PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Zhou, Jian-Xin; Wu, Yuan-Xing; Chen, Han

VERSION 1 - REVIEW

REVIEWER	Grace Korula DM Wayanad Institute of Medical Sciences Kerala, India
REVIEW RETURNED	12-Aug-2014

GENERAL COMMENTS	Limitation of the study in my opinion is that the dose of remifentanyl used in this study is arbitary as there is no proven dose of of remifentanyl which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator. 1.The sample size is calculated with the assumption that there will be a 30% reduction in severe pain. There are no previous studies to support this. 2. Have they taken into account the possibility that some patients that may fail to reach criteria for extubation. This is not clear in the calculation. Documentation of a sedation scale such as Vancouver interaction scale, after administration of remifentanyl, till 20 mins past extubation will add value to the study. This will show if patients are capable of responding or how soon after stopping sedation they can respond to the questions regarding pain score and if there is significant difference in sedation between the two groups.

REVIEWER	Yoanna Skrobik Université de Montréal Canada
REVIEW RETURNED	13-Aug-2014

GENERAL COMMENTS	The manuscript proposes a methodological description of a protocolized study in neuro-critically ill patients. According to the authors, pain is common upon extubation in neuro-critically ill patients. Consequently, the protocol plans to stratify patients into patients given remifentanyl on extubation vs. saline. Although the patients argue removal of an artificial airway is a nociceptive stimulus, this reviewer remains unconvinced that this transient discomfort requires opiate analgesics; indeed, even though the SCCM guidelines cited by the authors suggest opiates be used as pharmacologic analgesic intervention, this recommendation follows careful administration of co-analgesics, and the understanding many patients do not require opiates at all (as explicitly shown in several general ICU studies published in the last few years in general ICU populations and quoted in the SCCM guidelines). This premise makes the proposed comparison of remifentanyl to placebo all the more fitting. The confounding effect of co-analgesics such as paracetamol or steroidal or non-steroidal anti-inflammatories should be considered. Finally, the ability to self-report clearly limits the patient populations eligible for the study, bur, on the other hand, clearly defines the population (awake) and establishes a standard of practice in the neurosurgically 'well' post-operative population. It is not clear to this reviewer why the HR and other vital signs are considered as part of the secondary end-points for the study. The SCCM guidelines repeatedly cited by the authors clearly state that vitals are unrelated to pain assessment. My concern is that these vitals will inappropriately be considered surrogate pain markers.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Grace Korula
Institution and Country DM Wayanad Institute of Medical Sciences
Kerala, India

Limitation of the study in my opinion is that the dose of remifentanyl used in this study is arbitary as there is no proven dose of of remifentanyl which can prevent sedation and respiratory depression in a neurosurgical patient being weaned off ventilator.
Response: have been added to the section of "Main strengths and limitations of the study" (page 3).

1.The sample size is calculated with the assumption that there will be a 30% reduction in severe pain. There are no previous studies to support this.
Response: have been added to the section of "SUMMARY" as limitations to the study protocol (page 17). However, we stated that there will be a 15% reduction in severe pain, not a 30%.

2. Have they taken into account the possibility that some patients that may fail to reach criteria for extubation. This is not clear in the calculation.
Response: have been stated in the “Secondary endpoints” (page 11-12) in the first submitted manuscript.

Documentation of a sedation scale such as Vancouver interaction scale, after administration of remifentanyl, till 20 mins past extubation will add value to the study. This will show if patients are capable of responding or how soon after stopping sedation they can respond to the questions regarding pain score and if there is significant difference in sedation between the two groups.
Response: We evaluated patient’s suitability for extubation by screening checklist showed in Table 1 (page 23). The first evaluation item is “Awake and alert with cerebral function adequate for patient co-operation or equivalent preoperative state of consciousness”. We agree the reviewer’s comment, and we will report how many patients do not pass this evaluation as a result of study.

Reviewer: 2
Reviewer Name Yoanna Skrobik
Institution and Country Université de Montréal
Canada

The manuscript proposes a methodological description of a protocolized study in neuro-critically ill patients. According to the authors, pain is common upon extubation in neuro-critically ill patients. Consequently, the protocol plans to stratify patients into patients given remifentanyl on extubation vs. saline. Although the patients argue removal of an artificial airway is a nociceptive stimulus, this reviewer remains unconvinced that this transient discomfort requires opiate analgesics; indeed, even though the SCCM guidelines cited by the authors suggest opiates be used as pharmacologic analgesic intervention, this recommendation follows careful administration of co-analgesics, and the understanding many patients do not require opiates at all (as explicitly shown in several general ICU studies published in the last few years in general ICU populations and quoted in the SCCM guidelines). This premise makes the proposed comparison of remifentanyl to placebo all the more fitting.
Response: we agree the reviewer’s comment.

The confounding effect of co-analgesics such as paracetamol or steroidal or non-steroidal anti-inflammatories should be considered.
Response: we agree the reviewer’s comment. Data collected at study entry include the use of analgesics during anesthesia and ICU stay, and the formulation and dose of PCA pump after operation (page 9 in the first submitted manuscript). These data include the use of co-analgesics.

Finally, the ability to self-report clearly limits the patient populations eligible for the study, bur, on the other hand, clearly defines the population (awake) and establishes a standard of practice in the neurosurgically ‘well’ post-operative population.
Response: we agree the reviewer’s comment.

It is not clear to this reviewer why the HR and other vital signs are considered as part of the secondary end-points for the study. The SCCM guidelines repeatedly cited by the authors clearly state that vitals are unrelated to pain assessment. My concern is that these vitals will inappropriately be considered surrogate pain markers.
Response: yes, we agree the reviewer’s comment. However, on the other hand, pain results in stress response. Appropriate analgesia, not only reduces pain, but attenuates stress responses (stated in introduction section, page 4 in the first submitted manuscript). Secondly, 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.

VERSION 2 – REVIEW

REVIEWER	Grace Korula DM Wayanad Institute of Medical Sciences Kerala, India
REVIEW RETURNED	16-Aug-2014

GENERAL COMMENTS	The authors have mentioned 'consecutive patients are randomly assigned to one of the two treatment study groups, labeled as ‘Remi group’ or ‘Saline group’.' They also mention '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.' Please clarify. The authors have defined Peri-extubation as the period of time from immediately before extubation to 20 minutes after extubation. However they are closely monitoring the patients only during drug infusion for adverse events. My concern is the period immediately after extubation as the pain stimulus due to the presence of endotracheal intubation and the stress of extubation is no longer there. This is the period of possible worsening of consciousness. I realise the study has already started and so documenting sedation scale is not an option but the gap of 17 mins for documentation of vital signs and VAS scale appears too long.

REVIEWER	Yoanna Skrobik Université de Montréal
REVIEW RETURNED	09-Sep-2014

GENERAL COMMENTS	None of my comments from an earlier review of the methods have been considered, and the limitations pointed out remain unadressed. The only circumstance where I would consider looking at this proposal again (given the unresponsiveness to my comments) would be if the lack of response by the authors wsa in some way related to their unawareness as to their content. Otherwise, further review appears futile.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Grace Korula
Institution and Country DM Wayanad Institute of Medical Sciences
Kerala, India
Please state any competing interests or state ‘None declared’: None declared

The authors have mentioned 'consecutive patients are randomly assigned to one of the two treatment study groups, labeled as ‘Remi group’ or ‘Saline group’.' They also mention '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.' Please clarify.

Response: have been clarified (page 8)

The authors have defined Peri-extubation as the period of time from immediately before extubation to 20 minutes after extubation. However they are closely monitoring the patients only during drug infusion for adverse events. My concern is the period immediately after extubation as the pain stimulus due to the presence of endotracheal intubation and the stress of extubation is no longer there. This is the period of possible worsening of consciousness. I realise the study has already started and so documenting sedation scale is not an option but the gap of 17 mins for documentation of vital signs and VAS scale appears too long.
Response: have been revised as one of limitations in Summary section (page 18)

Reviewer: 2
Reviewer Name Yoanna Skrobik
Institution and Country Université de Montréal
Please state any competing interests or state 'None declared': none declared

Respond to reviewer 2's original queries

The manuscript proposes a methodological description of a protocolized study in neuro-critically ill patients. According to the authors, pain is common upon extubation in neuro-critically ill patients. Consequently, the protocol plans to stratify patients into patients given remifentanyl on extubation vs. saline. Although the patients argue removal of an artificial airway is a nociceptive stimulus, this reviewer remains unconvinced that this transient discomfort requires opiate analgesics; indeed, even though the SCCM guidelines cited by the authors suggest opiates be used as pharmacologic analgesic intervention, this recommendation follows careful administration of co-analgesics, and the understanding many patients do not require opiates at all (as explicitly shown in several general ICU studies published in the last few years in general ICU populations and quoted in the SCCM guidelines). This premise makes the proposed comparison of remifentanyl to placebo all the more fitting.
Response: have been revised in Summary section and Limitation of the study (page 3 and page 17)

The confounding effect of co-analgesics such as paracetamol or steroidal or non-steroidal anti-inflammatories should be considered.
Response: have been revised in Summary section (page 17)

Finally, the ability to self-report clearly limits the patient populations eligible for the study, bur, on the other hand, clearly defines the population (awake) and establishes a standard of practice in the neurosurgically 'well' post-operative population.
Response: have been revised in Summary section and Limitation of the study (page 3 and page 18-19)

It is not clear to this reviewer why the HR and other vital signs are considered as part of the secondary end-points for the study. The SCCM guidelines repeatedly cited by the authors clearly state that vitals are unrelated to pain assessment. My concern is that these vitals will inappropriately be considered surrogate pain markers.
Response: have been revised in Summary section (page 18)