PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: study protocol of a randomized controlled trial
AUTHORS	Peng, Kun; Zeng, Min; Dong, Jia; Yan, Xiang; Wang, Dexiang; Li, Shu; Peng, Yuming

VERSION 1 - REVIEW

REVIEWER	Harsha Shanthanna McMaster University Canada
REVIEW RETURNED	02-Oct-2019

GENERAL COMMENTS	Thank you for the opportunity to review. I think it is a good study question. However, I have several questions and comments which needs to be addressed. All of those are included or noted in the attached do The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Guillaume Besch Department of Anesthesiology and Intensive Care Médicine, University Hospital of Besançon, France and EA3920, University of Bourgogne Franche-Comté, Besançon, Franc
REVIEW RETURNED	08-Oct-2019

GENERAL COMMENTS	The authors address the quite interesting issue of postoperative pain relief after craniotomy via sub occipital retrosigmoid approach. The authors present the protocol of a well-designed randomized trial aiming at investigating whether a preoperative ultrasound guided superficial cervical plexus block could improve postoperative pain relief. The manuscript is well presented and very pleasant to read. I have only one minor concern about the manuscript: could the authors precise what the '6 different time-point after surgery' mentioned in the 'secondary outcomes' paragraph refer to? Kind regards.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Thank you for the opportunity to review. I think it is a good study question. However, I have several questions and comments which needs to be addressed. All of those are included or noted in the attached document.

1. Page 4 paragraph 1 - Shorten the BACKGROUND section-may be maximum of 2.5 pages from the present 4 plus pages. This should include a description of STUDY OBJECTIVES in the end.

Response: Thank you for your important comments. We have shortened the BACKGROUND section and added the description of STUDY OBJECTIVES in the end. Please see Page 4-6.

2. Page 4 paragraph 1- Enormous catastrophe does not clearly describe anything. Note the adverse effects of inadequate pain relief.

Response: We have deleted this sentence. Please see Page 4 paragraph 1.

3. Page 4 paragraph 1 - use a different word for “enormous”

Response: We have rephrased “enormous” as “abundant”. Please see Page 4 paragraph 2.

4. Page 5 paragraph 2 - Rephrase- “It is obvious”

Response: We agree with your opinion that this study is not appropriate to focus changes in persistent pain. So, we take the content about persistent pain out including this sentence. Please see page 5 paragraph 1.

5. Page 5 paragraph 2 - What is compound analgesia?

Response: We have removed the statement about “compound analgesia” according to your suggestions.

6. Page 5 paragraph 2 - You have provided evidence to show that infra-tentorial surgeries can be painful. I think it is not appropriate for this study to focus or expect changes in persistent pain. Please focus on saying that you are exploring an analgesic modality that can effectively provide surgical analgesia (intraoperative and postoperative) for this population.

Response: We have removed the statement about “persistent pain” according to your suggestions and focused on saying on exploring an analgesic modality that can effectively provide surgical analgesia (intraoperative and postoperative) for this population.

7. Page 5 paragraph 3 - Rephrase this sentence. It is confusing and complicated. The message should be- An ideal analgesic should be able to provide analgesia for the entire surgical period and with minimal or no systemic changes.

Response: We have rephrased this sentence as “an ideal analgesic should be able to provide analgesia for entire surgical period and with minimal or no systemic changes.” Please see page 5 paragraph 1.

8. Page 6 paragraph 1 - I am not sure if most centers go with PCIA for these surgeries? Substantiate your statement with a reference.

Response: Thank you for your suggestion, we have added the reference. And we have moved this description into DISCUSSION section. Please see page 15 paragraph 2.

Akcil, E. F., et al. (2017). "Which one is more effective for analgesia in infratentorial craniotomy? The scalp block or local anesthetic infiltration." Clin Neurol Neurosurg 154: 98-103.

Song, J., et al. (2015). "Preemptive scalp infiltration with 0.5% ropivacaine and 1% lidocaine reduces postoperative pain after craniotomy." Acta Neurochir (Wien) 157(6): 993-998.

9. Page 6 paragraph 2 - Revise this sentence. If scalp nerve block has been proven as an excellent choice-in which population-say for supratentorial surgeries?

Response: We have revised the sentence as “Scalp nerve block (SNB) has been proven to be an excellent alternative analgesic choice in supratentorial surgeries” according to your suggestions. Please see page 5 paragraph 1.

10. Page 6 paragraph 2 - Revise; you are not exploring a comprehensive analgesic model; but only cervical plexus block plus other analgesics

Response: We have rephrased “a comprehensive analgesic model” as “an analgesic modality”. Please see page 5 paragraph 1

11. Page 7 paragraph 1 - What about the area innervated by the Greater Occipital and Third Occipital?

Response: The skin incision of the suboccipital retrosigmoid approach may be 2 cm behind the external ear with 1/3 upper proportion extend to auricular helix and remaining 2/3 extended to neck muscle. Generally, the incisions might be 5-7 cm in length and might be straight incision, S-shaped incision or crutch incision according to surgeon’s technical preference. However, none of above three skin incision would involve with the greater occipital or the third occipital nerve.

12. Page 7 paragraph 1 - Are you saying they did not do a sample size estimate? please clarify.

Response: What we mean is that they made sample size estimation, but the sample size is too small. We didn't make it clear in the manuscript. Now we have revised it. Please see page 5 paragraph 2.

13. Page 7 paragraph 1 - To guarantee analgesic effect in your method; will you be testing patients? or you are assuming that because it is US guided it is more effective? Superficial cervical plexus block is a plane block and is it not necessary to visualize the nerves.

Response: Thank you for raising this issue. In our study, SCPB will be performed after anesthesia induction, we can’t test patient. Although SCPB is a plane block, we assume that US guided block will be more effective. Because the operator can directly see adjacent anatomical structure and inject the local anesthetic into the correct anatomical level (Senapathi, Widnyana et al. 2017).

Senapathi, T. G. A., et al. (2017). "Ultrasound-guided bilateral superficial cervical plexus block is more effective than landmark technique for reducing pain from thyroidectomy." J Pain Res 10: 1619-1622.

14. Page 8 paragraph 1 - Substantiate by citing studies to show that US guided Superficial Plexus Block is superior to non-image guided

Response: We have substantiated by citing studies (Senapathi, Widnyana et al. 2017, Ho and De Paoli 2018) to show that US guided Superficial Plexus Block is superior to non-image guided in our manuscript. Please see page 6 paragraph 2

Senapathi, T. G. A., et al. (2017). "Ultrasound-guided bilateral superficial cervical plexus block is more effective than landmark technique for reducing pain from thyroidectomy." J Pain Res 10: 1619-1622.

Ho, B. and M. De Paoli (2018). "Use of Ultrasound-Guided Superficial Cervical Plexus Block for Pain Management in the Emergency Department." J Emerg Med 55(1): 87-95.

15. Page 8 paragraph 2 - Take this out. You are not observing for long term effects。Response: We have taken the observation of long term effects out according to your suggestions. Please see page 6 paragraph 3.

16. Page 8 paragraph 3 - Take out this word “strategy”

Response: We have taken out this word “strategy” according to your suggestions. Please see page 7 paragraph 4.

17. Page 8 paragraph 3 - revise this- registered within clinicaltrials.gov on June 29 with the registration number-

Response: We have revised the sentence as “registered within clinicaltrials.gov on June 29 with the registration number” according to your suggestions. Please see page 7 paragraph 4.

18. Page 8 paragraph 3 - replace purposes with objectives

Response: We have replaced purposes with objectives. Please see page 7 paragraph 4.

19. Page 8 paragraph 3 -Why legal representatives? for unconscious patients? Make sure to include an Informed Consent Form as an appendix

Response: In china, informed consent forms are signed by patients or their immediate family members indicating that they understand the risks involved in the study and they agree to participate. Legal representatives of patients commonly see their immediate family members. Informed consent form of this study has been uploaded as an appendix to this manuscript.

20. Page 9 paragraph 1 - When will you collect baseline information and what will be collected?

Response: After obtaining informed consent, an independent research assistant will initiate baseline information collection one day before surgery. Basic demographic information, including: gender, age, vital signs, height, weight, past medical history/family history, medication history, pre-treatment supplementary examination, pre-treatment assessment (ASA classification, headache and severity, treatment, dizziness, tinnitus, facial paralysis, nausea, vomiting and other symptoms) will be collected. We have revised this section and adjusted its position in the manuscript. Please see page 8 paragraph 2.

21. Page 9 paragraph 2 - If you are excluding them, why do you want consent from legal representative?

Response: We exclude the patients of consciousness and cognitive function not because informed consent could not be obtained, but because it is impossible to assess the analgesic effects of SCPB. In china, informed consent forms are signed by patients or their immediate family members indicating that they understand the risks involved in the study and they agree to participate. Legal representatives of patients commonly see their immediate family members.

22. Page 9 paragraph 2 - why exclude severe hepatic, diabetes, severe arrhythmia and unstable angina pectoris?

Response: Thank you for raising this issue. After careful consideration, we think the patients of severe hepatic, renal dysfunction, diabetes, severe arrhythmia and unstable angina pectoris should not be excluded. We have taken them out from exclusion criteria. Please see page 7 paragraph 3.

23. Page 9 paragraph 2 - what do you mean by this? why would anyone refuse to receive post-operative analgesia?

Response: Thank you for raising this issue. Some patients with high pain threshold feeling that craniotomy is not so painful; and others due to financial constraints all may refuse to receive post-operative analgesia. Although patients who refuse to receive post-operative analgesia will not be included. So, we have taken it out from exclusion criteria.

24. Page 9 paragraph 2 - why exclude drug abuse; history of chronic headache

Response: Drug abuse and/or history of chronic headache will interfere with evaluation of the analgesic requirement and pain. To ensure uniformity at baseline and to maximally eliminate the interference of confounding factors, we exclude patients with a history of drug abuse and/or chronic headache.

25. Page 9 paragraph 2 - why exclude body mass index > 30.0 kg/m2 In the present context of Obesity, a BMI of 30 is quite close to being average!

Response：Thank you for your important comments. I think you're right that in the present context of obesity, exclusion of patients with a BMI greater than 30 is not appropriate. We have revised the exclusion criteria. We will exclude body mass index > 35.0 kg/m2 according to your suggestions. Please see page 7 paragraph 3.

26. Page 9 - Please clarify the following clearly in your revised submission. Randomization will be computer generated (when will this happen)? Is the same research assistant randomizing or getting the allocation collecting study outcomes? if so, he/she is not blinded.

Response: the same researcher assistant randomizes and allocate the sequence who is also be blind to the grouping. Please refer to page 7 paragraph 4.

27. Page 10 - Which anesthetist will perform the block and who will manage the patients?

Response: An independent researcher who will not involve in intraoperative management or postoperative follow-up will perform the block. The anesthesiologists-in-chief responsible for intraoperative management and outcome assessors will be blinded to the participants' group assignment. We have clarified these contents clearly in our revised submission. Please refer to page 8 paragraph 3.

28. Page 10 paragraph 2 - replace locating with located

Response: We have replaced "locating" with "located". Please see page 9 paragraph 1.

29. Page 10 paragraph 2 - Is it 10 or 15? why is this variation? and on what basis?

Response: We have revised the dose of local anesthetic as 10 ml referring to the study of Senapathi and Girard. Senapathi et al. compared the effectiveness of US-guided and Landmark technique for SCPB in thyroidectomy(Senapathi, Widnyana et al. 2017). They performed bilateral SCPB, using 10 ml of 0.25% plain bupivacaine on each side of the neck. Girard et al. compared the quality of transitional analgesia provided by SCPB with that provided by intravenous morphine for infratentorial or occipital craniotomy(Girard, Quentin et al. 2010). The block was performed, using a mixture of 2% lidocaine 10 ml and 0.5% bupivacaine 10 ml. We have made corresponding revision in the manuscript. Please see page 9 paragraph 1.

Senapathi, T. G. A., et al. (2017). "Ultrasound-guided bilateral superficial cervical plexus block is more effective than landmark technique for reducing pain from thyroidectomy." J Pain Res 10: 1619-1622.

30. Page 11 paragraph 2 - It would have been good to control it with saline injection. Why is this not done? What is the point of only doing US guidance when the patient knows he did not get a poke? Are you expecting patient to know (unblinded) but not tell the person collecting the data (who you expect is blinded)?

Response: Thank you for your important comments. It would have been good to control it with a puncture. So, we have made corresponding revision. In the control group, the puncture will also be performed by ultrasound guidance, covered with opaque infusion dressing but performed without infusion. Please see page 9 paragraph 2.

31. Page 11 paragraph 3 - Will you not have access before performing the block? How is it safe?

Response: In our study, SCPB will be performed after the establishment of peripheral venous access and anesthesia induction. It might be we haven't stated clearly enough. We have made revision in the manuscript. Please see page 8 paragraph 3.

32. Page 11 paragraph 3 - why not before the block?

Response: As mentioned above, midazolam will be premedicated before the block. SCPB will also be performed after anesthesia induction in our study. Please see page 8 paragraph 3.

33. Page 12 paragraph 2 - Define what is NRS in your study

Response: Thank you for the careful review of our manuscript. In our study, the definition of NRS is 0-10, 0 = no pain and 10 = worst pain imaginable. We have revised the definition of insufficient postoperative analgesia that an NRS score exceeds 6 or exceeds 4 lasted for 15 minutes. Please see page 11 paragraph 1.

34. Page 12 paragraph 2 - When is this? in PACU or ward? Why is Tramadol being given on top of Sufentanyl PCIA?

Response: Our original plan was to use tramadol as a rescue analgesic for postoperative analgesia. In postoperative Day 1-2, PACU or ward, tramadol is considered as rescue analgesic, when PCIA is inadequate (NRS score >4 over 15 minutes or >6) even if the maximum dose of sufentanil was given (6 μg/h for safety, in case of respiratory depression or hypnosis effect). After careful consideration, in order to improve the feasibility of the trial, we decide not to limit the type, the frequency and the total dose of rescue analgesic, only to record them, and finally to perform statistical analysis. So, we rephrase "tramadol" as "rescue analgesic". Antiemetic treatment is the same regimen. We have made revision in the manuscript. Please see page 11 paragraph 1.

35. Page 13 - what about those patients who are still intubated?

Response: We will make PP analysis and ITT analysis for the primary outcome. So the patients who are still intubated will be analyzed in ITT analysis, but not in PP analysis. Please see page 14 paragraph 1, the statistical analysis section.

36. Page 13 paragraph 3 - This can be confusing when some patients also receive Tramadol for whatever reasons. How can you eliminate the effect of Tramadol for their analgesia?

Response: Thank you for raising this issue. When we give drugs with analgesic effect, we will record the reason for administration and the type, the frequency and the dose of rescue analgesic. Comparison of two groups after drug equivalent conversion will be used in later statistical analysis. We have made the corresponding additions in the manuscript. Please see page 11 paragraph 1.

37. Page 13 paragraph 3 - Define NRS pain score, analgesic satisfaction score, sleep quality score here.

Response: We have defined NRS pain score, analgesic satisfaction score, sleep quality score here according to your suggestions. Please see page 12-13.

38. Page 13 paragraph 3 - Please don't be vague. What Other Criteria?

Response: We have clarified other criteria such as anesthesia recovery quality score in this paragraph according to your suggestions. Please see page 12 paragraph 3

39. Page 13 paragraph 3 - Use either PCA or PCIA

Response: We have unified all abbreviations as PCIA according to your suggestions.

40. Page 13 paragraph 5 - what are the 6 different time points after surgery? For example; if the patient had surgery @ 4 pm, will you wake him up @ 1 am (or anytime during the night) and ask for pain score?

Response: Thank you for your commons. After careful consideration, we have adjusted the time points of observation to 5 time-points after surgery (1, 2, 4, 24, 48 hours). Furthermore, all enrolled patients will be the first case of the surgical day. Therefore, it is feasible to follow up at 1, 2, 4, 24, 48 hours after operation. We have made corresponding revision in the manuscript. Please see page 12 paragraph 1.

41. Page 13 paragraph 6 - What is 1) surgical incisional pain; 2) Head, 3) Neck pain-definitions for your study? How will head pain be different from incisional pain?

Response: In order to focus on saying surgical analgesia, we have only retained the surgical incisional pain, removed the head and neck pain. We have made corresponding revision in the manuscript. Please see page 12 paragraph 2.

42. Page 13 paragraph 6 - Here you say NRS of 0-10; but above you say that insufficient analgesia is NRS >40?

Response: Thank you for your kind reminder. This is our mistake. The definition of NRS is 0-10 in our study. We have revised insufficient analgesia is NRS >6 or NRS >4 for 15 minutes. We have made corresponding revision in the manuscript. Please see page 12 paragraph 2.

43. Page 15 paragraph 1 - Why are you doing an interim analysis?

Response: Thank you for raising this issue. The sample size of our study is not large, so we do not need to do interim analysis. We have taken interim analysis out.

44. Page 15 paragraph 2 - You say yours is the first study?

Response: based on the PICOs principle, our study is the first study. The previous study is only similar to our population, which provided the evidence to estimate the sample size.

Akcil, E. F., et al. (2017). "Which one is more effective for analgesia in infratentorial craniotomy? The scalp block or local anesthetic infiltration." Clin Neurol Neurosurg 154: 98-103

45. Page 15 paragraph 2 - this is nearly 40-50% relative risk reduction?

Response: Thank you for raising this issue. What we mean is not nearly 40-50% relative risk reduction, perhaps our description is unclear. We estimated the sample size based on the effect size of mean and standard deviation. We have made corresponding revision in the manuscript. Please see page 13 paragraph 2.

Akcil, E. F., et al. (2017). "Which one is more effective for analgesia in infratentorial craniotomy? The scalp block or local anesthetic infiltration." Clin Neurol Neurosurg 154: 98-103

46. Page 15 paragraph 2 - why do you expect a drop-out rate of 10%?

Response: We expect a drop-out rate of 10% because it is impossible to assess PCA sufentanil cumulative consumption within 24 hours after surgery due to prolonged ventilation, re-surgery, etc.

47. Page 15 - You mention Interim analysis earlier?

Response: The sample size of our study is not large, so we do not need to do interim analysis. So, we have taken interim analysis out. We don't include the content of interim analysis in statistical analysis.

48. Page 16 paragraph 2 - Are you aware of SAE? and SUSAR (Suspected unexpected serious adverse reactions)?

Response: Thank you for raising this issue. We realize that we mistake the concept of SAE and SUSAR. SAE see the events occurred during the clinical trial, including disability, impact on work ability, life-threatening or death, congenital malformation, hospitalization, prolongation of hospitalization, etc. Our study will focus on assessing AEs related to SCPB. The SCBP-related AEs include but are not limited to: hematoma, allergy, overdose and hoarseness. We have revised the manuscript. Please see page 14 paragraph 2

49. Page 16 paragraph 2 - Responsible for what? causing it? managing it? reporting it? dealing with it?

Response: The chief investigator will be responsible for getting the details about causes of AEs, treatment measures, prognosis, and reporting serious adverse events to the Ethics Committee immediately. We have revised the manuscript. Please see page 14 paragraph 2.

50. Page 16 - Earlier, interim analysis was mentioned? will the DMC request for it? What is the reason for having a DMC?

Response: Thank you for raising this issue. SCBP is a routine practice, so we don't need a DMC. And the sample size of our study is not large, so we don't need to do interim analysis and similarly, we don't need a DMC. So, we take the content about DMC out.

51. Page 17 paragraph 1 - you are assessing-not exploring rephrase it as -to assess the

Response: We have rephrased "explore" as "assess" according to your suggestions. Please see page 16 paragraph 2

52. Page 17 paragraph 1 - Superficial cervical plexus block is not an advanced level block. I think this statement is wrong? what is the anatomical complexity? It is a plane block and not a nerve block!

Response: Thank you for your comments. We agree with you that superficial cervical plexus block is not an advanced level block. Although the description of the complex structure of the superficial cervical plexus is not accurate, superficial cervical plexus block still has several complications. We have taken "for the anatomic complexity of superficial cervical plexus" out. Please see page 16 paragraph 2.

53. Page 17 paragraph 1 - are you performing both superficial and deep cervical plexus blocks?

Response: Thank you for your comments. We only perform superficial cervical plexus block and its puncture level was relatively superficial. So, the risk of high epidural anesthesia was not significant. We have removed "high epidural block or total spinal anesthesia, overdose" and kept "hematoma,

dizziness, fatigue, hematoma, local anesthetic poisoning and hoarseness” in the manuscript. Please see page 16 paragraph 2.

54. Page 17 paragraph 1 - Does not carry any meaning.

Response：Thank you for your comments. We have taken this sentence out.

Reviewer 2

The authors address the quite interesting issue of postoperative pain relief after craniotomy via sub occipital retrosigmoid approach. The authors present the protocol of a well-designed randomized trial aiming at investigating whether a preoperative ultrasound guided superficial cervical plexus block could improve postoperative pain relief.

The manuscript is well presented and very pleasant to read.

I have only one minor concern about the manuscript: could the authors precise what the '6 different time-point after surgery' mentioned in the 'secondary outcomes' paragraph refer to?

Response: Thank you for your kind suggestion. We have added '6 precisely different time-point after surgery' mentioned in the 'secondary outcomes' paragraph. Please see page 13.