# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial

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Keywords: remifentanil, analgesia, prophylactic, extubation, craniotomy

Word count: 4409

## ABSTRACT

**Introduction:** Acute pain is common during endotracheal extubation period, and is related to complications and adverse outcomes. Patients with delayed extubation after craniotomy are vulnerable to pain and complications of extubation. However, pain control during extubation is still inadequate. Remifentanil, a new opioid with rapid onset and short duration of action, provides adequate analgesia during procedures with minimal effect of respiratory depression.

**Methods and analysis:** The study is a prospective, randomized, double-blinded, controlled, parallel-group design. Patients with delayed extubation after intracranial surgery are screened daily. Adult patients ready for extubation are enrolled and assigned randomly to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Pain intensity is measured by visual analog scale (VAS) pain score. Adverse events during drug infusion are documented and reported. Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Incidence of re-intubation and re-operation within 72 hours after extubation, length of stay in intensive care unit and hospital and mortality are collected. The primary endpoint is the incidence of severe pain (defined as VAS pain score more than 5 cm) during peri-extubation period (defined as the period of time from immediately before extubation to 20 minutes after

extubation).

**Ethics and dissemination:** The study was approved by the IRB of Beijing Tiantan Hospital, Capital Medical University. Study findings will be disseminated through peer-reviewed publications and conference presentations.

**Trial Registration:** ClinicalTrials (NCT): ChiCTR-PRC-13003879.

**Main strengths and limitations of the study**

Pain is common during extubation period, and related to complications and adverse outcome. Adequate analgesia is needed in this situation. The main strength of the study is that we will provide the evidence of a new opioid (remifentanil) with minimal respiratory depression effect and a rapid onset and short duration of action, for prophylactic analgesia during extubation in patients after craniotomy.

Pain management is a comprehensive algorithm, which includes pharmacologic and non-pharmacologic interventions. In present study, only remifentanil is investigated for prophylactic analgesia during extubation. This is the main limitation of the study.

Because there is no proven dose of remifentanil which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator, the dose of remifentanil used in present study is arbitrary. The evaluation of visual analog scale requires the patient's ability to self-report clearly, and this may limit the patient population eligible for the present study. So, the results of this study will not be applied to all patients after craniotomy, especially for those with consciousness impairments.

## INTRODUCTION

Clinical epidemiology studies have shown that critically ill patients in intensive care unit (ICU) are at high-risk of pain, and inadequate treatment of pain is associated with adverse outcomes [1,2]. Appropriate analgesia, not only attenuates stress response resulted from pain, but also reduces the incidence of iatrogenic complications, shorten the duration of mechanical ventilation and length of stay (LOS) in ICU [3-5]. In addition to pain at rest, pain related to procedures is common in ICU patients, and inadequate treatment of procedural pain remains a significant problem for many patients [6]. The revised clinical practice guidelines for management of pain, agitation, and delirium from Society of Critical Care Medicine (SCCM) also recommend that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to chest tube removal and other types of potentially painful procedures, and suggest that intravenous opioids should be considered as the first-line drug class of choice [7]. Manipulation of artificial airway, especially endotracheal extubation is among the high pain-intensity procedures in ICU. By using the patient's self-report pain scale as pain evaluation method, Gacouin et al. found that 45% of patients experienced severe pain at the time of endotracheal extubation [8]. Acute pain during extubation is associated with sympathetic nervous system activation, which could result in respiratory and circulatory instability [9]. Therefore, it is reasonable to control pain and stress responses at the time of endotracheal extubation in some high-risk patients, such as those after intracranial surgery. It has been reported that the proportion of patients who underwent delayed extubation after craniotomy is about 10% to 50% [10,11]. These

patients are vulnerable to pain and complications of extubation [12]. On the other hand, despite a greater awareness of pain during endotracheal extubation, clinicians remain reluctant to administer opioids in patients following craniotomy. The major concern is the side effects of respiratory depression and influence on consciousness of these drugs. To our knowledge, up to now, no study has been published for adequate management of pain during extubation in patients with delayed extubation after craniotomy.

Remifentanil is a potent synthetic selective μ-opioid receptor agonist with a rapid onset and short duration of action, regardless of the duration of its administration [13,14]. Remifentanil differs from other synthetic opioids in its metabolism by non-specific plasma and tissue esterases. Study in human volunteers has shown that the respiratory depression of remifentanil by bolus injection is mild and easily treated with requests to breathe or the administration of oxygen [15]. These pharmacological properties suggest that remifentanil could be a potentially safe and effective analgesic in clinical situations requiring a brief period of intense control of pain, such as painful procedures in ICU [16]. There have been reported remifentanil used as prophylactic analgesia during removal of chest drain [17], insertion and removal of long-term central venous access [18], dressing change [19], and endotracheal suctioning [20]. However, although a plenty of studies have shown that the remifentanil facilitates emergency in general anesthesia and weaning process in mechanical ventilation [14,16,21], study for prophylactic use of remifentanil in endotracheal extubation is limited.

There has been increased interest in use of remifentanil in brain injured patients. In patients with traumatic brain injury, it has been demonstrated that remifentanil has no

significant changes in systematic and cerebral hemodynamics, such as intracranial pressure, mean blood pressure, cerebral perfusion pressure, and cerebral blood flow velocity [22]. Several studies also compared remifentanil with fentanyl or morphine as analgesic in neurologic ICU patients. A randomized multicenter study in patients with brain injury showed that mean neurologic assessment times were significantly shorter with remifentanil than with fentanyl or with morphine, and patients were extubated significantly faster after remifentanil than after morphine [23]. Another retrospective study investigated patients with delayed extubation after brain tumor surgery, and found that mean extubation times were significantly shorter after remifentanil/propofol than after fentanyl/midazolam, and LOS in ICU was significantly reduced [24]. These results indicate that the rapid metabolism and lack of accumulation of remifentanil facilitate faster waking and neurological assessment, and suggest that remifentanil might be a better choice of analgesic in patients with brain injury.

In present study, remifentanil is used as prophylactic analgesics in patients with delayed extubation after craniotomy. The aim is to evaluate the efficacy and safety of remifentanil for control of pain and stress responses due to extubation. The primary hypothesis is that prophylactic use of remifentanil will reduce the incidence of severe pain during endotracheal extubation.

## METHODS AND ANALYSIS

### Study design overview

The present study is a prospective, single-center, randomized, double-blinded, placebo-controlled, two-arm trial in patients with delayed extubation after craniotomy. Trial schematic diagram is shown in Figure 1.

### Study setting and population

The study setting is neurosurgical ICU (30 beds), Beijing Tiantan Hospital (1100 beds), Capital Medical University, Beijing, China.

All patients after intracranial surgery with delayed extubation admitted to our ICU are screened daily for study eligibility.

Inclusion criteria are:

1) Age between 18-65 years-old;
2) Within 72 hours after operation;
3) Awaken and able to cope with the assessment of visual analog scale (VAS) pain score;
4) Ready for extubation after evaluated by neurosurgeon and ICU physician in charge.

Exclusion criteria are:

1) Operation relating to medulla oblongata region;
2) Hepatic Insufficiency;

3) Renal insufficiency;

4) Pregnant or lactating women;

5) Need continuous infusion of vasopressor before the start of study drug infusion;

6) Chronic opioid use over three months;

7) Known opioids allergy;

8) Readmitted to ICU after randomization to the study;

9) Enrolled in another trial.

Patient's endotracheal tube is extubated at the discretion of neurosurgeon and ICU physician in charge of the patient. Neurosurgeon and ICU physician discuss the patient's status and evaluate the patient by a screen checklist (Table 1) [10]. When answers of all items in checklist are "yes", the patient is ready for extubation. At this time, a 24-hour on-call study coordinator will be informed immediately, and patient's eligibility for the study is evaluated and confirmed.

**Randomization, double-blind and allocation concealment**

The study has a prospective, randomized, double-blinded, controlled, parallel-group design. Randomization is based on computer generated random digits table. The allocation sequence is sealed in numbered and opaque envelopes to ensure that the sequence is concealed. Enrolled patients are randomly assigned 1:1 to receive remifentanil (labeled as Remi group) or placebo (labeled as Saline group) infusion. Patients may be randomized into this study only once unless they were discharged from the hospital and were re-admitted beyond 180 days of the first enrollment. The study

does not allow cross-over and, if any occur, they will be reported as protocol violations. Experimental drug and placebo with the same character are prepared by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.

**Data collected at study entry**

At baseline, data on demographic, history of past illness characteristics and diagnosis of the patients are obtained. The surgical site, operation time, use of sedatives and analgesics during anaesthesia and ICU stay, time of mechanical ventilation, formulation and dose of postoperative patient-control-analgesia (PCA) pump, and time between end of operation and study drug infusion are recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II) is calculated.

**Trial interventions**

All patients are randomized 1:1 to receive remifentanil (Remi group) or placebo (Saline group) infusion. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Study drugs are administered by using syringe pump.

Immediately after drug infusion, ICU physician evaluate the patient by using extubation screen checklist shown in Table 1. If the patient passes the evaluation, endotracheal extubation will be carried out immediately by registered ICU nurses. The patient will be labeled as "failing to pass extubation test after drug administration" if he or she does not pass the evaluation. The reason of test failure will be documented. The patient will be re-evaluated every hour thereafter, and data about extubation will be documented.

Vital signs, which including heart rate (HR), respiratory rate (RR), non-invasive blood pressure (BP) and pulse oxygen saturation ($SpO_2$), are continuously monitored. VAS pain score is used to measure the pain intensity by the study investigator [25]. Each patient is instructed and asked to point to a mark on a 10-cm horizontal line labelled with descriptors of pain intensity ('No pain' at the 0 cm point and 'Extreme pain' at the 10 cm point). VAS and vital signs (HR, RR, BP and $SpO_2$) are documented at four time points: before drug infusion (baseline), immediately before extubation, immediately to 3 minutes after extubation and 20 minutes after extubation.

Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Following data are collected: incidence of re-intubation within 72 hours after extubation, incidence of re-operation due to intracranial hemorrhage or edema within 72 hours after extubation, LOS in ICU and hospital and mortality.

**Adverse events management and emergency stop of the study drug**

Patients are closely monitored during study drug infusion. Taking into account the potential adverse effects of remifentanil, experimental drugs must be immediately terminated when the following occurs:

1) Unresponsive to calling and patting on the shoulder;
2) RR less than 8 respirations per minute and $SpO_2$ less than 92%;
3) HR less than 50 beats per minute after atropine in 0.25 mg bolus;
4) Systolic BP less than 90 mmHg;
5) Serious allergic reaction such as throat swelling, bronchospasm or skin rash.

These data will be documented and reported as adverse events.

**Study endpoints**

The primary endpoint of present study is the incidence of severe pain during peri-extubation period. Peri-extubation is defined as the period of time from immediately before extubation to 20 minutes after extubation. Severe pain is defined as one of the VAS pain scores is more than 5 cm.

Secondary endpoints include:

1) VAS pain score and vital signs (HR, RR, BP and $SpO_2$) during peri-extubation period;
2) Incidence of failing to pass extubation evaluation after experimental drug infusion;
3) Incidence of re-intubation within 72 hours after extubation;
4) Incidence of re-operation due to intracranial hemorrhage or edema within 72

hours after extubation;

5) Incidence of adverse events during experimental drug infusion;

6) LOS in ICU and hospital;

7) Mortality.

**Current sample size justification**

Primarily, we expect the incidence of severe pain during peri-extubation period to decrease after remifentanil infusion in delayed extubation patients after craniotomy. Previous investigation showed that severe peri-extubation pain was occurred in 45% of patients [8]. It is expected that the incidence of severe pain would decrease to 30% after remifentanil infusion. Using the Power and Sample Size Calculation program, we will need to study 74 experimental subjects and 74 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability with testing this null hypothesis is 0.05.

**Statistical analysis**

All analyses will be according to the intention-to-treat principle, that is, all randomized patients will be analyzed in the groups to which they were originally allocated and will be blinded to treatment assignment.

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the $\chi^2$-test.

Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

We use repeated measure of analysis of variance (ANOVA) for comparing VAS pain score and vital signs (HR, RR, BP and $SpO_2$) across different time points (before drug infusion and during peri-extubation period) between the two groups.

All tests of significance will be at the 5% significance level, and two-sided. Analyses are conducted by using SPSS 17.0.

## ETHICS AND DISSEMINATION

### Ethical aspects and informed consent

Patients with delayed extubation after craniotomy are often unable to provide consent before extubation. After patient's eligibility for the study is confirmed, the ICU physician will introduce the family to the study coordinator. The physician will make sure the family knows the credentials of the study coordinator, and says that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that the patient may experience pain during extubation and, if so, the patient could become worse. The coordinator will say that a new opioid drug, remifentanil provides adequate analgesia with minimal respiratory depression. He (or she) will explain that in a small percentage of patients, remifentanil could cause bradycardia, hypotension and respiratory depression. The potential advantages of using or not using remifentanil will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study

coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

A register is kept of all patients evaluated for inclusion and of patients who withdraw from the study. The latter are clinically followed up without their data being analyzed in the study.

The study protocol and consent forms were approved on November 1, 2013 by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (approval number KY2013-002-01). The study was registered on November 8, 2013 at the Chinese Clinical Trial Registry (ChiCTR-PRC-13003879).

**Dissemination plan**

Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.

## TRIAL STATUS

The patient recruitment began on January 6, 2014, and the first patient was enrolled on the same day. The study will be completed in December 2014.

## SUMMARY

Endotracheal extubation is a critical step during post-operative care in neurosurgical patients [9]. Pain is common during extubation period, and related to complications and adverse outcome [8]. Adequate analgesia is needed in this situation. Although revised Clinical Practice Guidelines from SCCM have recommended that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to potentially painful procedures [7], study for analgesia during endotracheal extubation is still limited. As a new opioid with minimal respiratory depression effect and a rapid onset and short duration of action, remifentanil seems suitable for prophylactic analgesia during extubation in patients after craniotomy [13-16]. We want to provide such evidence in present study. Even a neutral result will provide important insight, as this would mean that more studies are needed to explore a safe and effective way of pain management during endotracheal extubation. This is the main strength of present study. It should be emphasized the comprehensive characteristics of pain management. Apart from opioids, other analgesics (such as steroidal or non-steroidal anti-inflammatory drugs) and/or non-pharmacologic interventions (such as relaxation) have been shown to alleviate pain in adult ICU patients [7]. Although the main purpose of present study is not to clarify the effect of comprehensive approach on manipulation of pain during extubation, we will collect data of the use of analgesics during anaesthesia and ICU stay, and the formulation and dose of postoperative PCA pump. The use of non-opioids and non-pharmacologic interventions during extubation needs further investigation. Currently, vital signs are not recommended to be used alone for pain assessment [7].

However, we still incorporated changes of vital signs during peri-extubation period as a secondary endpoint for two reasons. First, nociceptive stimulus during endotracheal extubation may result in adverse events in patients after craniotomy, such as brain swelling and hemorrhage. We want to know whether remifentanil could diminish this stress response. Second, because large doses of opioid agents usually result in respiratory and circulatory depression, this secondary endpoint will provide safe consideration about the use of these agents.

There are some limitations to our study protocol. First, because there is no proven dose of remifentanil which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator, the dose of remifentanyl used in present study is arbitrary. Second, we assumed a 15% reduction in severe pain after the administration of remifentanil in the calculation of sample size. There are no previous studies to support this. However, an effectivity of 15% is generally adopted in clinical studies. Third, opioids may result in change of consciousness. We only observe the response to calling and patting on the shoulder during the infusion of study agents. Documentation of sedation scales (such as Vancouver interaction scale or sedation-agitation scale) will add value to the study. Finally, evaluation of VAS requires the patient's ability to self-report clearly, and this may limit the patient population eligible for the present study. So, the results of this study will not be applied to all patients after craniotomy, especially for those with consciousness impairments.

## Authors' contributions

All authors listed on the title page fulfill the authorship criteria given by the ICMJE. YXW and JXZ participated in the design of the study and drafted the manuscript. HC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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## Competing interests

The authors declare that they have no competing interests.

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**Table 1: Screening checklist used to determine the patient's suitability for extubation**

| Question | Answer |
|---|---|
| 1. Awake and alert with cerebral function adequate for patient co-operation or equivalent preoperative state of consciousness? | Yes/No |
| 2. Hemodynamic stability (lack of vasopressor support and mean arterial pressure within 10-15% of baseline)? | Yes/No |
| 3. Adequate recovery of muscle strength? | Yes/No |
| 4. Normal tidal volumes, normocapnia (end-tidal carbon dioxide 30-45 mmHg), minimum pulse oximetry > 95% with $FiO_2$ 0.5? | Yes/No |
| 5. Intact gag reflex and swallow function (presence of clearly audible cough during suctioning)? | Yes/No |

The answer to all questions must be "yes" in order for extubation to be approved.

$FiO_2$: fraction of inspired oxygen

**Figure legend**

Figure 1: Trial schematic diagram

# Short-term use of remifentanil during endotracheal extubation for prophylactic analgesia in neurosurgical patients after craniotomy (SURE after Craniotomy Study): a study protocol and statistical analysis plan for a randomized controlled trial

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Keywords: remifentanil, analgesia, prophylactic, extubation, craniotomy

Word count: 4409~~2569~~

## ABSTRACT

**Introduction:** Acute pain is common during endotracheal extubation period, and is related to complications and adverse outcomes. Patients with delayed extubation after craniotomy are vulnerable to pain and complications of extubation. However, pain control during extubation is still inadequate. Remifentanil, a new opioid with rapid onset and short duration of action, provides adequate analgesia during procedures with minimal effect of respiratory depression.

**Methods and analysis:** The study is a prospective, randomized, double-blinded, controlled, parallel-group design. Patients with delayed extubation after intracranial surgery are screened daily. Adult patients ready for extubation are enrolled and assigned randomly to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'. Patients in Remi group receive intravenous bolus dose of remifentanil 0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Pain intensity is measured by visual analog scale (VAS) pain score. Adverse events during drug infusion are documented and reported. Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Incidence of re-intubation and re-operation within 72 hours after extubation, length of stay in intensive care unit and hospital and mortality are collected. The primary endpoint is the incidence of severe pain (defined as VAS pain score more than 5 cm) during peri-extubation period (defined as the period of time from immediately before extubation to 20 minutes after

extubation).

**Ethics and dissemination:** The study was approved by the IRB of Beijing Tiantan Hospital, Capital Medical University. Study findings will be disseminated through peer-reviewed publications and conference presentations.

**Trial Registration:** ClinicalTrials (NCT): ChiCTR-PRC-13003879.

**Main strengths and limitations of the study**

Pain is common during extubation period, and related to complications and adverse outcome. Adequate analgesia is needed in this situation. The main strength of the study is that we will provide the evidence of a new opioid (remifentanil) with minimal respiratory depression effect and a rapid onset and short duration of action, for prophylactic analgesia during extubation in patients after craniotomy.

Pain management is a comprehensive algorithm, which includes pharmacologic and non-pharmacologic interventions. In present study, only remifentanil is investigated ~~Other opioids may be suitable~~ for prophylactic analgesia during extubation. This is the ~~The~~ main limitation of the study ~~is that we do not use other opioids, such as morphine or fentanyl, as control groups~~. Because there is no proven dose of remifentanil which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator, the dose of remifentanil~~remifentanyl~~ used in present study is arbitrary. The evaluation of visual analog scale requires the patient's ability to self-report clearly, and this may limit the patient population eligible for the present study. So, the results of this study will not be applied to all patients after craniotomy,

especially for those with consciousness impairments.

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## INTRODUCTION

Clinical epidemiology studies have shown that critically ill patients in intensive care unit (ICU) are at high-risk of pain, and inadequate treatment of pain is associated with adverse outcomes [1,2]. Appropriate analgesia, not only attenuates stress response resulted from pain, but also reduces the incidence of iatrogenic complications, shorten the duration of mechanical ventilation and length of stay (LOS) in ICU [3-5]. In addition to pain at rest, pain related to procedures is common in ICU patients, and inadequate treatment of procedural pain remains a significant problem for many patients [6]. The revised clinical practice guidelines for management of pain, agitation, and delirium from Society of Critical Care Medicine (SCCM) also recommend that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to chest tube removal and other types of potentially painful procedures, and suggest that intravenous opioids should be considered as the first-line drug class of choice [7]. Manipulation of artificial airway, especially endotracheal extubation is among the high pain-intensity procedures in ICU. By using the patient's self-report pain scale as pain evaluation method, Gacouin et al. found that 45% of patients experienced severe pain at the time of endotracheal extubation [8]. Acute pain during extubation is associated with sympathetic nervous system activation, which could result in respiratory and circulatory instability [9]. Therefore, it is reasonable to control pain and stress responses at the time of endotracheal extubation in some high-risk patients, such as those after intracranial surgery. It has been reported that the proportion of patients who underwent delayed extubation after craniotomy is about 10% to 50% [10,11]. These

patients are vulnerable to pain and complications of extubation [12]. On the other hand, despite a greater awareness of pain during endotracheal extubation, clinicians remain reluctant to administer opioids in patients following craniotomy. The major concern is the side effects of respiratory depression and influence on consciousness of these drugs. To our knowledge, up to now, no study has been published for adequate management of pain during extubation in patients with delayed extubation after craniotomy.

Remifentanil is a potent synthetic selective μ-opioid receptor agonist with a rapid onset and short duration of action, regardless of the duration of its administration [13,14]. Remifentanil differs from other synthetic opioids in its metabolism by non-specific plasma and tissue esterases. Study in human volunteers has shown that the respiratory depression of remifentanil by bolus injection is mild and easily treated with requests to breathe or the administration of oxygen [15]. These pharmacological properties suggest that remifentanil could be a potentially safe and effective analgesic in clinical situations requiring a brief period of intense control of pain, such as painful procedures in ICU [16]. There have been reported remifentanil used as prophylactic analgesia during removal of chest drain [17], insertion and removal of long-term central venous access [18], dressing change [19], and endotracheal suctioning [20]. However, although a plenty of studies have shown that the remifentanil facilitates emergency in general anesthesia and weaning process in mechanical ventilation [14,16,21], study for prophylactic use of remifentanil in endotracheal extubation is limited.

There has been increased interest in use of remifentanil in brain injured patients. In patients with traumatic brain injury, it has been demonstrated that remifentanil has no

significant changes in systematic and cerebral hemodynamics, such as intracranial pressure, mean blood pressure, cerebral perfusion pressure, and cerebral blood flow velocity [22]. Several studies also compared remifentanil with fentanyl or morphine as analgesic in neurologic ICU patients. A randomized multicenter study in patients with brain injury showed that mean neurologic assessment times were significantly shorter with remifentanil than with fentanyl or with morphine, and patients were extubated significantly faster after remifentanil than after morphine [23]. Another retrospective study investigated patients with delayed extubation after brain tumor surgery, and found that mean extubation times were significantly shorter after remifentanil/propofol than after fentanyl/midazolam, and LOS in ICU was significantly reduced [24]. These results indicate that the rapid metabolism and lack of accumulation of remifentanil facilitate faster waking and neurological assessment, and suggest that remifentanil might be a better choice of analgesic in patients with brain injury.

In present study, remifentanil is used as prophylactic analgesics in patients with delayed extubation after craniotomy. The aim is to evaluate the efficacy and safety of remifentanil for control of pain and stress responses due to extubation. The primary hypothesis is that prophylactic use of remifentanil will reduce the incidence of severe pain during endotracheal extubation.

## METHODS AND ANALYSIS

### Study design overview

The present study is a prospective, single-center, randomized, double-blinded, placebo-controlled, two-arm trial in patients with delayed extubation after craniotomy. Trial schematic diagram is shown in Figure 1.

### Study setting and population

The study setting is neurosurgical ICU (30 beds), Beijing Tiantan Hospital (1100 beds), Capital Medical University, Beijing, China.

All patients after intracranial surgery with delayed extubation admitted to our ICU are screened daily for study eligibility.

Inclusion criteria are:

1) Age between 18-65 years-old;
2) Within 72 hours after operation;
3) Awaken and able to cope with the assessment of visual analog scale (VAS) pain score;
4) Ready for extubation after evaluated by neurosurgeon and ICU physician in charge.

Exclusion criteria are:

1) Operation relating to medulla oblongata region;
2) Hepatic Insufficiency;

3) Renal insufficiency;

4) Pregnant or lactating women;

5) Need continuous infusion of vasopressor before the start of study drug infusion;

6) Chronic opioid use over three months;

7) Known opioids allergy;

8) Readmitted to ICU after randomization to the study;

9) Enrolled in another trial.

Patient's endotracheal tube is extubated at the discretion of neurosurgeon and ICU physician in charge of the patient. Neurosurgeon and ICU physician discuss the patient's status and evaluate the patient by a screen checklist (Table 1) [10]. When answers of all items in checklist are "yes", the patient is ready for extubation. At this time, a 24-hour on-call study coordinator will be informed immediately, and patient's eligibility for the study is evaluated and confirmed.

**Randomization, double-blind and allocation concealment**

The study has a prospective, randomized, double-blinded, controlled, parallel-group design. Randomization is based on computer generated random digits table. The allocation sequence is sealed in numbered and opaque envelopes to ensure that the sequence is concealed. ~~Consecutive~~ Enrolled patients are randomly assigned 1:1 to receive remifentanil (labeled as Remi group) or placebo (labeled as Saline group) infusion~~to one of the two treatment study groups, labeled as 'Remi group' or 'Saline group'~~. ~~Randomization is based on computer generated random digits table and follows~~

~~a concealed process using sealed and numbered envelopes that allocate the patient to either of the two arms of the study.~~ Patients may be randomized into this study only once unless they were discharged from the hospital and were re-admitted beyond 180 days of the first enrollment. The study does not allow cross-over and, if any occur, they will be reported as protocol violations.

Experimental drug and placebo with the same character are prepared by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.

**Data collected at study entry**

At baseline, data on demographic, history of past illness characteristics and diagnosis of the patients are obtained. The surgical site, operation time, use of sedatives and analgesics during anaesthesia and ICU stay, time of mechanical ventilation, formulation and dose of postoperative patient-control-analgesia (PCA) pump, and time between end of operation and study drug infusion are recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II) is calculated.

**Trial interventions**

All patients are randomized 1:1 to receive remifentanil (Remi group) or placebo (Saline group) infusion. Patients in Remi group receive intravenous bolus dose of remifentanil

0.5 μg/kg over 60 seconds followed by a continuous infusion 0.05μg/kg/min for 20 minutes. Patients in Saline group receive intravenous infusion of 0.9% sodium chloride at a volume and rate equal to that of remifentanil. Study drugs are administered by using syringe pump.

Immediately after drug infusion, ICU physician evaluate the patient by using extubation screen checklist shown in Table 1. If the patient passes the evaluation, endotracheal extubation will be carried out immediately by registered ICU nurses. The patient will be labeled as "failing to pass extubation test after drug administration" if he or she does not pass the evaluation. The reason of test failure will be documented. The patient will be re-evaluated every hour thereafter, and data about extubation will be documented.

Vital signs, which including heart rate (HR), respiratory rate (RR), non-invasive blood pressure (BP) and pulse oxygen saturation ($SpO_2$), are continuously monitored. VAS pain score is used to measure the pain intensity by the study investigator [25]. Each patient is instructed and asked to point to a mark on a 10-cm horizontal line labelled with descriptors of pain intensity ('No pain' at the 0 cm point and 'Extreme pain' at the 10 cm point). VAS and vital signs (HR, RR, BP and $SpO_2$) are documented at four time points: before drug infusion (baseline), immediately before extubation, immediately to 3 minutes after extubation and 20 minutes after extubation.

Patients will be followed up until hospital discharge, death or 60 days after the trial intervention, on first-served basis. Following data are collected: incidence of re-intubation within 72 hours after extubation, incidence of re-operation due to

intracranial hemorrhage or edema within 72 hours after extubation, LOS in ICU and hospital and mortality.

**Adverse events management and emergency stop of the study drug**

Patients are closely monitored during study drug infusion. Taking into account the potential adverse effects of remifentanil, experimental drugs must be immediately terminated when the following occurs:

1) Unresponsive to calling and patting on the shoulder;
2) RR less than 8 respirations per minute and $SpO_2$ less than 92%;
3) HR less than 50 beats per minute after atropine in 0.25 mg bolus;
4) Systolic BP less than 90 mmHg;
5) Serious allergic reaction such as throat swelling, bronchospasm or skin rash.

These data will be documented and reported as adverse events.

**Study endpoints**

The primary endpoint of present study is the incidence of severe pain during peri-extubation period. Peri-extubation is defined as the period of time from immediately before extubation to 20 minutes after extubation. Severe pain is defined as one of the VAS pain scores is more than 5 cm.

Secondary endpoints include:

1) VAS pain score and vital signs (HR, RR, BP and $SpO_2$) during peri-extubation period;

2) Incidence of failing to pass extubation evaluation after experimental drug infusion;

3) Incidence of re-intubation within 72 hours after extubation;

4) Incidence of re-operation due to intracranial hemorrhage or edema within 72 hours after extubation;

5) Incidence of adverse events during experimental drug infusion;

6) LOS in ICU and hospital;

7) Mortality.

**Current sample size justification**

Primarily, we expect the incidence of severe pain during peri-extubation period to decrease after remifentanil infusion in delayed extubation patients after craniotomy. Previous investigation showed that severe peri-extubation pain was occurred in 45% of patients [8]. It is expected that the incidence of severe pain would decrease to 30% after remifentanil infusion. Using the Power and Sample Size Calculation program, we will need to study 74 experimental subjects and 74 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability with testing this null hypothesis is 0.05.

**Statistical analysis**

All analyses will be according to the intention-to-treat principle, that is, all randomized

patients will be analyzed in the groups to which they were originally allocated and will be blinded to treatment assignment.

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the $\chi^2$-test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

We use repeated measure of analysis of variance (ANOVA) for comparing VAS pain score and vital signs (HR, RR, BP and $SpO_2$) across different time points (before drug infusion and during peri-extubation period) between the two groups.

All tests of significance will be at the 5% significance level, and two-sided. Analyses are conducted by using SPSS 17.0.

## ETHICS AND DISSEMINATION

### Ethical aspects and informed consent

Patients with delayed extubation after craniotomy are often unable to provide consent before extubation. After patient's eligibility for the study is confirmed, the ICU physician will introduce the family to the study coordinator. The physician will make sure the family knows the credentials of the study coordinator, and says that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that the patient may experience pain during extubation and, if so, the patient could become worse. The coordinator will say that a new opioid drug, remifentanil provides adequate analgesia with minimal respiratory depression. He (or she) will explain that in a small percentage of patients, remifentanil could cause bradycardia, hypotension and respiratory depression. The potential advantages of using or not using remifentanil will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study

coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

A register is kept of all patients evaluated for inclusion and of patients who withdraw from the study. The latter are clinically followed up without their data being analyzed in the study.

The study protocol and consent forms were approved on November 1, 2013 by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (approval number KY2013-002-01). The study was registered on November 8, 2013 at the Chinese Clinical Trial Registry (ChiCTR-PRC-13003879).

**Dissemination plan**

Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.

## TRIAL STATUS

The patient recruitment began on January 6, 2014, and the first patient was enrolled on the same day. The study will be completed in December 2014.

**SUMMARY**

Endotracheal extubation is a critical step during post-operative care in neurosurgical patients [9]. Pain is common during extubation period, and related to complications and adverse outcome [8]. Adequate analgesia is needed in this situation. Although revised Clinical Practice Guidelines from SCCM have recommended that prophylactic analgesia should be used to alleviate pain in adult ICU patients prior to potentially painful procedures [7], study for analgesia during endotracheal extubation is still limited. As a new opioid with minimal respiratory depression effect and a rapid onset and short duration of action, remifentanil seems suitable for prophylactic analgesia during extubation in patients after craniotomy [13-16]. We want to provide such evidence in present study. Even a neutral result will provide important insight, as this would mean that more studies are needed to explore a safe and effective way of pain management during endotracheal extubation. This is the main strength of present study.

It should be emphasized the comprehensive characteristics of pain management. Apart from opioids, other analgesics (such as steroidal or non-steroidal anti-inflammatory drugs) and/or non-pharmacologic interventions (such as relaxation) have been shown to alleviate pain in adult ICU patients [7]. Although the main purpose of present study is not to clarify the effect of comprehensive approach on manipulation of pain during extubation, we will collect data of the use of analgesics during anaesthesia and ICU stay, and the formulation and dose of postoperative PCA pump. The use of non-opioids and non-pharmacologic interventions during extubation needs further investigation.

Currently, vital signs are not recommended to be used alone for pain assessment [7].

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However, we still incorporated changes of vital signs during peri-extubation period as a secondary endpoint for two reasons. First, nociceptive stimulus during endotracheal extubation may result in adverse events in patients after craniotomy, such as brain swelling and hemorrhage. We want to know whether remifentanil could diminish this stress response. Second, because large doses of opioid agents usually result in respiratory and circulatory depression, this secondary endpoint will provide safe consideration about the use of these agents.

There are some limitations to our study protocol. First, because there is no proven dose of remifentanil which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator, the dose of remifentanyl used in present study is arbitrary. Second, we assumed a 15% reduction in severe pain after the administration of remifentanil in the calculation of sample size. There are no previous studies to support this. However, an effectivity of 15% is generally adopted in clinical studies. Third, opioids may result in change of consciousness. We only observe the response to calling and patting on the shoulder during the infusion of study agents. Documentation of sedation scales (such as Vancouver interaction scale or sedation-agitation scale) will add value to the study. Finally, evaluation of VAS requires the patient's ability to self-report clearly, and this may limit the patient population eligible for the present study. So, the results of this study will not be applied to all patients after craniotomy, especially for those with consciousness impairments.

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**Authors' contributions**

All authors listed on the title page fulfill the authorship criteria given by the ICMJE.

YXW and JXZ participated in the design of the study and drafted the manuscript. HC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

**Funding statement**

The study was funded by Beijing Health Bureau (No: 2009-3-28). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

**Competing interests**

The authors declare that they have no competing interests.

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**Table 1: Screening checklist used to determine the patient's suitability for extubation**

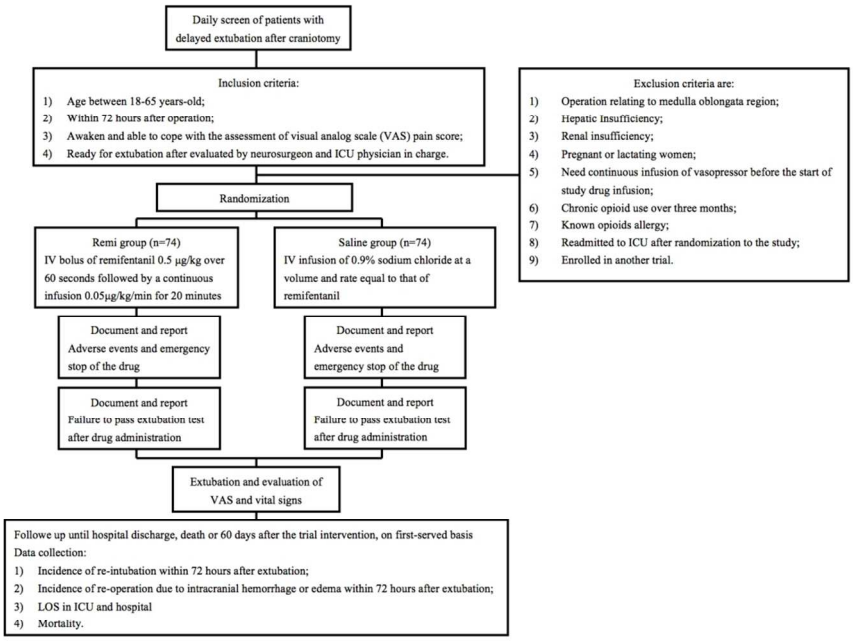
| Question | Answer |
|---|---|
| 1. Awake and alert with cerebral function adequate for patient co-operation or equivalent preoperative state of consciousness? | Yes/No |
| 2. Hemodynamic stability (lack of vasopressor support and mean arterial pressure within 10-15% of baseline)? | Yes/No |
| 3. Adequate recovery of muscle strength? | Yes/No |
| 4. Normal tidal volumes, normocapnia (end-tidal carbon dioxide 30-45 mmHg), minimum pulse oximetry > 95% with $FiO_2$ 0.5? | Yes/No |
| 5. Intact gag reflex and swallow function (presence of clearly audible cough during suctioning)? | Yes/No |

The answer to all questions must be "yes" in order for extubation to be approved.

$FiO_2$: fraction of inspired oxygen

**Figure legend**

Figure 1: Trial schematic diagram

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# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-6 |
| | 2b | Specific objectives or hypotheses | 6 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 7, 9 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | Not applicable |
| Participants | 4a | Eligibility criteria for participants | 7 |
| | 4b | Settings and locations where the data were collected | 7 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9-11 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11-12 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | Not applicable |
| Sample size | 7a | How sample size was determined | 12 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | Not applicable |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 8-9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 8-9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 8-9 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 8-9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 8-9 |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | 8-9 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 12-13 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | Not applicable |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Not applicable in items 13a to 22 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | |
| | 14b | Why the trial ended or was stopped | |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | ChiCTR-PRC-13003879 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | Not applicable |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | The study was supported by Beijing Health |

| | |
|---|---|
| | Bureau (No: 2009-3-28). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.